ACKNOWLEDGEMENTS

The publisher acknowledges and thanks the following for their assistance throughout the preparation of this book:

ANAND AND ANAND
ANTHIAZAMMIT LEGAL
BIRD & BIRD
CASTRÉN & SNEILLMAN ATTORNEYS LTD
CHANDLER MHM LIMITED
CIRIO ADVOKATBYRÅ
COVINGTON & BURLING LLP
DE GAULLE FLEURANCE & ASSOCIÉS
ESTUDIO BECCAR VARELA
FIALDINI EINSFELD ADVOGADOS
GORODISSKY & PARTNERS LAW FIRM
JONES DAY
KABRAJI & TALIBUDDIN
KIM & CHANG
LATIN LEX
LEE AND LI, ATTORNEYS-AT-LAW
LEГА ABOGADOS
MANNHEIMER SWARTLING ADVOKATBYRÅ
NYBORG & RØRDAM LAW FIRM P/S
POLAK & PARTNER RECHTSANWÄLTE GMBH
RODRIGO, ELÍAS & MEDRANO ABOGADOS
SÁNCHEZ DEVANNY
SHUSAKU YAMAMOTO
SOŁTYSIŃSKI, Kawecki & Szlezak
Studio Professionale Associato a Baker & McKenzie
Vieira de Almeida
Walter Wyss Ltd
Wolf Theiss
Wong Partnership LLP
<table>
<thead>
<tr>
<th>Chapter 1</th>
<th>INTERNATIONAL HARMONISATION</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Richard Kingham</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 2</th>
<th>ARGENTINA</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emilio N Vogelius</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 3</th>
<th>AUSTRALIA</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anthony Muratore and Jenny Wong</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 4</th>
<th>AUSTRIA</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Karina Hellbert</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 5</th>
<th>BELGIUM</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bart Van Vooren and Rosa Oyarzabal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 6</th>
<th>BRAZIL</th>
<th>67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alexandre Einsfeld, Joaquim Augusto Melo de Queiroz and Ivan Cunha</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 7</th>
<th>CHINA</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>John Balzano and Aaron Gu</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 8</th>
<th>CZECH REPUBLIC</th>
<th>115</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kamila Seberová</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 9</th>
<th>DENMARK</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Karin Absalonsen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter 10</th>
<th>EUROPEAN UNION</th>
<th>145</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grant Castle and Robin Blaney</td>
<td></td>
</tr>
</tbody>
</table>
## Contents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>FINLAND</td>
<td>170</td>
</tr>
<tr>
<td>Hanna Paloheimo and Hilma-Karoliina Markkanen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>FRANCE</td>
<td>182</td>
</tr>
<tr>
<td>Cécile Théard-Jallu and Xavier Vuitton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>INDIA</td>
<td>193</td>
</tr>
<tr>
<td>Pravin Anand and Archana Shanker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>ITALY</td>
<td>203</td>
</tr>
<tr>
<td>Roberto Cursano, Riccardo Ovidi and Irene Carlet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>JAPAN</td>
<td>215</td>
</tr>
<tr>
<td>Takeshi S Komatani</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>LATIN AMERICA OVERVIEW</td>
<td>243</td>
</tr>
<tr>
<td>Felipe Coronel C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>MALTA</td>
<td>254</td>
</tr>
<tr>
<td>Anthia A Zammit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>MEXICO</td>
<td>273</td>
</tr>
<tr>
<td>José Alberto Campos-Vargas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>PAKISTAN</td>
<td>285</td>
</tr>
<tr>
<td>Arlin Merchant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>PERU</td>
<td>298</td>
</tr>
<tr>
<td>Maria del Carmen Alvarado Bayo and Ricardo De Vettor Pinillos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>POLAND</td>
<td>310</td>
</tr>
<tr>
<td>Ewa Skrzydło-Tefelska and Jacek Myszko</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>PORTUGAL</td>
<td>324</td>
</tr>
<tr>
<td>Francisca Paulouro and Inês Caldas de Almeida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>RUSSIA</td>
<td>339</td>
</tr>
<tr>
<td>Evgeny Alexandrov and Ilya Goryachev</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>SINGAPORE</td>
<td>353</td>
</tr>
<tr>
<td>Melanie Ho and Chang Man Phing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2020 Law Business Research Ltd
The eighth edition of *The Life Sciences Law Review* covers a total of 33 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged so as to describe requirements throughout the life cycle of a regulated product, from discovery to clinical trials, the marketing authorisation process and post-approval controls. Certain other legal matters of special interest to manufacturers of medical products – including administrative remedies, pricing and reimbursement, competition law, special liability regimes and commercial transactions – are also covered. Finally, there is a special chapter on international harmonisation, which is of increasing importance in many of the regulatory systems that are described in the national chapters.

The past year has seen a number of significant developments. Shortly after the publication date for this edition, the European Union will begin enforcing significant changes in the regulatory regime for medical devices. The United States is considering measures to improve the transparency of pricing for prescription drugs. The United Kingdom is addressing changes to drug regulatory systems that must accompany the country’s withdrawal from the EU, and drug and device manufacturers are actively planning for the effects of Brexit on their supply chains. The governments in India and China continue to consider changes in their regulatory systems for drugs and medical devices.

It is vitally important that lawyers who advise companies in the life sciences sector and the business executives whom they serve have a working knowledge of the regulations and policies that govern drugs, biologics and medical devices. It is equally important to keep up to date with developments in the regulatory systems, which govern access to the market, pricing and reimbursement, advertising and promotion, and numerous other matters that are essential to success. It is our hope that this annual publication will be helpful in this respect.

All of the chapters have been written by leading experts within the relevant jurisdiction. They are an impressive group, and it is a pleasure to be associated with them in the preparation of this publication.

**Richard Kingham**  
Covington & Burling LLP  
Washington, DC  
February 2020
I INTRODUCTION

Over the past 25 years, major efforts have been made to harmonise the technical requirements relating to the drug regulatory process and – to a lesser extent – those for medical devices. By far the most successful initiative has been the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH guidelines have now been incorporated into the drug regulatory systems in the European Union, the United States, Japan and many other jurisdictions, and the ICH Common Technical Document (CTD) and its electronic version (eCTD) have become the standard format for the submission of data in support of marketing authorisation applications in most major developed countries. In addition to the ICH, there are a number of other harmonisation initiatives, including the International Medical Device Regulators Forum (IMDRF) and a variety of regional harmonisation programmes.

II ICH

i History

For many years, certain major drug regulatory agencies maintained informal arrangements for cooperation and communication, but there was no formal mechanism for agreeing on the harmonisation of technical requirements for the drug development and approval process. Experience with successful harmonisation initiatives in the European Community during the 1980s led to the establishment of the ICH, following a meeting of regulators and industry representatives in Brussels in 1990 that was hosted by the European Federation of Pharmaceutical Industries and Associations. The original parties to the ICH were the European Community (now the European Union), the US Food and Drug Administration (FDA), the Japanese Ministry of Health, Labour and Welfare, and the national trade associations of the pharmaceutical industry in the European Union, the United States and Japan. The World Health Organization (WHO), the European Free Trade Association and Canada were given observer status.

1 Richard Kingham is a senior counsel at Covington & Burling LLP.
2 These included the European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Research and Manufacturers of America and the Japan Pharmaceutical Manufacturers Association.
3 Detailed information on the ICH and its programmes is contained on the website, www.ich.org.
Initial efforts focused on well-defined technical issues, such as the design of stability studies and standard toxicology studies, about which there was no serious disagreement on general principles and objectives. There was no effort made to establish requirements for the mutual recognition of approval decisions or to address other potentially controversial topics.

Over the years, the ICH has broadened the base of organisations that contribute to its processes. For example, in 1996, generic industry experts and manufacturers of non-prescription medicines were invited to participate in technical discussions of issues of special interest to them. More recently, several regional harmonisation initiatives have participated in meetings of the ICH, as have the drug regulatory agencies and ministries of health of countries outside the European Union, the United States and Japan.

### ii Organisation and procedures

The ICH is governed by a steering committee – composed of members from the regulatory authorities and industry groups from the European Union, the United States and Japan – which determines policies and procedures, selects topics for harmonisation, monitors and facilitates the progress of expert working groups, and signs off ICH documents. There is also a secretariat, based in Switzerland and supported by the International Federation of Pharmaceutical Manufacturers Associations. A separate managing board within the ICH supervises the Medical Dictionary for Regulatory Activities (MeDRA), which establishes standardised terminology for communicating regulatory information concerning pharmaceuticals, including information in drug safety reports.

The main work of the ICH is done by expert working groups, which are organised into four broad categories: safety, efficacy, quality and multidisciplinary topics. These groups, which include experts from regulatory agencies and the pharmaceutical industry, draft guidelines and other documents and propose them for adoption through the ICH process. That process consists of five steps, which involve:

- development of the scientific consensus for a guideline;
- agreeing on the draft text of a guideline;
- consulting with regional regulatory agencies;
- adoption of harmonised guidelines; and
- implementation of guidelines in the ICH regions.

Although participants in the ICH process undertake to adopt harmonised guidelines as part of their national or regional regulatory requirements, full implementation may not be automatic if changes are required in local legislation or regulations. Final guidance may be supplemented by Q&As or other explanatory documents.

---

4 These are the Association of Southeast Asian Nations, the Asia-Pacific Economic Cooperation countries, the Cooperation Council for the Arab States of the Gulf, the Pan-American Network for Drug Regulatory Harmonization, the Southeastern African Development Community and the East African Community.

5 These are Australia, Brazil, China, Chinese Taipei, India, Korea, Russia and Singapore.

6 When the CTD was adopted, the European Union issued secondary legislation to make its use a legally binding requirement for applicants, whereas the FDA chose not to amend its regulations governing the content and format of a new drug application, on the theory that the same information was required to be submitted and only the organisation of the information was changed.
### Principal ICH guidelines

#### Quality

One of the first topics identified for harmonisation by the ICH relates to drug quality – specifically, stability studies of drug products. Since then, the ICH has pursued harmonisation efforts in connection with analytical validation,7 impurities,8 pharmaceutical development,9 pharmaceutical quality systems10 and development and manufacture of drug substances,11 inter alia. Of particular significance are workstreams relating to pharmacopoeias, which support efforts to harmonise compendial requirements in the European Union, the United States and Japan;12 quality of biotechnology products,13 including important issues such as viral safety and comparability of biological products following manufacturing changes; good manufacturing practice (GMP);14 and quality risk management.15

#### Safety

Harmonisation of the major categories of non-clinical safety studies has been a major accomplishment of the ICH. Until the ICH process began, the FDA actually maintained few formal guidelines for non-clinical safety studies of drug products, and requirements were based largely on custom and informal compilations of documents written by agency staff. Today, there are agreed standards for studies of carcinogenicity,16 genotoxicity,17 toxicokinetics and pharmacokinetics,18 toxicity generally,19 reproductive toxicity20 and immunotoxicity,21 as well as procedures for studies of biotechnology products,22 pharmacology,23 non-clinical evaluation of anti-cancer pharmaceuticals24 and photosafety.25

#### Efficacy

The ‘efficacy’ category includes topics relating to human safety studies and pharmacovigilance as well as studies to determine the effectiveness of drug products. One of the most significant guidelines, relating to good clinical practice and originally adopted in 1996,26 has become the internationally recognised standard for conducting clinical trials. It deals with the full

---

7 ICH Q1A-Q1F.  
8 ICH Q3A-Q3D.  
9 ICH Q8.  
10 ICH Q10.  
11 ICH Q11.  
12 ICH Q4-Q4B.  
13 ICH Q5A-Q5E.  
14 ICH Q7.  
15 ICH Q9.  
16 ICH S1A-S1C.  
17 ICH S2.  
18 ICH S3A-S3B.  
19 ICH S4.  
20 ICH S5.  
21 ICH S8.  
22 ICH S6.  
23 ICH S7A-S7B.  
24 ICH S9.  
25 ICH S10.  
26 ICH E6.
range of topics, including study design, protection of human subjects, assurance of quality and reliability of data in clinical trials, the roles of sponsors, investigators and institutions, and many other issues. Of similar importance is the guideline on the format and content of clinical study reports,\(^{27}\) which also serves as the model for all major developed jurisdictions. Other topics are clinical safety (including pharmacovigilance),\(^ {28}\) dose-response studies,\(^ {29}\) ethnic factors,\(^ {30}\) clinical trials generally (including statistical principles),\(^ {31}\) clinical evaluation,\(^ {32}\) clinical evaluation by therapeutic category\(^ {33}\) and pharmacogenomics.\(^ {34}\)

**The Common Technical Document**

One of the most important accomplishments of the ICH process has been adoption of the CTD, which is now the generally accepted format for submission of data and analyses in support of marketing authorisation applications in major developed countries.\(^ {35}\) Use of the CTD became mandatory in the European Union and Japan in 2003, and its use was strongly recommended – and in practice is required – by the FDA. It has greatly reduced duplication of effort in the preparation of dossiers for submission in major markets around the world.

The CTD comprises five modules:

- **Module 1** consists of regional administrative information, which varies by jurisdiction;
- **Module 2** contains summaries and overview documents;
- **Module 3** contains information on the quality of the drug product, including components, manufacturing procedures, facilities and similar matters (what the FDA calls chemistry, manufacturing and controls);
- **Module 4** contains reports of non-clinical studies (safety); and
- **Module 5** contains reports of clinical studies (efficacy).

**MeDRA**

MeDRA establishes common terminology for use in individual case safety reports, periodic safety update reports and similar documents used for monitoring and evaluating safety signals related to drug products. It is supervised by the MeDRA Oversight Board, which contracts with the Maintenance and Support Services Organisation to ensure that the dictionary is kept up to date. The MeDRA system is coordinated with an earlier international dictionary developed by the WHO (the WHO Adverse Reaction Terminology).

\(^{27}\) ICH E3.

\(^{28}\) ICH E1-E2F.

\(^{29}\) ICH E4.

\(^{30}\) ICH E5.

\(^{31}\) ICH E7-E11.

\(^{32}\) ICH E14.

\(^{33}\) ICH E12A.

\(^{34}\) ICH E15-E16.

\(^{35}\) The CTD was adopted as a multidisciplinary topic (ICH M4), as was the electronic version, or eCTD (ICH M8).
III OTHER HARMONISATION INITIATIVES

i PIC/S

The Pharmaceutical Inspection Convention (PIC), originally agreed among several European nations in 1970, established procedures for common standards for drug manufacturing quality, mutual recognition of inspections and other matters. It was supplemented in 1995 by the Pharmaceutical Inspection Co-operation Scheme, and today the two entities are commonly referred to as PIC/S. Members include 44 regulatory authorities and international organizations. PIC/S seeks to establish common standards for GMP, training of inspectors, conduct of inspections, information sharing (including a rapid alert system) and other multinational initiatives relating to drug quality. Some member state authorities will accept GMP certificates from other PIC/S members, and membership in the PIC/S programme can facilitate bilateral mutual recognition agreements for GMP inspections.36

ii IMDRF and other medical device initiatives

The IMDRF is a voluntary group of medical device regulators that seeks to advance harmonisation of regulatory requirements for medical devices. Established in 2011, it is the successor to the Global Harmonisation Task Force on Medical Devices. Current members are Argentina, Brazil, Canada, the European Union, Japan and the United States, with the WHO as an observer; China and Russia are currently under consideration for membership. Guidelines have been issued concerning requirements and training for auditing organisations and regulatory assessors for medical devices, unique device identification and software medical devices.37

The International Organisation for Standardisation (ISO) and the International Electrotechnical Commission have issued numerous standards that have important practical effects on regulation of medical devices. Perhaps most important has been the ISO 9000 series of standards, relating to quality-management systems, which was adopted as one of the key standards for the implementation of the EU medical device legislation.38 Concepts derived from ISO 9000 have also been incorporated into device quality system regulations in the United States.39

---

36 Further details are set out in the PIC/S website, www.picscheme.org.
37 Details can be found at www.imdrf.org.
39 21 CFR. Part 820.
INTRODUCTION

The pharmaceutical industry continues to be a highly regulated sector that has a very important presence in Argentina. Its financial results are highly affected by the influence of agreements entered into with social security organisations — mainly the social security organisation that covers retired people — and private health insurance companies. These organisations agree on coverage that favours its affiliates with regard to prices from laboratories, wholesalers and pharmacies. Despite the fact that these kinds of agreements continue to be in place, at least until March 2020, there have been changes in the financial politics these organisations have, owing to the fact that they are now calling for bids and joint purchases of certain products — mainly those related to oncologic and special treatment prognosis, which are usually the most expensive products.

An important change in the commercialisation of pharmaceutical products in the social organisation, that covers retired and challenged people (it includes the higher percentage of sales in the market), is the fact that this organisation decided to terminate agreements with the whole industry, switching to agreements company by company, in an additional effort to reduce the impact of the price of products. We cannot assure that this effort has been successful.

With the exception of regulation related to the acquisition of products not registered in the country, not many changes have occurred during 2019 regarding the issuance of regulations. Carlos A Chiale continued as head of the National Administration of Drugs, Food and Medical Devices (ANMAT). However, due to the recent change in the authorities it is impossible for us to know whether he will continue as head of the ANMAT. It is probable he will be replaced.

At the time of writing, a new Minister of Health has recently been appointed – Ginés González García, who previously acted as Minister during the 2002–2007 period.

The patentability of pharmaceuticals continues to be the main issue affecting the industry and is a source of never-ending discussions related to the extension of the novelty requirement that a product or procedure should have to determine its eligibility for a patent. The 2012 joint resolutions of the Ministry of Industry 118/2012, the Ministry of Health 546/2012 and the Patent Office 107/2012 add requirements to obtain the patentability of pharmaceutical products. Said regulation is still being challenged through the lawsuit triggered by several companies, which has been ongoing since August 2013. This major

1 Emilio N Vogelius is a partner at Estudio Beccar Varela.
lawsuit has not even reached the stage in which evidence has been produced, given the fact that it was always a window to carry on negotiations related to patentability being allowed to state that the mentioned joint resolution was never consented to.

The protection of research and consequent patentability of product has, however, created broad divisions between the different types of laboratories that operate in the country. These are:

a laboratories that have products based on previous research, mainly subsidiaries of foreign laboratories;
b local capital laboratories that work through licences negotiated with research laboratories;
c laboratories that sell branded generic products that are not patented in the country; and
d laboratories that sell generic products.

The differences between these laboratories are apparent at an intellectual property level. The primary means of commercialisation of pharmaceutical products is the same in all cases and follows the course of laboratory–wholesaler–pharmacy. Product distribution is carried out through specialised companies that usually act on behalf of the different laboratories that constitute their clientele. Another means of commercialisation is through participation in specific bids issued by the public administration or by different hospitals. In these bids the laboratories participate directly and do not follow the usual commercialisation channel. Social security entities are highly involved in calculating discounts to its affiliates working through the regular commercialisation channel mentioned above. Nevertheless, in some cases, bids are called by either public or private social security entities, but these are specific to certain products, such as orphan drugs or vaccines.

Generic products – excluding branded generic products – have very little market relevance.

As well as providing a broad description of the pharmaceutical market, it should be added that the regulation of the commercialisation of pharmaceutical products, medical devices and dietary supplements is controlled and regulated by the Ministry of Health through ANMAT. ANMAT has published on its website a vade mecum of all products registered with it, indicating not only their active principles, but also commercial names and prices.

II THE REGULATORY REGIME

The principal piece of legislation is Law No. 16,463, the Law of Medicines, issued by Congress, which has been in force since 1964. Law No. 16,463 is further complemented by decrees issued by the Executive Power. These decrees are subject to more specific regulation by means of resolutions issued by ministries, mainly the Ministry of Health. Finally, ANMAT also establishes multiple specific regulations.

ANMAT, consisting of a decentralised controlling entity on matters related to pharmaceutical products, food and medical devices, was created in 1992, through the enactment of Decree No. 1490/92. ANMAT is dependent upon the Ministry of Health, usually through the intervention of the Secretary of Health. There has been a recent change of the administrative authorities in the country but it all indicates that this scenario will be the one in force.
The faculties granted to ANMAT in connection with the pharmaceutical industry not only relate to the approval of laboratories, storehouses and products, but also enable it to act as the controlling public office with respect to the industrialisation and commercialisation of pharmaceutical products.

As a general principle, importers, exporters, manufacturers and distributors of pharmaceutical products must be qualified by ANMAT to develop their activities within the pharmaceutical industry. This authorisation, once granted, is valid throughout the country. Nevertheless, provincial laboratories (authorised to act only at a provincial level) may also be qualified.

ANMAT also plays an important role in the approval and control of clinical trials that take place in the country.

Law No. 16,463 establishes that in order to be authorised, laboratories must manufacture their own products. Considering scientific, economic and political environments, certain laboratories have been authorised to import and commercialise pharmaceutical products without the obligation to manufacture them. There are rules by which ANMAT authorises the referral to third-party laboratories for specific stages of manufacturing. Despite these exceptions and other specific situations that exceed the general scope of this chapter, laboratories are required to have their own quality control laboratory that should be in accordance with the products commercialised by the laboratory, a storehouse and a technical director. Licensing to authorised laboratories is a common way to enter the market when the laboratory is not registered in Argentina. Another way is related to import through exceptional channels as named patients programmes, although this way implies a use of such imports for a different purpose from the one the regulation was issued for.

Owing to the industry's development, ANMAT has issued certain specific regulations that apply to clinical trials, traceability of products and other matters. Additionally, some specific laws that deal with the pharmaceutical industry have been enacted, such as Law No. 26,529, which relates to the patient’s rights, and Law No. 26,689, which relates to orphan diseases.

### Classification

The regulatory regime is broad and covers regulations that apply to the commercialisation of all products of its incumbency.

The principal regulations that deal with pharmaceutical products are Decree No. 150/92 and Resolution No. 233/1996, which establish requirements to register pharmaceutical products and qualify as a laboratory (including manufacturer, importer and distributor laboratories); Decree No. 1299/97, which regulates the commercialisation of products; Disposition 3602/2018, No. 3287/2018 and others, which establish the good manufacturing practice (GMP) to be followed classifying all different product alternatives; and Resolution No. 627/2007, which regulates the promotion of ethical products.

Regulation No. 4890/2005 establishes regulations that deal with free-sale pharmaceutical products (over-the-counter (OTC)), medical devices including those that apply to dentistry, cosmetic products, food, dietary supplements, household cleaning products, and in vitro and self-testing diagnostic products.

As mentioned above, for pharmaceutical products to be authorised, they must be registered with ANMAT. For such registration, the following information must be provided:

a. product information;

b. technical information;
In cases where the product to be registered is imported from the countries listed in a specific annex to Decree No. 150/92 (these are countries that have highly developed methods of health control), the certificate of commercialisation of the health authority of the corresponding country shall also be provided. Marketing authorisations are granted for a five-year term and can be renewed as many times as required by the holder.

**ii Biological products**

Regulations Nos. 3397, 7075 and 7729 have been issued by ANMAT to establish specific requirements for approving biological products.

Biological products listed in Regulation No. 7075 include hemoderivatives, products obtained with recombinant DNA techniques, monoclonal antibodies and biological medicines produced from animal tissues.

To register biological products, strict requirements must be met, including providing detailed information regarding the active principle and the manufacturing process of the active principle. Requirements vary in the case of monoclonal antibodies.

The approval of biological products was, during the past year, a matter subject to claims made by laboratories – mainly those that develop innovative products. The fact that triggered such claims was that the regulations issued to approve biological products included the obligation for the authorities (mainly ANMAT) to issue specific guidelines to be complied with to obtain the approval of such products.

These guidelines were listed during the last quarter of 2018. They appeared on ANMAT’s website on 12 October, but were not published with any detail as to when they would have to come into force. In addition, these guidelines have not been identified with any regulation number.

The guidelines refer to biological products establishing the need to file a guide, the requirements to register biological products related to the plants, a location of the plants, a report of the clinical aspects, etc. They also refer to vaccines, radiopharmaceutical products, medicines for advanced therapies, blood banks and related products.

Unfortunately such guidelines are only listed and not described. It is not clear if the purpose of complying with them is for internal purposes only, if they would contribute to a final report or how the information compiled would be kept.

**iii Non-clinical studies**

No specific legislation refers to the welfare of animals in clinical trials carried out in Argentina. However, there are several references to how these kinds of trials should take place in Regulation No. 6677/2010 issued by ANMAT and related to the performance of
clinical trials. Several articles written on this topic relate to bioethical concerns about clinical trials and, moreover, it has been stated that, if possible, this kind of trial should be replaced according to the circumstances of the matter under investigation.\(^2\)

iv Clinical trials

Requirements to perform clinical trials are regulated by Resolution No. 1480/2011 issued by the Ministry of Health, complemented by Regulation No. 6677/2010 issued by ANMAT – the regulatory authority in charge of authorisation and control of any clinical trials to be performed. Additionally, ANMAT has created the National Registry in Health Investigations. Last year Regulation 4009/17 issued by ANMAT established the requirements needed to perform Phase 1 trials.

A clinical trial is an area that has shown a constant increase in activity in the past few years. Investments in research and development in the private sector and pharmaceutical industry reached 22 per cent of the total investments of this sector, according to the most recent information.

ANMAT must grant prior authorisation for any clinical trial. The sponsor, which must be a locally domiciled company or a foreign company’s representative in Argentina, must request authorisation from ANMAT. Information about the sponsor is required, not only for legal purposes, but also for financial purposes to substantiate that it will be able to afford any eventual damages. In addition, a guarantee may be required.

Information related to the clinical trial is also required, such as:

- the name of the study;
- the phases of the trial;
- the product involved;
- the number of subject participants;
- consent forms that are required from subjects participating in the trial;
- information about the principal investigator; and
- information about the site.

The informed consent of the participating subject is required and the wording of the form should prove that the subject clearly understood the implications of participating in the trial. It is the principal investigator’s duty to obtain and keep the consent forms. Certain requirements apply to subjects who are vulnerable owing to educational disadvantage. The informed consent form must be approved by ANMAT, the ethics committee appointed in connection with the trial and the Data Protection Registry.

v Named-patient and compassionate use procedures

Regarding orphan drugs, closely related to the named-patient situation, ANMAT issued Resolution No. 4616/2019 to rule over compassionate use of drugs. This resolution regulates the mechanism for the import of products that are not commercialised in the country and in the instance that a patient requires a specific treatment duly prescribed by his or her physician. The import of such drugs has to be requested in each case by the patient or its

---

\(^2\) See 'Animal welfare and the use of laboratory animals in scientific research' by Ana M Jar in Argentina Journal of Microbiology, volume 46, No. 2, Buenos Aires, June 2014, also available online at www.scielo.org.ar/pdf/ram/v46n2/v46n2a01.pdf.

© 2020 Law Business Research Ltd
legal representative. Patients must file a declaration by the manufacturer of the drug, the prescription of such drug by the physician and the informed consent of the patient to be treated with such drug. The total amount of drugs to be imported shall be for a treatment that does not exceed 90 days. For long treatments the authorisation is granted for up to 90 days. If the treatment is longer, a new and different request shall be made in each case.

According to Resolutions Nos. 942 and 426 of 2001, the import of these drugs is exempted from the payment of custom taxes and fees.

Resolution No. 4616/2019 establishes that the import of these products is allowed from high standard pharmaceutical developed countries listed in Annex I of Decree 150/1992, when requested by public authorities to attend a sanitary crisis and medicines are not in the country at a certain moment or are not accessible to patients for justified reasons.

Law No. 26,689 could be defined more as a list of intentions and ‘to dos’ rather than a specific regulation on the matter. In practice these cases assume the presence of the patient before ANMAT and compliance with specific steps to obtain the import of the necessary drugs, which is usually granted. Specific organisations, such as associations of patients or foundations, usually help to support the psychological state of the patient and family during the procedure.

**vi Pre-market clearance**

No pharmaceutical product or medical device can be commercialised without having the approval of the Board of Health, with the exception of products included in clinical trials duly authorised.

The approval of pharmaceutical products by ANMAT should be required by a laboratory duly qualified as such before the Argentine authorities. Laboratories that are not qualified are not allowed to register pharmaceutical products. Nevertheless, it is possible for such laboratories to appoint a local laboratory (either a local subsidiary of a foreign laboratory or a national laboratory) as its representative to obtain the marketing authorisation issued by ANMAT in the name of the local laboratory acting on behalf of the foreign laboratory that is not qualified in the country.

General aspects of the procedures have been described in Section II.i.; however, it is important to highlight that products registered in highly sanitary developed countries can be locally registered through a fast-track procedure that implies local recognition of the foreign marketing authorisation. Once a product is registered, similar products may be registered through a fast-track procedure to be carried out before ANMAT.

**vii Regulatory incentives**

There are no regulatory incentives that would grant an extension of the patent term in cases in which a specific product has been subject to a patent application.

Nevertheless, a law that deals with confidentiality issues was enacted on 18 December 1966 (Law No. 24,766). This law establishes that during the process to authorise a new product, the confidentiality of the file related to that process should not be
made public.\textsuperscript{3} Nevertheless, the same law establishes that if a patent has been granted for a product, it is possible to perform trials with it, but commercialisation should be kept on standby until the patent expires.\textsuperscript{4}

In contrast, Law No. 25,649 (enacted on 18 September 2002), favours the use of generic drugs and obliges doctors to prescribe pharmaceutical products using the name of the active principle of products. Law No. 25,649, however, does not prohibit use of the trademark in the packaging of the product, nor does it prohibit prescribing the use of the commercial name. The concrete application of the Law has not been clearly effective to date.

viii Post-approval controls

Post-approval controls are managed by ANMAT, principally by means of reports made by parties on infringements to current regulations. Nevertheless, ANMAT is authorised to carry out inspections and to review products already authorised for commercialisation. Technical directors, being jointly and severally liable with the laboratory for any damage that a product may cause, are also keen to review batches of products during the manufacturing process and once finalised.

Additionally, laboratories usually carry out pharmacovigilance of their products, and agreements specifically related to such issues are commonly executed between laboratories that license their products to third parties.

In connection with this aspect of the business, the Ministry of Health issued Resolution No. 435 in April 2011, concerning traceability of pharmaceutical products that follow a specific product from its manufacture or importing stage, to the time it is exhibited for sale.

In connection with the control of products currently on the market, although not specifically pharmaceutical products, ANMAT prohibited the use of cloflucarban, fluorosalan, hexylresorcinol, triclosan and other antibacterial substances to be used in personal hygiene products.\textsuperscript{5}

ix Manufacturing control

Regulation No. 3602/2018, issued by ANMAT and including GMP, is the main rule that regulates the manufacture of pharmaceutical products. This Regulation was drafted in line with the Recommendations on Good Manufacturing Practices and Control issued in 2003, by the World Health Assembly and reports of the Pharmaceutical Inspection Corporation Scheme (PE 009–1) and International Conference on Harmonisation – Guide of GMP (Q7A).

For the purpose of verifying the compliance of GMP, ANMAT is empowered to supervise the manufacturing laboratory as well as the sites in which commercial companies and importers develop their business. ANMAT may carry out technical inspections that cover the functioning conditions and quality control used in such places. Additionally, the manufacturing sites should also be approved by the municipality in which they are located and specific approvals on certain aspects, such as disposal of residues and other environmental issues, also apply. Some of these approvals are incorporated at a municipal level.

\textsuperscript{3} Article 4, Law No. 24,766.
\textsuperscript{4} Article 8, Law No. 24,766.
\textsuperscript{5} Regulation No. 13832/2016.
Advertising and promotion

Section 19 of Law No. 16,463 prohibits any form of public announcement of products that require an authorised prescribed delivery. The Supreme Court of Justice has supported this rule in several judgments by stating that the mere release of prescription medicines to the public without professional control may endanger public health.

The Ministry of Health Resolution No. 627/2007 regulates permissible practices for the promotion of pharmaceutical products requiring a medical prescription. Importantly, the resolution forbids pharmaceutical companies from, directly or indirectly, granting, offering or promising healthcare professionals (HCPs) any kind of incentive, such as bonuses or financial perks.

The promotion of medicinal products can only be addressed to practitioners authorised to prescribe or deliver medicines. The promotion should provide sufficient information, both technical and scientific, to allow practitioners to learn about therapeutic properties of the product. Promotion should be accompanied by informational material supporting the specification data of the approved product. Information should include the generic name and trade name of the pharmaceutical product and its quantitative and qualitative composition, form, counter-indications, adverse effects, warnings and doses. The only possibility of mentioning non-approved medicinal products is in the frame of specific congresses addressed to medical practitioners, and even in this case products should be identified by their active principle denomination, not being allowed to use the commercial brand.

Only the holder of a marketing authorisation may promote a product. While the holder of a marketing authorisation may entrust promotion to a third party, it maintains responsibility for all promotional communications and materials. The holder of the marketing authorisation must ensure that its agents or visiting practitioners receive the necessary guidance and comply with the requirements of Resolution No. 627/2007.

The aforementioned regime for promotion does not apply to OTC products or medical devices. Subject to control, advertising of OTC products is permitted. The advertising of OTC products should act as an incentive to use the products. The inclusion of a disclaimer recommending a consultation with a physician is mandatory.

Distributors and wholesalers

The work of distributors and wholesalers is also under the supervision of ANMAT. Two clear distinctive functions are differentiated: one is the physical storage and distribution of the products, and the other relates to the collection of purchase orders and invoicing of the products. Storage facilities are subject to the approval and control of ANMAT.

The latter are companies that represent several laboratories and, acting on their behalf, invoice the products to be sold to wholesalers or pharmacies. These companies later render accounts and are compensated through a commission.

Classification of products

The classification of products is outlined in Section II.i. All products (both ethical and OTC) are considered to be pharmaceutical products and should be sold only in pharmacies.

Some years ago, it was possible to find OTC products sold outside pharmacies (e.g., kiosks); however, settled jurisprudence has established that OTC products should only be sold in pharmacies and kept behind the counter.
Products for hospital use are usually sold through bids and can be delivered without following the usual commercialisation chain directly to hospitals, both private and public, and without needing to comply with all packaging and labelling requirements that need to be followed for the sale of these products through pharmacies.

In cases in which products are delivered as free samples, the products must include the generic name and brand name in accordance with Article 6 of Law No. 25.649, which requires both names to be of the same size and be given the same emphasis. Samples should also state: ‘Free sample – sale forbidden’.

**xiii Imports and exports**

Imports of pharmaceutical products are only authorised after following the regular procedures before the customs authorities, and a prior authorisation granted by ANMAT. These procedures usually include a visit and clearance of the plant in which the product to be imported is manufactured. The only entity authorised to import a pharmaceutical product is the laboratory that holds the marketing authority granted by ANMAT. The import is subject to clearance before going to marketing by means of a control held by the technical director of the laboratory intervening in the import of the product. The import of products to be used in clinical trials, which are not authorised for marketing, is subject to prior authorisation by the health authorities.

The export of products is authorised in cases in which the marketing authorisation, or a specific document, states that the product is available to be exported.

The donation of pharmaceutical products and medical devices from abroad is also subject to the control of ANMAT, as well as the customs authorities, and is subject to specific regulations. For example, products to be donated should be individually described and are subject to control; simply providing a general description of the products is not adequate.

**xiv Controlled substances**

Psychotropics are subject to a strict, specific regulation that is continuously updated, with strict control carried out by ANMAT. Manufacture, import and use of psychotropics in products is subject to specific procedures and requirements, such as keeping an inventory, which helps to control which psychotropics and precursor chemicals are used in the manufacture of legitimate products.

In addition to measures strictly related to the pharmaceutical industry, a specific public entity – the Planning Secretariat for the Prevention of Drug Addiction and the Fight against Drug Trafficking – has been created to control and take action against the illegal use of such products. Laboratories are also obliged to register before the entity and to comply with its regulations.

**xv Enforcement**

ANMAT is authorised to carry out inspections on working plants and raise any kind of observations it may deem appropriate. In these cases, ANMAT issues a deed that includes all objections and then serves notice to the company to file its defence. After reviewing any evidence that might have been provided, ANMAT issues a resolution. Eventual penalties are a call for attention, fines, closure of the facility and the suspension or even annulment of the authorisation to function.
Depending on the case, the imposition of penalties can also include a penalty for the technical director of the laboratory.

The decision issued by ANMAT is subject to appeal before the federal courts.

III Pricing and Reimbursement

The general principle is that each laboratory may set the prices for the sale of its products. A new government has recently been put in place. We cannot anticipate what measures it could issue regarding pricing of products, nor what kind of agreements it may require public health insurance companies to enter into regarding the supply of products to its affiliates. Nevertheless, there is a good chance that price vigilance, either direct or indirect through agreements or different measures, could be put in place. Again, at the time of writing the Ministry of Health has requested the reduction of pharmaceutical products prices by approximately 8 per cent, grounding the request in what was called a health emergency.

Since 1997, there has been an agreement in place between all the laboratories that integrate the pharmaceutical industry and social security entities, some public, some controlled by unions and some private (also known as medical insurance companies). This agreement was terminated in 2019. The agreement was executed by the three major industry chambers (the Argentine Chamber of Medical Specialities, the Industrial Chamber of Argentine Pharmaceutical Laboratories and the Business Chamber of Argentine Pharmaceutical Laboratories) acting as representatives of their member laboratories. In late 2019 it was the intention of the major social security organisation to enter into agreements with each laboratory, either through bids or contracts.

In addition to these agreements, the above-mentioned chambers entered into others with wholesalers and pharmacies to ensure the provision of products to affiliates throughout the country at the same price and with the same discounts.

Around the year 2000, the chambers also created a local company in which no chamber has a majority equity control (the auditing company), the purpose of which is to manage and audit the agreements entered. The creation of this company was authorised by the local antitrust agency.

Regarding the agreements, their purpose is not to supply products to social security entities, but rather to benefit the affiliates of the different entities with discounts on products prescribed by their doctors and sold by pharmacies that adhered to the agreement mentioned. Some entities have closed lists of doctors, or products or pharmacies, but in general the lists are very broad. Discounts vary according to the products involved. An important purpose of these agreements is to ensure the provision of products throughout the whole country at the same price, without prejudice to the chain of commercialisation or to the affiliates.

These discounts are made in each pharmacy on products sold from its own stock and, once audited, later compensated by the social security entity. This means that at the time the products are sold by each laboratory through the regular chain of commercialisation, it is impossible for them to know if the final destination of the products will be an affiliate to any social security entity or not.

No industry chamber negotiates prices of products on behalf of any laboratory. Prices are fixed by the laboratory and are published in specialist magazines. Discounts are calculated based on the published price (i.e., the price of the product for any person not belonging to any social security entity).
The real parties to the agreements are each laboratory and the social security entity. The chambers represent the laboratories for practical reasons. Laboratories must each ratify the agreement. If a laboratory does not want to enter into such an agreement, it may refuse to do so.

The following example illustrates how the system works. A product is prescribed by a qualified doctor to an affiliate. The affiliate goes to his or her usual pharmacy and acquires the product. The pharmacist will sell the product to the affiliate with discounts and inform the social security entity of the sale to obtain its approval. Assuming the prescription is approved, the entity will reimburse the pharmacy through the auditing company, which will check the amount received and pay the amount of the discount afforded by the social security entity to the laboratories, which will then issue credit notes in favour of the wholesaler and, further, from the wholesaler to the pharmacy to compensate the full amount invoiced and paid by the pharmacy and the wholesaler at the time the product was sold by the laboratory. This is a summarised explanation. Much of the system is currently managed technologically (e.g., affiliates have carnets, pharmacies use online systems) and, usually, reimbursements by social security entities are made every two weeks covering various sales, so in practice the system is a bit more complicated; however, the general principles work as explained.

Some products are not subject to discounts.

Wholesalers and pharmacies are also joined in chambers that are very active in the protection of their associates (the Argentine Pharmaceutical Confederation, the Argentine Federation of Pharmacy Chambers, the Association of Mutual and Union Pharmacies of the Republic of Argentina, the Association of Distributors of Medical Specialities, and others).

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The administrative remedies are the responsibility of ANMAT and are described in Section II.xiv. Similar procedures apply in the case of faulty products and infringements of the commercialisation regulations.

Additionally, Sections 200 and onwards of the Criminal Code penalise with imprisonment and fines any person who modifies or falsifies medicinal products and compromises public health.

There continues to be a slow increase in judicial summary actions being brought to courts by patients with the aim of getting their social security organisation, their medical insurance company or the state to allow or afford the provision of products. This is mainly related to cases in which expensive pharmaceutical treatments apply, despite whether or not said product can be imported or locally acquired. It should be noted that sometimes it is the conduct of the social security organisation or medical insurance that triggers the response of a claimant through courts, especially in cases in which a change of treatment (usually for a cheaper one) is suggested or tried to be put into force by the financer.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Most of the financial aspects of the pharmaceutical industry and its relations with prescribers and patients, including those affiliated with social security entities and medical insurance companies, are described in Section II, subsections iv, vi and ix, and Section III.
In addition, there are special regimes in which public aid for the acquisition of certain products has been established by law, such as in the case of AIDS patients. Other programmes in place are the Health Programme, the Haemophilia National Programme and the Newborn Programme.

Medical attention is publicly supported through municipal, provincial or national hospitals. Medical assistance in public hospitals is free of charge. Private medical insurance companies have special agreements with private hospitals.

Resolution No. 500/2004 manages specific programmes to help patients afford medical treatments that are very expensive. The programme consists of total or partial subsidies or reimbursement for medical treatments, medical devices and medicinal products. It is not mandatory for the Public Health Administration to grant the aid.

The Ministry of Health Resolution No. 627/2007 regulates permissible practices for the promotion of pharmaceutical products requiring a medical prescription. This resolution forbids pharmaceutical companies from, directly or indirectly, granting, offering or promising HCPs any kind of incentive, such as bonuses or financial perks.

Doctors and other HCPs are also regulated by Law No. 17,132, which prohibits them from obtaining benefits from pharmaceutical companies.

VI SPECIAL LIABILITY AND COMPENSATION ISSUES

Product liability is based on general principles included in the Argentine Civil and Commercial Code and in the Consumer Protection Law No. 24,240 (CDL), as amended by Law No. 26,361. In general, in cases that are related to claims concerning whether certain trials or products should be covered by the social security organisations to which the claimant subscribes, both public and private, the courts tend to favour the consumer (in this case, the patient). To this extent, the patient is considered to be a consumer, which means that the CDL is also applicable. Nevertheless, all cases are different and should be analysed individually.6

The general practice according to the civil law obliges the affected party to prove that the product caused the damage suffered. If the party’s statement is supported with evidence, a specific indemnification is fixed by the courts according to the circumstances of the case (e.g., age, disability, expenses incurred, moral damage).

The CDL incorporates a certain type of class action and allows consumer organisations to initiate actions when collective interests are affected or threatened. Section 52 bis of the CDL allows a request for punitive damages – a clear contrast to the civil law.

The CDL was enacted in September 1993. The first cases have related to newly produced pharmaceutical products and it is not yet possible to define a trend regarding application of the CDL to such products.

There are no special compensation issues in place.

6 Case included in AR/JUR/33790/2016.
VI  VII  TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

The competition regulations in place have been applied by public entities to control prices on pharmaceutical products. Legal actions have been initiated but, to date, no decisions have been issued.

The government has tried to reduce the cost of medical products, principally by enacting Law No. 25,649 on 18 September 2002, which favours the use of generic drugs, obliges doctors to prescribe pharmaceutical products using the generic and non-proprietary name of the product, and requires the inclusion of the generic name in the packaging of the product.

ii  Transactional issues

There are no special transactions (other than those available in all countries) that are worth mentioning in this chapter. The pharmaceutical industry has, in general, adapted the commercialisation of products to the method described in Section III, which maintains a level of commercial competition with similar products.

Commercial discounts are common practice, as well as distribution agreements or co-marketing agreements that allow the promotion of products by laboratory representatives who are not the owners of the product being promoted.

VIII  CURRENT DEVELOPMENTS

We do not know what Argentina’s politics will look like in the future regarding public health. Owing to the new government’s characteristics it appears there will be a higher involvement in the industry. To date, no restrictive rules on commerce in general, other than the one mentioned above consistent with a reduction of the price of products, and to pharmaceutical commerce in particular have been announced.

Regulations enacted by previous administrations that made difficult or impeded the possibility of patenting pharmaceutical products in Argentina are still in place and we expect they will remain in effect. The pharmaceutical research industry reacted by filing an administrative and judicial action that has not been resolved.

Clinical trials have increased and continue to grow in the country.

Discussions on the regulatory area are centred on the regulations needed to qualify biological products in the country.
I INTRODUCTION

The Australian life sciences sector is subject to regulation by both Commonwealth and state or territory legislation.

The manufacture and supply of therapeutic goods is primarily regulated by Commonwealth legislation, in particular the Therapeutic Goods Act 1989 (TG Act) and its accompanying regulations, namely the Therapeutic Goods Regulations 1990 (TG Regulations) and the Therapeutic Goods (Medical Devices) Regulations 2002 (Medical Devices Regulations). Commonwealth legislation also provides a system of pricing and reimbursement of certain pharmaceutical products, known as the Pharmaceutical Benefits Scheme (PBS), through the National Health Act 1953 (NH Act) and its associated regulations.

Also relevant are the consumer protection provisions of the Competition and Consumer Act 2010 (CCA), and the equivalent state and territory legislation, which apply to all consumer transactions. State and territory legislation may impose additional requirements, including in relation to clinical and non-clinical trials, wholesale of medicines, and possession and distribution of controlled substances.

The Therapeutic Goods Administration (TGA) is the national authority responsible for regulating medicines and medical devices. The Australian Competition and Consumer Commission (ACCC) is the national authority that administers the CCA (although the CCA also provides a private right of action for enforcement of certain consumer law provisions). The Commonwealth government’s Department of Health (DOH) manages, and the Department of Human Services administers, the PBS.

II THE REGULATORY REGIME

i Classification

Broadly, there are three categories of therapeutic goods under the TG Act, namely biologicals, non-biologicals and medical devices. Biological and non-biological therapeutic goods are distinguished on the basis that biologicals comprise, contain or are derived from human cells or human tissues, whereas, as the name suggests, non-biologicals do not. Medical devices are products whose principal intended action is not by pharmacological, immunological or

---

1 Anthony Muratore is of counsel and Jenny Wong is an associate at Jones Day. Stephen Rohl was a co-author of this chapter with Anthony Muratore in previous editions, including the seventh edition of The Life Sciences Law Review.
metabolic means. The TGA has the power to specify products that do, or do not, fall into these categories; for example, recombinant products (such as recombinant antibodies) are not biologicals.²

Devices that are used to administer medicines, for example a transdermal patch containing medicine, are regulated as a medicine rather than a medical device. The TGA provides guidance on the appropriate classification of products that are on the device-medicine boundary.³

The TG Act also applies to foods, cosmetics, chemicals and general consumer products in respect of which therapeutic claims are made. For example, a moisturising preparation that contains a sunscreen agent as a secondary component and has a stated therapeutic purpose (e.g., ‘helps protect skin from the damaging effects of UV radiation’) is regulated as a medicine.

ii Non-clinical studies

Although the use of animals in research is separately regulated by each state and territory, all require compliance with the Australian Code for the Care and Use of Animals for Scientific Purposes (Animal Code).⁴ The purpose of the Animal Code is ‘to promote the ethical, humane and responsible care and use of animals for scientific purposes’. In most cases, an institution must be licensed to conduct such research.

The TGA has adopted a number of the European Medicines Agency’s scientific guidelines for non-clinical studies.⁵

iii Clinical trials

Generally, a therapeutic good must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia (see Section II.v). Any product not entered in the ARTG (including any new formulation, strength, dosage form, brand, etc.) is classified as an unapproved therapeutic good (UTG) and can only be supplied in certain circumstances. One such circumstance is a clinical trial.

A clinical trial in Australia must have an Australian sponsor (whether it be an individual (e.g., medical practitioner), an organisation (e.g., hospital) or a company) and must be approved by a human research ethics committee (HREC).

An HREC must have notified its existence to the Australian Health Ethics Committee of the National Health and Medical Research Council (NHMRC) and provided assurances that it is operating within NHMRC guidelines. HRECs in Australia generally provide both an ethical and a scientific review of the proposed trial and ensure compliance with the NHMRC’s National Statement on Ethical Conduct in Human Research.⁶

---

² See, for example, for medical devices: Therapeutic Goods (Articles that are Medical Devices) Specification 2014 and Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2017; and for biologicals: Therapeutic Goods (Things that are Biologicals) Specification 2019, Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011 and Therapeutic Goods (Excluded Goods) Determination 2018.
Sponsors must also ensure compliance with the relevant guidelines as to good clinical practice\(^7\) and safety monitoring and reporting,\(^8\) and ensure that the use of personal information complies with the Privacy Act 1988.

Two of the avenues for supply of UTGs for clinical trials are the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial Notification (CTN) Scheme. The choice of which scheme to follow lies first with the sponsor and then with the HREC.

The CTX Scheme is an approval process. The sponsor submits an application, including proposed guidelines for use, to the TGA. The trial may not commence until written advice is received from the TGA and approval obtained from an HREC and the institution at which the trial will be conducted. Any number of clinical trials can be conducted without further assessment by the TGA, provided that the use of the product falls within the approved guidelines for use and notification is given to the TGA of each trial conducted.

The CTN Scheme is a notification scheme. All material relating to the proposed trial is submitted directly to the HREC, which is responsible for reviewing the scientific validity of the trial design, the balance of risk versus harm of the therapeutic good, and the ethical acceptability of the trial and approval of the trial protocol. The institution at which the trial will be conducted gives the final approval. The TGA does not evaluate any data relating to the trial.

Studies in which products already entered in the ARTG are used within the conditions of their marketing approval are not subject to CTN or CTX requirements but still need to be approved by an HREC.

Commercial sponsors of clinical trials are required to hold insurance of at least A$10 million or A$20 million depending on the state or territory. Additionally, members of Medicines Australia are recommended, and other sponsors encouraged, to comply with the Compensation Guidelines.\(^9\)

iv Named-patient and compassionate use procedures

The TG Act provides mechanisms that allow individuals to gain limited access to UTGs (defined in Section II.iii). Any UTG can potentially be obtained via these mechanisms, with the exception of drugs of abuse where the manufacture, possession, sale or use is prohibited by law or where other customs controls apply. Generally, the Commonwealth government does not subsidise the cost of UTGs.

The Special Access Scheme (SAS) provides three pathways for access to UTGs:

\(\text{a}\) Category A is a notification pathway that can only be accessed by medical practitioners (i.e., doctors) for patients who are ‘seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment’.


b Category B is an application pathway that can be accessed by health practitioners (e.g., doctors, dentists, radiographers, nurses, pharmacists and psychologists) for patients who do not fit the Category A definition and where the UTG is not deemed to have an ‘established history of use’. Approval from the TGA is required before the UTG may be accessed.

c Category C is a notification pathway that allows health practitioners to supply UTGs that are deemed to have an ‘established history of use’ without first seeking prior approval. The TGA has published lists of goods deemed to have an ‘established history of use’ and the types of health practitioners who may supply those goods.¹⁰

There is no obligation to supply a UTG merely because it has been approved under the SAS, but if a supplier chooses to do so it must comply with reporting obligations to the TGA, including six-monthly reports detailing the supply of UTGs under the Scheme and communication of any information that has an important bearing on the benefit-risk assessment of the product.

Access to UTGs is also possible through an authorised prescriber, the personal importation scheme or a clinical trial. An authorised prescriber is a medical practitioner who is allowed to prescribe a specified UTG (or class of UTGs) to specific patients (or classes of recipients) with a particular medical condition. An authorised prescriber does not need to notify the TGA when they are prescribing the UTG but must report to the TGA the number of patients treated on a six-monthly basis. Under the personal importation scheme, an individual can import a UTG to be used by that individual or a member of their immediate family. Quantity restrictions and customs rules apply.

In 2018, an online system was introduced to enable electronic submission of SAS and authorised prescriber applications to the TGA.

v Pre-market clearance

A therapeutic good must be entered in the ARTG before it can be supplied in Australia, subject to certain exceptions (see Sections II.iii and II.iv). The sponsor of the good must be a resident of Australia or be an incorporated body in Australia and conducting business in Australia where the representative of the company is residing in Australia.

The route of evaluation, including time frame and fees, depends on the category of the application. The TGA’s guidelines for the regulation of prescription medicines,¹¹ biologicals¹² and medical devices¹³ provide detailed guidance on the application processes.

Medicines are either ‘registered’ or ‘listed’. Registration involves individual evaluation of the quality, safety and efficacy of the product and is required for higher risk medicines

---


(including all prescription medicines). Listing typically does not require demonstration of efficacy and is reserved for lower risk medicines (including some over-the-counter medicines and most complementary medicines). See also Section IX.i.

The approval process can be expedited where the medicine has been approved by a ‘comparable overseas regulator’ (COR) or through the priority review pathway. To rely on a COR, the medicine must be identical (in terms of dosage form, strength, formulation and manufacture), and the indications must be identical or equivalent (to allow for minor textual differences), to the overseas approval. To be eligible for the priority review pathway, the medicine must satisfy a number of conditions: it must be indicated for the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition; there must be no other goods registered on the ARTG for that condition (or there must be substantial evidence demonstrating a significant improvement in efficacy or safety compared to those goods); and there must be substantial evidence demonstrating that the medicine provides a major therapeutic advance.

The application and evaluation fees for a new chemical entity are A$48,800 and A$195,700, respectively (or A$51,700 and A$207,000, respectively, for the priority pathway) and for a new biological are A$1,110 and A$73,700 to A$239,500, respectively.

In relation to follow-on products, to gain registration a generic medicine must demonstrate bioequivalence to the originator product and a biosimilar must demonstrate comparability (biosimilarity) to the reference biological medicine. Applications to register biosimilars are managed through the prescription medicines process and, as such, guidance is currently set out in the Australian Regulatory Guidelines for Prescription Medicines.14

Medical devices are ‘included’ on the ARTG, which requires compliance with the ‘essential principles’15 as to quality, safety and performance, and the appropriate conformity assessment procedures. There are three slightly different application processes depending on whether the medical device is classified as being Class I (as defined in the Medical Devices Regulations), export-only or other than Class I.

Similarly to medicines, the approval process may be expedited where the medical device has been approved by a COR or through priority review designation. The application fees for new medical devices vary depending on the class of the device and the level of audit and conformity assessment required.

vi Regulatory incentives

Patent term extension

The Patents Act 1990 provides that in situations where the time taken for regulatory approval of a pharmaceutical substance claimed by the patent exceeds five years, the term of the patent may be extended. However, the period of extension cannot exceed five years. Extensions are not available for patents for medical devices.

---

15 There are six general essential principles that apply to all medical devices and a further nine essential principles regarding design and construction that apply to medical devices on a case-by-case basis. These are set out in Parts 1 and 2, respectively, of Schedule 1 of the Medical Devices Regulations.
On 25 August 2018, the Commonwealth government repealed Section 76A of the Patents Act, removing the financial reporting requirements (as to the amount spent in Australia, and Commonwealth funds spent, on research and development of the drug that is the subject of the patent) imposed upon grant of an extension.

**Data exclusivity**

The TG Act provides a data exclusivity period of five years in relation to therapeutic goods containing a new active component (that is, an active substance that has not previously been a component of a product entered in the ARTG). The exclusivity period applies to information provided to the TGA in relation to an application for registration, provided that the information is not available to the public and the TGA has not been given written permission to use it.

**Products for rare diseases**

Orphan drugs are medicines, vaccines or in vivo diagnostic agents that are intended to treat, prevent or diagnose a life-threatening or seriously debilitating condition that is rare or for which supply to do so is not likely to be financially viable. As an incentive to develop products for these small markets, the TGA waives the application and evaluation fees normally required.

**vii Post-approval controls**

Sponsors are typically required to have a nominated contact person responsible for fulfilling the sponsor’s reporting requirements to the TGA. Under the TG Act, a sponsor must provide to the TGA, in writing, information relevant to the benefits and risks of products entered in the ARTG as soon as the sponsor becomes aware of it. This includes information that: indicates that the goods may have an unintended harmful effect or are less efficacious than reported in the original application; is contradictory to that previously provided to the TGA; and indicates that the quality, safety or efficacy of the goods is unacceptable. Failure to notify the TGA can lead to removal of the product from the ARTG as well as civil and criminal penalties. Sponsors are also required to submit regular periodic safety update reports and, from 1 January 2019, report shortages of, or decisions to permanently discontinue, reportable medicines (see Section IX.i).

The TGA also takes an active role in post-market surveillance, including random and targeted laboratory testing of approved products, GMP audits, and inspections of manufacturer’s or sponsor’s records. In addition, there are systems in place by which anyone can report adverse effects involving medicines, vaccines and medical devices. Adverse event reports are published online.

The transfer of product approvals is relatively straightforward but may only take place once all the regulatory issues have been addressed.

**viii Manufacturing controls**

The manufacture of therapeutic goods must meet an acceptable standard of good manufacturing practice (GMP), the nature of which depends on the type of therapeutic good.

---

Medicines, active pharmaceutical ingredients, and biologicals that comprise or contain live animal cells, tissues or organs must meet the Guide to Good Manufacturing Practice for Medicinal Products published under the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S Guide to GMP). The Australian Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products applies to blood, human tissues and human cellular product manufacturers that undertake the collection, processing, testing, storage, release for supply, and quality assurance of such products. Australian manufacturers of medicines and biologicals are required to obtain a licence from the TGA, while overseas manufacturers may either be approved by the TGA itself or the TGA may accept certification by a comparable overseas regulator. The TGA has the right to undertake an audit of an overseas manufacturing site at any time and fees apply.

Manufacturers of medical devices need to comply with the appropriate conformity assessment procedures and may require certification by the TGA.

Transfer of ownership of manufacturing facilities is straightforward but might trigger an audit, particularly if the transferee is not an entity that has previously been audited by the TGA.

ix Advertising and promotion

All advertising of therapeutic goods must comply with the TG legislation.

Advertising to the public of certain therapeutic goods, including biologicals, prescription medicines and controlled substances, is prohibited. For those goods that can be advertised to the public, compliance with the Therapeutic Goods Advertising Code (No. 2) (2018 Code) is required (see also Section IX.i regarding the transition from the 2015 Code). The TGA is responsible for handling complaints about the advertising of therapeutic goods to the public.

All claims must be valid, accurate, and substantiated (i.e., supported by evidence), and consistent with the indications or intended purpose as entered in the ARTG.

Certain advertisements require approval by the TGA before publication. These include advertisements referring to a serious form of a disease, condition, ailment or defect, being a form for which: it is medically accepted that diagnosis, treatment or supervision by a suitable qualified health professional is required; or a diagnostic, preventative, monitoring, susceptibility or pre-disposition test requires medical interpretation or follow-up.

Advertisements must also be in accordance with the CCA, which imposes penalties on persons who engage in conduct that is (or is likely to be) misleading or deceptive, or make false representations (e.g., in relation to the quality, benefits or performance characteristics of goods).

Advertising and promotion of therapeutic goods is also subject to codes of conduct maintained by the relevant industry bodies. The four main codes are: the Medicines Australia

---

Code of Conduct (MA Code), covering the discovery-driven pharmaceutical industry; the Generic and Biosimilar Medicines Association Code of Practice, covering generic and biosimilar suppliers; the Medical Technology Industry Code of Practice, covering the medical devices sector; and the Australian Self Medication Industry Code of Practice, covering the non-prescription consumer healthcare sector.

Membership of each of the sponsoring bodies, and hence applicability of the relevant code, is effectively voluntary but regulatory conditions may mandate code compliance. For example, it is typically a condition of registration of prescription medicines that any promotion complies with the requirements of the MA Code, regardless of whether the sponsor is a member of Medicines Australia.

x  Distributors and wholesalers

Distributors and wholesalers are regulated at a state and territory level. Typically, a licence or permit is required to wholesale medicines and controlled drugs listed in the Poisons Standard (see Section II.xi) and compliance with the PIC/S Guide to GMP and the Australian Code of Good Wholesaling Practice for Medicines in Schedules 2, 3, 4 and 8 is mandated.20

xi  Classification of products

Australia has a national scheduling system for the categorisation of medicines, the Poisons Standard,21 which is adopted by each state and territory as part of its poisons and controlled substances legislation. Products are divided into 10 schedules, the most relevant for human applications being:

a  Schedule 2 – pharmacy medicines;
b  Schedule 3 – pharmacy-only medicines;
c  Schedule 4 – prescription-only medicines;
d  Schedule 8 – controlled drugs; and
e  Schedule 9 – prohibited substances.

The scheduling of a product determines the level of regulatory control, in particular in relation to availability and advertising restrictions. Scheduling decisions are made by the secretary to the DOH or a delegate.

Medical devices are classified in accordance with the Medical Devices Regulations. In vitro diagnostic (IVD) medical devices are classified separately from other medical devices. Criteria for classification include degree of invasiveness, intended length of use, and whether it contains a medicine or matter of animal origin (for non-IVD devices) or the intended purpose of the device in accordance with the degree of personal and public health risk (for IVD devices).

xiıı Imports and exports
Therapeutic goods typically must be entered in the ARTG to be imported into or exported from Australia. The import or export of goods not entered in the ARTG, such as for use in clinical trials, requires approval from the TGA unless an exemption applies (see Section II.iv). See also Section II.xiii.

xiii Controlled substances
Australia is a signatory to the Single Convention on Narcotic Drugs 1961. Commonwealth legislation embodies the obligations of this convention through the Narcotic Drugs Act 1967 (Drugs Act) and requires licences and permits to manufacture, import and export certain narcotic drugs, psychotropic substances, precursor chemicals, antibiotics and androgenic or anabolic substances. The possession, use and sale of controlled substances (and relevant licences) are also regulated at a state and territory level.

The Drugs Act was amended in 2016 to permit the cultivation and supply of cannabis for medicinal and related scientific purposes and again in 2018 to permit export of Australian manufactured medicinal cannabis products. Licences are granted by the Office of Drug Control, which is part of the DOH. The DOH, together with state and territory governments, has developed new clinical guidance documents for prescribers of medicinal cannabis for treating chemotherapy-induced nausea and vomiting, epilepsy, multiple sclerosis, chronic non-cancer pain and palliative care. Access is provided under the SAS or through an authorised prescriber (see Section II.iv).

xiv Enforcement
The TGA is primarily responsible for enforcement actions and has the power to suspend or cancel non-compliant goods from the ARTG, issue infringement notices, accept court-enforceable undertakings, and commence civil and criminal actions. The degree of the TGA’s response is dependent on whether non-compliance is accidental, opportunistic or intentional. The TGA supports voluntary compliance and, in practice, a number of issues are resolved by the relevant industry body and code, such as in relation to the marketing and promotion of products.

In addition, the ACCC has powers in relation to misleading and deceptive conduct, product recall obligations, and consumer rights and remedies (see also Sections VII and VIII).

III PRICING AND REIMBURSEMENT
Under the PBS, the Commonwealth government subsidises the cost of certain prescription medicines. While manufacturers have a choice as to whether they supply their products under the PBS, it is generally accepted that PBS listing is a prerequisite to the commercial success of medicines.

Applications for listing of new medicines on the PBS are made to the Pharmaceutical Benefits Advisory Committee (PBAC), which in turn makes a recommendation to the Minister for Health. Under the NH Act, the PBAC must consider the effectiveness and cost of the proposed medicine compared with alternative therapies (comparators). The PBAC cannot make a positive recommendation for a medicine that is substantially more costly

---

than a comparator unless it is satisfied that the proposed medicine also provides a significant improvement in health. Claims of cost-effectiveness must be supported by appropriate economic models.

In recent years, there has been a significant policy emphasis on managing and minimising the cost to government of the PBS. To manage the overall cost of a new medicine, the government may require a sponsor to enter into a cost-sharing agreement. This arrangement may take the form of a rebate, for example, whereby the sponsor rebates a percentage of government expenditure for sales in excess of a set dollar value.23

Products listed on the F1 formulary (which contains single-branded medicines that are deemed not interchangeable at the patient level with another medicine that has multiple PBS-listed brands) are subject to automatic one-off price reductions on the fifth, 10th and 15th anniversaries of the PBS listing date of 5, 10 and 5 per cent, respectively. These reductions take effect on 1 April each year (up to 2022 for the fifth anniversary reduction and 2021 for the 10th and 15th anniversary reductions).

In relation to follow-on products, applications for the listing of biosimilars will be considered by the PBAC whereas applications for the listing of generic medicines will usually be considered by a delegate of the DOH.

Applications for the listing of biosimilars must be supported by a clinical evaluation, with an estimate of the expected use of the product and its consequent impact on government expenditure. Applications for the listing of generic medicines must include a statement from the TGA regarding the equivalence of the new brand to currently listed brands. In some instances, the new brand may not have TGA approval for all indications of the currently listed brands and will only be listed for its approved indications.

The listing of the first generic or biosimilar version of a product on the PBS results in a statutory reduction in the price of the listed brand. On 1 October 2018, the minimum reduction was increased from 16 to 25 per cent.24 If, however, the listed brand has experienced price reductions since 1 January 2016 (or, if it was listed on a later date, since that date) of: 40 per cent or more, no statutory reduction will apply; or between 15 and 40 per cent, the new price of the listed brand must not exceed 60 per cent of the price as at 1 January 2016 (or, if it was listed on a later date, as at that date). In addition, the Minister may now exercise his discretion not to apply the statutory price reduction in whole or part.

Following this, the PBS price disclosure regime requires sponsors of all brands of the drug to provide data to the DOH concerning sales revenue, volume of sales, and discounts or other incentives offered by sponsors, such as cash rebates. This information is then used to adjust the subsidy that the government pays to more closely reflect the price at which the medicines are supplied in the market.

There is no formal scheme specifically for reimbursement for medical devices. However, under Medicare, a wide variety of medical procedures are reimbursed by the government, including diagnostic tests, thus providing a de facto reimbursement scheme for the use of those devices.

24 This increase in the statutory price reduction will revert to 16% from 1 July 2022.
IV ADMINISTRATIVE AND JUDICIAL REMEDIES

i Challenging a decision under the Therapeutic Goods Act 1989
A person wishing to challenge a decision made under the TG legislation may: request an internal review by the TGA; apply to the Administrative Appeals Tribunal (AAT) pursuant to the Administrative Appeals Tribunal Act 1975; or apply to the Federal Court of Australia (FCA) pursuant to the Administrative Decisions (Judicial Review) Act 1977.

A request for an internal review will lead to a reconsideration of the merits of the ‘initial decision’ by the Minister of Health. An initial decision includes decisions relating to the registration and listing of therapeutic goods on the ARTG, suspension and cancellation of medical devices from the ARTG, and revocation or suspension of a manufacturing licence. Following such a request, the Minister must reconsider the initial decision and may confirm or revoke the initial decision, or revoke the initial decision and make a decision in substitution.

An application to the AAT can also involve a reconsideration of the merits of the decision (including discretionary matters) and may also, in certain circumstances, take into account new information not available when the initial decision was made.

A review by the FCA will be limited to correcting an error of law, including on the grounds that: the decision was an improper exercise of power or was unreasonable; the decision-maker took into account irrelevant factors or failed to take into account relevant factors; and there was a denial of natural justice.

ii Challenging a decision by the PBAC
An applicant whose submission to the PBAC has not resulted in a recommendation to list, or to extend the listing of, a drug on the PBS is entitled to apply to have the decision reviewed by the FCA. However, in circumstances where new information or evidence is likely to be relevant, the DOH encourages applicants to resubmit the drug for consideration by the PBAC, as such material will not be considered in judicial review.

V ACTIVE INGREDIENT PRESCRIBING
The government announced in its 2018–2019 Budget plans to implement electronic prescribing from late 2019. This included an initiative for active ingredient prescribing (AIP), which was aimed at increasing patient understanding of the active ingredients in their medicines, and at increasing the uptake of generic and biosimilar medicines.

The AIP initiative was implemented in the National Health (Pharmaceutical Benefits) Regulations Amendment (Active Ingredient Prescribing) Regulations 2019 (the Amending Regulations) and came into effect on 31 October 2019. This required all prescribers issuing electronic PBS scripts to identify medicines by the active ingredient rather than by brand name, which had been the preferred practice. Further, the prescribing software must not default to include brand names on prescriptions. The exceptions to this include the following:

a where the prescriber issues handwritten scripts;
b paper-based medication charts in residential aged care facilities;
c medicines that have four or more active ingredients;
d where it is deemed clinically necessary by the prescriber, the brand name can be included on a prescription provided it is included after the active ingredient; and
e other exceptions deemed necessary by the DOH for practicality and safety reasons.
A 12-month transition period has implemented to allow prescribers sufficient time to update prescribing software to meet the new AIP requirements.

VI  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The financial relationships between pharmaceutical or device companies and prescribers are largely regulated by industry codes. The scope and detail of the restrictions imposed differs depending on the relevant membership (see Section II.ix).

The MA Code requires that members report on payments or benefits provided to individual healthcare professionals, including fees paid for:

- speaking at an education meeting or event;
- sponsorship to attend an educational event;
- the purpose of market research where the identity of the healthcare professional is known to the pharmaceutical company that contracted the market research; and
- being an Advisory Board member.

Pharmaceutical companies must not make a transfer of value to a healthcare professional unless they have taken appropriate steps to give notice of this disclosure obligation. However, this does not include payments in relation to research and development work, including clinical trials.

There is no specific legislation dealing with relationships with payers but there are various provisions at both the Commonwealth and state or territory levels relating to bribery and facilitation payments. For example, under Commonwealth legislation, it is an offence to dishonestly provide or offer (directly or indirectly) a benefit with the intention of influencing a Commonwealth public official (such as from the TGA or the PBAC) in the exercise of their duties, or where the receipt of the benefit would tend to influence the exercise of those duties.

VII  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There are no specific liability or compensation systems designed to compensate persons injured by medicines or medical devices in Australia. Instead, product liability claims are made under common law (such as the tort of negligence or breach of contract) or state, territory or Commonwealth legislation (such as the CCA). The CCA provides that manufacturers are liable directly to consumers for goods that: do not correspond with their description; are not of acceptable quality; are unfit for their stated purpose; do not comply with a safety standard; or do not comply with express warranties.

As noted above, commercial sponsors of clinical trials are required to hold insurance of at least A$10 million or A$20 million, depending on the state or territory, and are encouraged to comply with Medicines Australia’s Compensation Guidelines. In relation to public sector clinical trials, an indemnity or insurance cover for the trial site and investigator is provided by the state or territory.
VIII TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law
The ACCC is responsible for enforcing Australia’s competition and restrictive trade practices laws, provided for primarily in the CCA (defined in Section I). Although the ACCC has successfully taken action against pharmaceutical companies for breaches of consumer law (e.g., for misleading and deceptive conduct), it has rarely pursued pharmaceutical companies for restrictive trade practices. In addition to the imposition of fines by the ACCC (which can be in the range of millions of dollars), there is the potential for class actions.

In 2014, the ACCC instituted proceedings for misuse of market power against a pharmaceutical company for the first time. The conduct in question was that company’s supply, directly to community pharmacies, of a generic version of its product shortly before expiry of the relevant patent and a scheme whereby those pharmacies would be paid rebates based on how much product (originator and generic brands) was purchased. In 2018, the Full Court of the FCA found that the company had taken advantage of its substantial market power but did not accept that it had acted for the purpose of substantially lessening, or deterring or preventing, competitive conduct. The ACCC’s application for special leave to appeal to the High Court was dismissed in October 2018, ending the action. Section 46 of CCA has now been amended to encompass conduct that has the effect or likely effect of substantially lessening competition.

ii  Transactional issues
Market authorisations are transferable pursuant to the TG Regulations. The secretary of the DOH must be notified in writing within three months of the transfer and may request further information before amending the ARTG.

If there is to be a change in the manufacturing site, this may take some time to process. This is an important consideration if the medicine is listed on the PBS where a condition of PBS listing is an obligation to ensure continuity of supply.

IX CURRENT DEVELOPMENTS

i  Medicine and medical device regulatory reforms
Australia’s regulatory framework for therapeutic goods is continuing to undergo reform in response to the Review of Medicines and Medical Devices Regulation. A number of key developments that were completed in 2018 are discussed below. Moving forward, the TGA plans to: designate conformity assessment bodies in Australia to undertake medical device conformity assessment certification; remove advertising pre-approvals to transition public advertisements of medicines to a more self-regulated model; enhance post-market monitoring of complementary medicines and medical devices; align the medical device regulations more fully with the European Union framework; and develop new processes for better use of evaluation reports from comparable overseas regulators.
Advertising of therapeutic goods

On 1 January 2019, the 2018 Code replaced the 2015 Code (defined in Section II.ix). The 2018 Code was developed following extensive consultation with stakeholders and is said to provide advertisers with clarity in relation to:

- definitions of terms (including ‘health warning’ and ‘prominently displayed or communicated’);
- the requirements for scientific or clinical claims and consistency with public health campaigns; and
- certain requirements relating to endorsements and testimonials.

The TGA has stated that, as part of the transition to the 2018 Code, it will take a pragmatic approach to its compliance activity during 2019, focusing on the risk posed to public health and safety. Thus, where an advertisement is not compliant with the 2018 Code but would have been compliant with the 2015 Code, in particular in relation to requirements such as mandatory statements, scientific citations and testimonial disclosures, it is unlikely that the TGA will consider such non-compliance to pose a significant risk to public health. Accordingly, complaints of this type received during the first half of the year will unlikely attract more serious action than a reminder of the obligations under the 2018 Code, whereas complaints received during the second half of the year will require information such as the process being applied to correct the advertising along with associated dates before the TGA will determine whether to apply enforcement discretion.

The 2018 Code was amended by the Therapeutic Goods Amendment (Therapeutic Goods Advertising Code) Instrument 2019 on 30 July 2019 in response to feedback from industry and the Therapeutic Goods Advertising Consultative Committee. The amendments to the 2018 Code include:

- correcting a small number of errors;
- clarifying the status of advertising statements for therapeutic goods in relation to pregnancy;
- ensuring that advertisers who are authorised to include information in their promotional materials highlighting that efficacy of their medicine has been assessed by the TGA can do so without breaching the 2018 Code; and
- a number of changes that provide more flexibility to advertisers in how they include mandatory information in their advertisements.

Relatedly, the Therapeutic Goods Amendment (2017 Measures No. 1) Act 2018 introduced new and enhanced penalties for advertising offences, including a three-tiered structure to the general advertising offences under Section 42DL of the TG Act comprising:

- a strict liability offence, which attracts a maximum penalty of A$21,000;
- an ordinary offence, which attracts a maximum penalty of A$210,000 or 12 months’ imprisonment, or both; and

c a high-level offence (whereby use of the goods in reliance on the advertisement (1) has resulted in, will result in, or is likely to result in, harm or injury to any person, or (2) if so used would result in, or would be likely to result in, harm or injury to any person), which attracts a maximum penalty of A$840,000 or five years’ imprisonment, or both.

The amending act also introduced continuing offences, whereby a person commits a separate offence for each day during which the contravention continues, with a maximum daily penalty of 10 per cent of the maximum pecuniary penalty that can be imposed in respect of that offence.

**New approval pathways**

The TGA has implemented a provisional approval pathway for prescription medicines whereby sponsors may apply for time-limited provisional registration on the ARTG (up to a maximum of six years). The eligibility criteria for provisional approval requires the registration to: 27

a be a new prescription medicine or a new indication of an already registered prescription medicine;
b provide a favourable comparison against existing therapeutic goods;
c provide a major therapeutic advance; and
d include evidence of a plan to submit comprehensive clinical data.

The medicine or use must be for the treatment, prevention or diagnosis of a life threatening or seriously debilitating condition and be likely to provide a major therapeutic advance, and there must be evidence of a plan to submit comprehensive clinical data. The pathway is intended to provide access to promising new medicines where the TGA assesses that the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required. On 17 July 2019, Pembrolizumab (KEYTRUDA) became the first medicine to have additional indications approved by the TGA via the provisional approval pathway.

The listed medicines regime has also been reformed with the introduction of ‘permitted indications’ and the ‘assessed listed medicines pathway’.

All medicines listed under Section 26A of the TG Act are now required to contain only indications that the TGA has determined to be ‘permitted indications’. 28 The intention is to provide transparency as to the indications suitable for listed medicines so as to reduce sponsor non-compliance and improve protection for consumers from misleading and inappropriate claims.

Sponsors wishing to list a medicine with an indication other than a permitted indication may either apply for new indications to be added to the list of permitted indications or utilise the assisted listed medicines pathway. The new pathway sits between the current listed (lower risk) and registered (higher risk) pathways and permits access to ‘intermediate indications’, such as references to:

a the prevention, alleviation, or cure of a non-serious disease, ailment, defect or injury (e.g., alleviates mild dermatitis); or

---


b a serious form of disease (e.g., relieves rheumatoid arthritis symptoms, such as inflammation and pain).

Under the assessed listed medicines pathway, the sponsor self-certifies the safety and quality of the product and the TGA conducts pre-market assessment of efficacy evidence supporting the proposed indications.

Sponsors of existing listed medicines must ensure that their products comply with the new regime before 6 March 2021.

**Reporting medicine shortages**

From 1 January 2019, it became mandatory for sponsors to report to the TGA shortages of, and decisions to discontinue, ‘reportable medicines’ (i.e., prescription medicines, controlled drugs and other medicines determined by the Minister).

A medicine is in ‘shortage’ if its supply in Australia will not, or will not likely, meet the demand for it at any time in the next six months for all the patients in Australia who take, or may need to take, the medicine. Shortages will be determined at a national level, with instances of short supply or unavailability at particular locations or from particular suppliers not requiring reporting.

The scheme imposes particular time limits, with sponsors required to report:

- **a** a shortage of ‘critical impact’ as soon as possible (but no later than two working days after the sponsor knows, or ought reasonably to have known, of the shortage) and any other shortage within 10 working days; and
- **b** a decision to discontinue of ‘critical impact’ at least 12 months before the discontinuation is proposed to occur (or, if this is not possible, as soon as practicable after the decision is made) and any other discontinuation at least six months beforehand (or as soon as practicable).

A shortage or discontinuation is deemed to have ‘critical impact’ if:

- **a** there are no registered goods that could reasonably be used as a substitute (or a substitute good exists but is not likely to be available in sufficient quantities to meet demand), and the shortage or discontinuation will have the potential to have a life-threatening impact on, or a serious impact on the physical or mental health or functioning of, patients who take, or may need to take, the medicine; or
- **b** the medicine is on the Medicines Watch List.

Failure to notify the TGA may result in a civil penalty of up to A$21,000 for an individual and A$210,000 for a body corporate.

**ii Competition law**

On 20 September 2018, the Commonwealth government introduced to Parliament the Treasury Laws Amendment (2018 Measures No. 5) Bill 2018. The Bill seeks to repeal Section 51(3) of the CCA, which exempts conditional licensing or assignments involving intellectual property from a number of competition law prohibitions. The proposed amendment is said to bring Australia into alignment with other comparable jurisdictions, including Canada, Europe and the United States.
If passed, any such arrangements, whether existing or new, will need to comply with the restrictive trade practices provisions of the CCA, although intellectual property owners will be afforded six months to review their existing arrangements.

The Bill was passed on 18 February 2019, and on 13 September 2019, the repeal of Section 51(3) of the CCA came into effect. Prior to the repeal, the ACCC had published guidelines to facilitate the transitional process. The guidelines set out the approach the ACCC would take following the repeal, including its understanding and interpretation of the law following the repeal.

Conduct involving intellectual property rights, previously the subject of exemptions, is now subject to the anticompetitive conduct prohibitions of the CCA. The ACCC guidelines summarise the main prohibitions as follows:29

- **a** cartel conduct (Division 1 of Part IV of the CCA);
- **b** making or giving effect to a contract, arrangement or understanding, or engaging in a concerted practice for the purpose, or with the effect or likely effect, of substantially lessening competition (Section 45 will of the CCA); and
- **c** engaging in exclusive dealing with a purpose, the effect or likely effect of substantially lessening competition (Section 47 of the CCA).

From 13 September 2019, conduct occurring before, on or after commencement in respect of granting a licence, making an assignment or entering into a contract, arrangement or understanding became subject to the prohibitions.

Corporations found by a court to have contravened the anticompetitive conduct prohibitions are subject to penalties for each act or omission (Section 76(1A)(b) of the CCA):

- **a** A$10 million;
- **b** if the court can determine that the benefit obtained by the corporation was a direct or indirect result of the contravening conduct – three times the value of the benefit; or
- **c** if the court cannot determine the value of benefit obtained – 10 per cent of the annual turnover of the corporation during the 12-month period following the contravening conduct.

For individuals, a court may impose a maximum pecuniary penalty of A$500,000 for each contravention of an anticompetitive conduct prohibition.

---

Chapter 4

AUSTRIA

Karina Hellbert

I INTRODUCTION

Austria spends approximately 11.2 per cent of its GDP on healthcare, amounting to €39.6 billion, of which 12.8 per cent is spent on medicinal products. In comparison with other European countries, Austria has a low production value per capita for medicinal products because it is mainly generic products that are produced in the country. From a regulatory point of view, at the beginning of 2019, approximately 13,357 medicinal products for human use were either authorised or registered. No concrete figures exist for the medical device sector, but it is assumed that around 13 per cent of healthcare expenditure relates to medical devices.

Medicinal products are regulated by the Medicines Act, providing the framework for the authorisation, manufacture, distribution, distance sale and advertising of medicinal products. The import of medicinal products is regulated separately, namely by the Act Governing the Importation of Medicinal Products. The Importation Act also regulates private importation of medicinal products via the internet. The Medicines Act contains various provisions authorising the Minister for Health to implement regulations governing the conduct of pharmaceutical companies, for instance, the Regulation governing the activities of companies producing, controlling or placing medicinal products on the market, or regulations concerning the labelling of package leaflets as adopted in 2008.

The production and distribution of medical devices is regulated by the Medical Devices Act and by various regulations, such as the Regulation for the Establishment, Manufacturing, Use and Maintaining of Medical Devices in Institutions Active in the Health Field. In addition, the Federal Office for Safety in the Health Field (the Federal Office) issued an ordinance obliging retailers and physicians providing end users with a medical device to pay a certain lump sum to the Federal Office as a contribution towards the vigilance tasks it carries out.

1 Karina Hellbert is a partner at Polak & Partner Rechtsanwälte GmbH. The information in this chapter was accurate as at March 2019.
8 Federal Law Gazette II No. 70/2007, as amended.
For medicinal products, normally the Federal Office is in charge, except for gene therapy products, where the Ministry for Health has competence. The Federal Office is supported by the Austrian Medical Surveillance Agency scientifically, as well as with respect to manpower.

II THE REGULATORY REGIME

i Classification

If a company is not sure whether a product qualifies as a medicinal product, it can ask the Borderline Counsel established at the Ministry for Health to issue an expert opinion on whether such a product would be classified as a medicinal product or not. In practice, these questions are normally clarified via civil proceedings based on the Unfair Trade Practices Act.9 The leading cases relate mostly to food supplement products, and whether such products, because of their presentation, can be considered as medicinal products. The Supreme Court held that the definition of 'presentation medicinal products' has not changed, even if the German wording of Directive 2004/27/EC would indicate that it has. Thus, products having disease-related claims still need a marketing authorisation.10 The Supreme Court classified the following product name and references as disease-related claims triggering the applicability of the Medicines Act (even for products that have been clearly promoted as an additive to animal feed): Zeolith Med Detox-Powder, Zeolith MED Detox-Capsulas, Bentonit MED-Detox Powder and Betonit MED Detox-Capsulas.11 The Supreme Court has dismissed the argument by the defendant that it clearly labelled the product as an additive to animal feed. It is not sufficient that in a print advertisement the product category is mentioned only on the displayed product, if based on the claims an average consumer is under the impression that a medicinal product is being advertised. Claims relating to 'natural detoxification', 'for detoxification in the health area for reducing disease related factors' and 'soft detoxification for travelling' are medical claims, and therefore the product classifies as a presentation medicinal product. The Supreme Court made it clear that a product can never from a legal perspective fall under the definition of a medicinal product as well as under the definition of a medical device.

In another case, the Supreme Court had to decide whether a cigarette dummy for supporting nicotine withdrawal would classify as a medicinal product, a medical device or food. The plaintiff argued that the substances contained in the nicotine dummy – menthol and valerian – must be considered as a food, because they are digested and the dummy is not intended for treatment of nicotine abuse but for modifying smoking habits because the device simply engages the hands and the mouth. The Supreme Court refused the argument by stating that the substances are only inhaled and not digested through the gastrointestinal tract, because the molecules of food products must be digested, and digestion means passing through the gastrointestinal system. The Supreme Court also classified the product as a medicinal product because of its claims, which mentioned that the product was developed by a 'pharmaceutical faculty' and can only be purchased via a pharmacy, and reduces stress and nervousness, which are disease-related side effects in the case of nicotine withdrawal. Therefore, the defendant clearly presented the product as a medicinal product.12

---
10 Supreme Court of 25 October 2016, 4 Ob 117/16h.
11 Supreme Court of 21 December 2017, 4 Ob 117/16h.
12 Supreme Court of 18 April 2008, 4 Ob 27/08m.
ii  Non-clinical studies

In 2006, the Ministry for Health issued an Ordinance with respect to Good Laboratory Practices (GLP). The Ordinance requires that pharmaceutical companies conducting non-clinical studies notify the Federal Office before starting the respective tests, and conformity must be proven in the context of an audit by the Federal Office. When such tasks are outsourced, the pharmaceutical company has to ensure by way of a written contract that the institution conducting the test complies with good clinical practices and was audited by the Federal Office prior to conducting such a study. Of course, inspections can occur without notice. The Federal Office has issued guidance with respect to the conduct of GLP inspections, stating, inter alia, that the OECD principles of GLP and Directive 2004/10/EC are the basis for evaluation of compliance. The audited company has the right to comment and to provide action plans with respect to corrective measures.

The use of animals in the development of a medicinal product is regulated by the Act on the Conduct of Research on Living Animals, which entered into force on 1 January 2013. Article 6 lays down the leading principles for conducting animal experiments:

a  animal experiments must comply with state-of-the-art scientific methods;
b  the assumption to be proven as well as the procedure must be sound and in accordance with state-of-the-art scientific methods;
c  animal experiments are only allowed in the context of projects;
d  experiments are only allowed to be conducted in institutions of registered users, except if there is a scientific reason for deviating, and must be approved by the relevant authority;
e  the animals must be in a suitable condition of health;
f  the experiment must be conducted so as to cause the minimum pain, suffering, distress or lasting harm; and
g  experiments shall only be conducted with animals that have the lowest capacity for suffering harm, distress or pain.

In addition, the law foresees that there should be a commission at a national level supporting the relevant ministry with respect to issues relating to such experiments. A person conducting an animal experiment without having the necessary approval can face an administrative fine of up to €10,000, or up to €20,000 in the event of recidivism. Fines can also be imposed in cases of negligence.

iii  Clinical trials

Neither the Medicines Act nor the Medical Devices Act require the sponsor to be established in Austria, but if the sponsor is established outside the EEA, a legal representative has to be appointed. Whether such a representative must actually be nominated depends on the institution in which the clinical trial is conducted. Ethics committees specifically focus on whether the insurance is indeed sufficient to adequately cover the risks of the trial. The Medicines Act requires that Austrian law must apply to the insurance contract, the subject must be able to file a claim in Austria and the Austrian judgment must be enforceable in the

---

country in which the sponsor is established. In addition, the ethics committees are rather reluctant to accept any compensation of clinical trial subjects going beyond the actual travel cost for participating in the clinical trial.

As required by EU legislation, the clinical trial must be approved by the Federal Office as well as by an ethics committee. In 2017 the Federal Offices received 235 applications for the conduct of clinical trials at the various stages. In the case of a multicentre study, the leading ethics committee must be specifically authorised to handle multicentre clinical trials. Although not specifically imposed by the Medicines Act, the authority normally requires a leading investigator to be appointed.

With respect to consent, the majority of ethics committees have agreed on a common consent form with respect to medical and medical devices trials, and a deviation from such a consent form must be specifically discussed in the application. There is also a specific template when genetic testing is involved. It is generally prohibited to conduct clinical trials on prisoners, conscripts and persons held in a special institution under the Hospitalisation Act.16

Concerning safety reports, the rules as implemented in Austria are in line with EU legislation. The Federal Office has published several forms on its website. The rules discussed above also apply in the case of investigator-initiated studies, which are not treated differently. With respect to clinical trials relating to medicinal products containing genetically modified organisms, the Ministry for Health is in charge.

iv Named-patient and compassionate use procedures

The Federal Office distinguishes between compassionate use, named-patient use and off-label use. According to the understanding of the Federal Office, named-patient use is regulated by Article 5 of Directive 2001/83/EC and is implemented via Article 8(1) No. 2 of the Medicines Act. Article 8(1) No. 2 stipulates that no marketing authorisation is needed if a physician or dentist has confirmed that the medicinal product is used for treating a life-threatening disease or for a disease resulting in severe health damages and, according to the most up-to-date methods, no accurate treatment can be achieved with a product authorised in Austria. Named-patient use always relates to one specific person.

This is also the difference with the compassionate use programme that relates to a group of patients, where the individual names are unknown. In addition, the compassionate use programme can only relate to products covered by Regulation (EC) No. 726/2004. An application can only be filed in conjunction with a protocol discussing the therapeutic treatment, and approval will be granted for one year. The Federal Office has specifically emphasised that it aligned the format and content of applications to those of German applications. The Federal Office will charge a fee of €530 if the report by the Committee for Medicinal Products for Human Use (CHMP) is already enclosed; without the report, the fee increases to €1,590.

Concerning off-label use, the Federal Office states that no definition is contained in the Medicines Act and it should be understood as the use of a medicinal product in the context of a medical treatment outside the approved summary of product characteristics. Off-label use always relates to one specific person.
use is not prohibited per se but the sole responsibility rests with the physician, who has more stringent information obligations as well as an enhanced duty of care. Physicians must also specifically justify via the Federal Office why off-label use should take place.

v Pre-market clearance

A marketing authorisation is issued by the Federal Office but the actual scientific review is carried out by the Medical Surveillance Agency, which is a limited liability company wholly owned by the Austrian state. Austria also handles the granting of marketing authorisations for Liechtenstein. Applicants for marketing authorisations must be established within the EEA, but there is no requirement that an EEA applicant must be specifically located in Austria or that such an applicant should appoint a local agent. All relevant forms for obtaining a marketing authorisation can be downloaded from the Federal Office website. General conditions for obtaining a marketing authorisation are as follows:

a according to the most up-to-date information and practical experience, the medicinal product must not be harmful when used;

b the ingredients (active substances as well as excipients) must be harmless and this must be proven scientifically;

c the product must be state of the art;

d any description of the medicinal product and the product per se must not be misleading; and

e its efficiency must be sufficiently proven and the labelling must comply with the relevant regulations.

The Federal Office must decide within 210 days whether to grant a marketing authorisation; however, the actual handling time for applications is currently not published. If Austria is acting as a reference member state (RMS) in the mutual recognition procedure for new active substances, the Federal Office charges €41,626; when acting as an RMS in the decentralised procedure it charges €52,959. If Austria is acting as a concerned member state (CMS), then in both cases the Federal Office charges €7,202.

With respect to homeopathic products as well as traditional herbal medicinal products, a simplified registration procedure applies if the products are only used orally or externally and comply with all the other obligations imposed by the relevant EU provisions. Pharmacy-own medicinal products are also covered by a simplified registration procedure.

Parallel-imported products are only allowed to be distributed if a parallel import licence has been granted by the Federal Office. The application must include:

a information on the name and marketing authorisation number of the product authorised in Austria;

b the state in which the parallel-imported product is authorised and marketed;

c the name and marketing authorisation number of the product to be parallel-imported;

d the name and address of the marketing authorisation holder established in the exporting country;

e a description of the packaging;

f the name and address of the person responsible for relabelling and repackaging; and

g a declaration that, for instance, the summary of product characteristics, packaging and labelling do not deviate from the product authorised in Austria.

© 2020 Law Business Research Ltd
The Federal Office has to decide within 45 days with respect to a parallel import application. For obtaining a parallel trade licence as well as a registration of a homeopathic product, a fee of €1,059 is charged.

With respect to generic products and biosimilar products, the provisions comply with the respective EU legislation; however, the fees are substantially reduced. For instance, if the Federal Office acts as an RMS in the decentralised procedure, the fees are reduced to €39,189; with respect to biosimilars in a national procedure, they are reduced to €7,414. If Austria acts as a CMS for Liechtenstein, the fees are the same for decentralised procedures and mutual recognition procedures, namely €1,431 (if Austria already acts as a CMS or RMS in this procedure).

Products meeting an unmet need are not regulated differently from ‘ordinary’ medicinal products.

The Medical Devices Act does not require authorisation by an authority, but relevant products must be examined by notified bodies. It is a requirement, however, that certain devices are registered prior to use, for instance, pacemakers, implantable cardiac defibrillators and loop recorders. Because notified bodies are private bodies, the fee depends on the negotiating power of the entity submitting a dossier to a notified body.

vi Regulatory incentives

The Austrian legislation does not provide any other incentives as adopted at EU level.

**Patents and supplementary protection certificates**

With respect to medicinal products, the Medicines Act specifically states that a patent or supplementary protection certificate (SPC) does not hinder the review by a marketing authorisation of a generic product. Also, the non-marketing of a product because of an existing patent or SPC would not automatically result in the withdrawal of the marketing authorisation of the generic product after three years of non-marketing, according to the sunset clause.

**Data protection**

The Highest Administrative Court stated that under the old data protection rules, there would not be a violation of innovator rights if the Federal Office evaluated an application before the data exclusivity expired but granted a marketing authorisation only one day after that period elapsed. Under the new provisions, the Federal Administrative Court ruled for the first time that an innovative company can challenge a Federal Office decision to grant a generic marketing authorisation by directly referring to data protection rights as granted by the Human Use Directive.18

Medical devices companies can only rely on the general instruments such as patent protection, utility model protection or the Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure as implemented in Austria, but not on data protection.

---

18 Federal Administrative Court of 23 December 2014, W187-20145776-1/2E.
vii Post-approval controls
With respect to pharmaceutical companies, the relevant rules, for example, for staffing, risk management and post-approval testing, can be found in the Regulation governing the activities of companies producing, controlling or placing medicinal products on the market, the Pharmacovigilance Ordinance and the Medicines Act, and with respect to medical devices in the Regulation for the establishment, manufacturing, use and maintaining of medical devices as well as the Vigilance Ordinance. In essence, the pieces of legislation concerning the manufacturing and distribution of such products provide only general guidelines except with respect to the qualification of persons being entrusted with certain tasks, for instance, the qualified person. Also, the Federal Office makes it clear that the appropriate measures with respect to risk management, post-approval testing, etc., depend on the harmfulness of the product and must either be dealt with appropriately by the dossier or by the quality assessment of medical devices.

Transfer of ownership must be notified to the Federal Office accompanied by two statements, namely that the original marketing authorisation holder will waive any rights with respect to the marketing authorisation and that the new owner will take over any and all obligations with respect to that marketing authorisation. Of course, the statements must be accompanied by the relevant documents with respect to a variation. Only after receipt of these statements will the company taking over be considered as the marketing authorisation holder. For medical devices, no specific rules apply. The notified body must be informed that the CE marking can be accordingly amended, and if the new owner is situated in Austria, the register of medical device manufacturers must be informed.

In cases of renewal of a marketing authorisation, the Medicines Act foresees a strict deadline by which an application can be filed – at the earliest, four years from the moment the marketing authorisation became legally binding, but at the latest nine months before the five-year term elapses.

viii Manufacturing controls
According to Section 63 of the Medicines Act, the manufacturing, distributing or controlling of medicinal products needs an authorisation from the Federal Office. The following information must be provided with the application:

- the kinds of tasks envisaged, the production volume and the place where such activities will be conducted;
- the building’s condition, size of the facility, zoning classification, equipment and the exact location; and
- a description of the technical equipment and, if needed, the name of the qualified person.

The Federal Office must grant an authorisation if the facility does not endanger human or animal health. However, the Federal Office is entitled to require trial operations to evaluate whether human beings or animals are endangered. The facility is normally inspected before an approval is granted. The Federal Office charges €1,054 per inspection day, if such an inspection occurs in Austria. For the approval itself, a fee of €3,177 is charged. A further prerequisite for obtaining a licence in accordance with Section 63 is that the company must engage a person that has passed the exam for the manufacturing of medicinal products, according to the Trade Act.

After having obtained a Section 63 licence, the facility is normally inspected at least every three years. The Federal Office has published guidance with respect to the conduct of
an inspection and what is expected from the facility. In addition, the Federal Office publishes a list of companies to be inspected and provides the date the inspection occurred, when a clock stop is imposed and when the final report was issued. In 2018, approximately 196 inspections were announced, assigned to an inspector and partially conducted according to the Medicines Act and the Tissue Safety Act. With respect to the transfer of a manufacturing licence, there are no specific rules contained in the Medicines Act; however, this must be notified to the Federal Office. It would also be required that the trade licence be adapted accordingly.

With respect to medical devices, there is no specific authorisation needed under the Medical Devices Act for operating such a facility; however, a licence is needed under the Trade Act.

ix  Advertising and promotion

The relevant rules can be found in the Medicines Act; Pharmig (the industry association) has also issued a code of conduct for compliance with advertisement rules. In general, any and all advertising must comply with certain core principles, namely that the properties of a medicinal product are not exaggerated, the information or pictorial presentations do not indicate that the product has an effect exceeding its actual effect and that a success can be expected in any event. No advertising should be misleading, either for consumers or for healthcare professionals.

Violations of advertising rules can be enforced by the public authorities or by competitors via the Unfair Trade Practices Act or arbitrated under the Pharmig Code of Conduct. Advertising of prescription-only products aimed at laypersons is prohibited, but advertising of over-the-counter products is generally permissible, except if the product is reimbursed by the social security fund. This prohibition does not apply if the product was included against the will of the marketing authorisation holder. Advertisements for non-approved medicinal products or non-approved indications are permissible at scientific events mainly targeting non-Austrian professionals.

The Pharmig Code of Conduct has specific rules for advertising via the internet, for instance, requiring them to reveal even the indirect support of a website by a pharmaceutical company. Websites may generally contain non-promotional information on medicinal products, for instance, with respect to side effects or interaction with other substances, but must state that a physician or a pharmacist must be consulted. Links to a complete evaluation report published by the CHMP or to websites of national authorities, medical research institutions, etc., are also acceptable. With respect to advertisements aimed at healthcare professionals, the Code requires that an access system be implemented to ensure that only healthcare professionals have access to the information.

The industry association for medical devices (Austromed) has also published a code of conduct, which provides further guidance concerning the restrictions imposed by the Medical Devices Act. The Austromed Code of Conduct specifically stipulates that financial means designated for research purposes must be transferred to accounts supervised by independent bodies. The costs for accommodation and participation in a congress not organised by the medical device company can be taken over if the congress aims to provide scientific knowledge with respect to the product of the supporting company. The participating physician must provide a report about the knowledge gained, and this is considered as a possible reason for taking over the accommodation and participation costs. If the medical device company organises the congress or an educational event, physicians can only be invited if the invitation
is issued to the department and not to the individual physician. It is envisaged that medical device companies shall not any longer directly support physicians, but only provide grants to organisations that arrange scientific events.

x Distributors and wholesalers
Wholesalers and distributors also need a licence, according to Section 63 of the Medicines Act. Furthermore, the wholesale and distribution of medicinal products is a regulated trade, meaning that a company must employ a special managing director in the terms of the trade law, who must have passed an exam, covering, inter alia, legal and scientific aspects of trading with medicinal products. This person must (1) be in charge of compliance with the provisions of the Trade Act; (2) be hired for at least 20 hours per week; (3) be in possession of EEA citizenship or Swiss citizenship; and (4) be replaced within six months of his or her departure, although the period granted by the authorities is normally less than six months. If the trade is conducted without appointing such a person, a company can face a fine of up to €3,600. A fine is also imposed if such a person is appointed, but that person actually works less than 20 hours per week for the company.

xi Classification of products
The Prescription Act provides the rules that apply when a product has to be classified as a prescription-only product or an over-the-counter product. The Act stipulates that the Ministry for Health must adopt a regulation concerning substances that can only be given out on prescription. When classifying such a substance, the Ministry has to take into account whether the labelling, the package leaflet, as well as the information provided by a pharmacist, indicates that the use of the product is associated with a low risk, by taking into account the duration of the intake as well as the affected target group. The Act also states that if a product is switched from being classified as a prescription-only product to an over-the-counter product, the data used for the switch cannot be relied upon for amending the respective regulation for one year. When evaluating such substances, the Ministry for Health is supported by the Prescription-Only Council, consisting of members of the Physicians’ Chamber, the Pharmacy Chamber, social security funds, an expert for producing medicinal products and a pharmacologist employed by an Austrian university.

With respect to the distinction between products intended only for hospitals or for outpatients, no specific provisions apply in Austria. This distinction is only relevant if such products may be reimbursed by the sickness funds, because they only have to pay for products that are prescribed in the outpatient scenario. The costs for hospital-only products are paid by the hospitals themselves.

The Medical Devices Act states that the Ministry for Health can issue a regulation with respect to products that, according to their low endangerment, could be directly distributed to laypersons, but because of the specific circumstances also need a prescription. The Ministry for Health issued one ordinance, namely with respect to magnetic resonance equipment. In addition, the Ministry has issued a regulation specifying which medical devices can be sold
directly by any retailer (e.g., condoms or blood-pressure products), by chemists (e.g., light therapy products), or only in a pharmacy or by specialised retailers with a licence to sell medical devices according to the Trade Act.21

For certain products, a prescription is needed because otherwise the medical device would not be reimbursed by the various sickness funds.

xii Imports and exports

An importation approval is necessary for any medicinal products not covered by an EEC marketing authorisation. Imported products with a marketing authorisation from somewhere in the EEA but without a national marketing authorisation, and which are either re-exported, used for scientific purposes or for medical purposes, must be notified to the Federal Office.22 Products either centrally approved or with an Austrian marketing authorisation, or products being used in clinical trials being manufactured in the EEA or in Switzerland, can be freely imported without any approval by or notification to the Federal Office. The Importation Act also regulates the purchase of non-prescription medicinal products over the internet within the EEA. It is permissible for a private person to purchase non-prescription medicinal products from a pharmacy established within the EEA if this is done for private purposes – this is normally assumed if no more than three packages per medicinal product are purchased. Prescription-only products can only be purchased in a national public pharmacy where the pharmacy has to comply with strict documentation requirements controlled by the Federal Office.

Different rules exist for blood products because the import of such products must always be notified even if the products are approved within the EEA. Products imported in violation of this Act have to be either sent back or destroyed at the purchaser’s expense. In addition, a fine of up to €3,600 can be imposed or, in the event of recidivism, up to €7,260. The Federal Office has far-reaching competence when dealing with imported blood products. Employees at the Office are specifically entitled to enter any premises where the products could be stored, and are also entitled to open any containers for taking samples. The Preparatory Parliamentary Materials to the Importation Act23 specifically stipulates that an inspection could also occur in customs warehouses when there is a risk that blood products could infiltrate the Austrian market.

No specific rules exist regarding medical devices.

xiii Controlled substances

The import, trade and export of substances covered by Schedule I or II of the Single Convention on Narcotic Drugs, respectively Schedules III and IV of the Convention of Psychotropic Substances, is strictly controlled.24 Substances can only be purchased:

a for medical, veterinary or scientific purposes by entities with a trade licence with respect to the manufacturing of medicinal products or for wholesale, as well as a licence issued by the Ministry for Health;

b by a scientific institution after the supervising authority has confirmed that the possession of such substances is needed for scientific purposes;

23 ErläuterR 773 BlgNR XXIV.GP 6.
by the police and customs authority for training purposes; or
by prisons that have facilities for the rehabilitation of prisoners for substance abuse.

Wholesalers have to apply for a licence every year, and it is only granted up to a certain maximum amount. Companies must file a report with the Federal Office by 31 January each year, and must justify when certain amounts are missing from the report.

Pharmacies are only allowed to provide controlled substances to end consumers based on a prescription issued by a trained physician. These products must always be stored separately from normal medicinal products and must be in locked containers. The authorities can also order special security measures for these products. Furthermore, only the Austrian Agency for Health and Food Safety is allowed to grow cannabis for producing medicinal products. This was recently confirmed by the Constitutional Court.25

For the export of products covered by the Addictive Substances Act, specific export documentation must be provided; in particular, there must also be a request from the importing country stating that the products are needed.

xiv Enforcement

Enforcement and the respective penalties are discussed in the various sections.

III PRICING AND REIMBURSEMENT

Currently, 22 social sickness funds exist in Austria, supervised by an umbrella organisation, the Main Social Security Association (the Association). The system is financed by mandatory contributions from employers, employees and self-employed people, with some exemptions; for instance, lawyers have their own healthcare systems. The Austrian system is a benefits-in-kind system, meaning that health services and medicinal products are provided instead of a financial contribution to health expenditure.

The Association decides whether a product will be reimbursed. Reimbursed products are included in a box system that distinguishes between red, dark yellow, light yellow and green boxes, as described below. Products in the red or dark yellow box lists must be approved by a physician employed by the Association; for products in the light yellow box list, a specific documentation system applies, and those in the green box list can be freely prescribed.

a. Green box: the free prescription by a physician must be medically and economically justifiable, meaning that the price must be less than the average EU price, and the volume of potential prescriptions must not be so high that it would trigger closer monitoring. If a comparable therapeutic alternative is already included in the Reimbursement Codex, the new product will only be accepted by the Association if there is a substantial price difference from the included product.

b. Light yellow box: this relates to innovative products, whose financial impact is considered by the Association as not requiring special approval by an Association physician. Producers are regulated via an ordinance of their own.

c. Dark yellow box: products with an additional therapeutic benefit, and are rather expensive, can be approved up to the average EU price. Physicians must justify why they want to prescribe these products.

Red box: products for which an application for being reimbursed is filed with the Association are automatically included in this list.

The Association must decide within 90 days whether the product is per se refundable – thus suitable for an outpatient scenario – and in the next 90 days, whether the product will be listed either in the green or yellow box, and how much it will cost.

A generic product will only be included in the Reimbursement Codex if it is at least 50 per cent cheaper than the original product; the second generic product must, again, be 18 per cent cheaper than the first generic product, and the third generic product 15 per cent cheaper than the second. In addition, if the first generic product is included in the Reimbursement Codex, the originator must lower its price by 30 per cent. For biosimilars the reduction is as follows: (1) for the first: 38 per cent less than the price of the original; (2) for the second: 15 per cent less than the first biosimilar; and (3) for the third: 10 per cent less than the second.

Negative decisions by the Association about whether a product will be included in the Reimbursement Codex can be appealed to the federal administrative court. The senate consists of one presiding judge, two pharmacologists or toxicologists and two economists with expertise in social security matters. An amendment now foresees that products not being included in the Reimbursement Codex, but being prescribed on behalf of the sickness funds exceeding an amount of €750,000, shall not exceed the Average European Price or the difference must be paid back by the distributing company to the sickness funds.

With respect to medical devices, the sickness funds only reimburse certain products. Co-payment of patients is always required; for instance, for glasses, the cost is €34.20 for children under 15 and €102.60 for adults. The various social security funds can also introduce caps, for instance, for prostheses.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

If a marketing authorisation is refused, the decision can now be appealed to the administrative national court. Therefore, the administrative procedure provides, for the first time, for at least three instances of review of such a decision, meaning that after the decision has been appealed to the administrative national court, a further appeal to the highest administrative court is now possible.

Violations of the Medicines Act are investigated by the Federal Office, but depending on the kind of violation the fines are actually imposed by the regional administrative authorities. Fines can be appealed to the newly established regional administrative courts.

The Federal Office can annul a manufacturing licence if the company violates a requirement imposed by the Office three times, or if the company refuses to let the officials of the Office enter the premises for taking samples. Such a decision can now be appealed to the national administrative court.

Fines regulated by the Medical Devices Act are also imposed by the regional authorities and can be appealed to the newly established regional administrative courts.
Austria has recently tightened its anti-bribery provisions. It has extended the applicability of the anti-bribery provisions to persons employed by companies or entities owned by majority by the state, a region or a community, or where the state, community or region has a decisive influence. Thus, university employees, as well as most of the employees of hospitals, are now covered by the relevant anti-bribery provisions. In addition, the Criminal Code now contains new criminal offences, such as trading in influence and a more restrictive sweetening provision.

For the first time, the Criminal Code provides some reliable guidance on what would not be considered undue advantages. This comprises those:

a) whose acceptance is permissible by law, for example, according to the Medicines Act, pharmaceutical companies can take over accommodation costs for physicians;

b) that are given during the course of an event and an official’s participation was justified by reasons of exercising his or her function, for example, a bouquet of flowers for giving a presentation;

c) that are in the form of donations given for charitable purposes where the official receiving the donation is not allowed to have any major impact on choosing who should receive such a donation; and

d) that are in the form of customary tokens and gifts of small value.

During the parliamentary discussion, a fixed limit for gifts of small value of €100 was nullified by arguing that it must be decided case by case whether a gift of €100 would still be considered a token or a gift of small value.

Both industry codes of conduct provide that cooperation with physicians must be based on a written contract, and the remuneration must be according to the arm’s-length principle. The cooperation must not be intended to influence the physician with respect to his or her prescription manner, or with respect to his or her treatment of the patient. Payments for a physician simply attending a congress are not permissible. Rebates in kind are normally permissible under the Medicines Act, except to physicians operating a physician’s pharmacy.

Within the first year in which the product is on the market, physician samples not exceeding an amount of 30 per medicinal product can be provided; in the following year only two per request, but not exceeding five in total per year. Of course, physician samples must be given for free and must be specifically labelled. Certain institutions require that physician samples are not given directly to the physician, but are submitted to the in-house pharmacy for further distribution.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There are two specific provisions with respect to compensation schemes in the case of damages caused by a medicinal product, namely in the case of clinical trials (provided in the Medicines Act) and, in cases of vaccination, for smallpox vaccination, vaccination required by the ‘mother-child pass’ or for any vaccination that was specifically recommended by the Ministry for Health.26

26 Federal Act of 3 July 1973 concerning compensation for vaccine damage, as amended.
Compensation will be paid only to persons aged 15 years and above, and whose ability to work is reduced by 20 per cent for more than three months. If the damage was substantial, a one-time payment as compensation for pain and suffering will be also granted. For children under 15, parents can apply for a special care allowance.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The Competition Authority has not issued any specific guidance concerning what it would consider as problematic with respect to settlement disputes, in particular, patent disputes. There is also no announcement that there will be a specific focus concerning enforcement activities with respect to the life sciences sector. The main focus of the authorities is currently on the food retail market, which is extremely oligopolistic, and the freight sector. There is a tendency for the authorities, when making a dawn raid, to focus more specifically on private homes of leading employees, assuming that business documents are more often stored in private surroundings. The Competition Authority announced that in 2019 it would again focus its activities on the ‘players in the health field’, in particular on the prices charged by the pharmaceutical companies, as well as relating to a fair completion in the pharmacy sector.27

ii Transactional issues

Owing to the fact that around Vienna a biotech cluster has established itself during the past few years, many transactions relate either to cooperation between start-ups and bigger pharmaceutical companies, or mergers between companies both currently in the process of obtaining marketing authorisations. In the case of cooperation between companies, it has to be carefully checked whether the merger will have an impact on the reimbursement status of the product, for instance, in the case of co-marketing agreements.

VIII CURRENT DEVELOPMENTS

The government has announced plans to completely restructure the social security system. The aim is to reduce bureaucracy by cutting down the number of sickness insurance funds and unify those remaining in one general Austrian sickness fund (instead of nine). There are currently strong concerns over whether the planned structure complies with the Austrian Constitution and whether the ambitious aims can be achieved at all. Furthermore, the regions have agreed to have expensive medicinal products used in the hospital assessed by an independent body, considering their benefit for in-house-patients. The company whose product is reviewed has no standing at all in this review process because this is aimed as an unofficial procedure ending in a recommendation by the independent body of whether such product should be used.

Chapter 5

BELGIUM

Bart Van Vooren and Rosa Oyarzabal

I INTRODUCTION

Belgium is an EU Member State and has thus implemented the EU medicines and medical devices regimes. This chapter will not repeat the substantive content of the EU chapter but instead will focus on unique features of the Belgian regime. It should be read in conjunction with the EU chapter. Medicines for human use are regulated primarily by the Medicines Act of 25 March 1964 (the Medicines Act) and the Royal Decree on Medicines for Human and Veterinary Use of 14 December 2006 (the 2006 Decree), but several other legislative documents regulate more specific aspects, such as advertising or clinical trials. Together, these rules implement Directive 2001/83/EC and most other EU medicines laws into Belgian law. They also supplement the EU Regulations, such as Regulation (EC) No. 726/2004 on the centralised procedure and Regulation (EC) No. 141/2000 on orphan medicinal products.

Medical devices are regulated by three Royal Decrees that implement the three EU Medical Devices Directives into Belgian law.

The Federal Agency for Medicines and Health Products (FAMHP), a public institution under the control of the Minister of Social Affairs and Public Health, is the Belgian national competent and control authority for the regulation of medicinal products and medical devices. The Agency supervises the quality, safety and efficacy of medicines for human or animal use and also has responsibilities for medical devices and blood, tissues and cells. It is also responsible for the EU procedures under the decentralised procedure, the mutual recognition procedure and referrals, and for participation in the centralised procedure.

1 Bart Van Vooren is a senior associate and Rosa Oyarzabal is an associate at Covington & Burling LLP.
4 Royal Decree of 18 March 1999 on Medical Devices; Royal Decree of 15 July 1997 on Active Implantable Medical Devices; Royal Decree of 14 November 2001 on Medical Devices for In Vitro Diagnostics; each as amended.
II THE REGULATORY REGIME

i Classification

The FAMHP plays an important role with regard to borderline decisions. It provides advice on product classification and assesses the correct regulatory classification of products when taking regulatory decisions, such as the granting or refusal of a marketing authorisation. In addition, the FAMHP operates a ‘mixed commission’ responsible for borderline reviews. The commission consists of representatives of the Federal Public Service of Public Health, the Federal Public Service for Economic Affairs, the Belgian food agency and the FAMHP itself. The commission reviews specific borderline aspects and provides an opinion to the Minister of Public Health, who takes a formal decision.

The FAMHP has issued a list of claims that are not considered medicinal, which helps in making borderline determinations based on the presentation of products. The claims are mainly relevant for determining the borderline between medicines and foods, and between medicines and cosmetics. Examples of non-medicinal product claims are statements suggesting that the products provide a soothing effect on the airways in the event of a sore throat, that they ensure regular bowel movements or that they prevent caries. Some of these claims are, however, subject to EU approval under the Nutrition and Health Claims Regulation for Foods. The Regulation takes precedence over the list. The mixed commission also issued guidance on the borderline between biocidal products, cosmetics and medicines, and on the classification of products containing Bach flowers.

Borderline determinations can also be made by the courts. This typically happens in criminal courts if the public prosecutor brings a criminal action for unlawful marketing of a product because, for instance, it is positioned as a cosmetic but in reality is an (unapproved) medicine; and by commercial courts in unfair trade practices litigation where, for instance, a competitor seeks an injunction against the marketing of a product as a food while, in reality, it is an (unapproved) medicine. Older case law is summarised in a ministerial circular of 1987.

ii Non-clinical studies

The Act on the Protection of Animal Welfare of 14 August 1986 implements Directive 2010/63/EU into Belgian law from early 2013. The Act, combined with an implementing Royal Decree, permits research involving animals only in premises licensed by the Federal Public Service of Health, by appropriately qualified staff and in accordance with procedures designed to minimise animal pain and suffering. The facilities must also have an ethics committee and there is a federal ethics committee that can provide recommendations to the Federal Public Service.

---

6 Royal Decree of 28 October 2008 Laying Down the Composition and Operation of the Joint Commission and Implementing Article 1, Paragraph 2 of the Medicines Act.
11 Royal Decree of 29 May 2013 on the Protection of Animals used for Experiments.
The Royal Decree on Good Laboratory Practices\(^\text{12}\) (GLP) lays down the main GLP requirements. It applies to non-clinical testing of ingredients used in medicines, cosmetics, pesticides, veterinary medicines, food and feed additives, and industrial chemicals. The Decree requires that all animal studies be conducted in accordance with sound standards of GLP. These standards reflect the Organisation for Economic Co-operation and Development requirements.

### iii Clinical trials

The Act on Experiments on Humans of 2004\(^\text{13}\) has a broad scope of application. It covers clinical trials with medicines and any other experiment that aims at ‘the development of the knowledge that is proper to the exercise of healthcare professions’ such as physicians, dentists, pharmacists, physiotherapists and nurses. It does not apply, however, to purely retrospective observational studies based on existing data. All experiments require scientific justification, a properly substantiated purpose, an acceptable level of risk and detriment for the subjects, an expected benefit that outweighs the possible risks, ethics committee approval and informed consent. Specific rules apply to clinical trials with medicines and, under the medical devices rules, to clinical trials with medical devices.

Sponsors of experiments are liable for damage suffered by subjects as a direct or indirect consequence of the experiment. The liability is not dependent on any fault or negligence and must be covered by an insurance policy. Subjects have a direct action against the insurance company. The liability regime sometimes raises complex questions, such as whether it extends to damage suffered by pregnant partners of trial subjects. A specific act regulates experiments on in vitro embryos.\(^\text{14}\)

### Medicines

The Act on Experiments on Humans of 2004 and the implementing Royal Decree contain specific provisions on clinical trials with medicines, which implement the EU Clinical Trials Directives 2001/20/EC\(^\text{15}\) and 2005/28/EC.\(^\text{16}\) Clinical trials of medicinal products in humans are generally only permitted if the FAMHP has granted a clinical trial authorisation and an ethics committee has issued a favourable opinion. Non-interventional trials, where the

---

\(^{12}\) Royal Decree of 6 March 2002 laying down the Principles of Good Laboratory Practice (GLP) and the Verification of their Application for Trials on Chemical Substances, as amended. There is so far no formal transposition of Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.


\(^{14}\) The Law on Research on Embryos In Vitro of 11 May 2003, as amended.


\(^{16}\) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
Belgium

medicinal product is used within the scope of the marketing authorisation, in line with current medical practice and without additional diagnostic measures or controls, are subject to the general rules on experiments.

The new Law on Clinical Trials with Medicines for Human Use of 7 May 2017 was adopted in response to the adoption of the EU Regulation on clinical trials, which will repeal the current Directive 2001/20/EC once it becomes applicable (the precise date is yet to be determined and depends on the progress with the EU portal, but the current expectation is that the Regulation will apply as of mid-2019. See the European Union chapter of this publication). The scope of the new law is limited to clinical trials that are covered by the EU Regulation, and will therefore exist in parallel with the law of 7 May 2004, which has a broader scope. The law was implemented by the Royal Decree on Clinical Trials with Medicines for Human Use of 9 October 2017. Some aspects of the new law and of the new Royal Decree became applicable in November 2017. These relate, for instance, to the organisation of the competent authorities for ethics committees. Some of these rules have been updated in November 2019. The other provisions will start applying when the Regulation becomes applicable.

Approval process under the current rules: applicants for an approval must first have obtained an EudraCT number and must then submit the relevant application form and investigational medicinal product dossier (IMPD) to the FAMHP. The agency must react within 15 days for single-centre Phase I trials and within 28 days for other trials. In the absence of objections, the trial is deemed approved. For trials with gene or cell therapy medicines and with medicines that contain genetically modified organisms, longer periods apply and an express approval is required.

All investigational medicinal products must have been manufactured or imported by the holder of a manufacturer’s authorisation in the European Economic Area (EEA). The manufacturer or importer must ensure that a qualified person has performed batch release of the products for clinical trial use, which is only possible if the product is in accordance with an appropriate standard of good manufacturing practice (GMP) and if the product conforms to the specifications in the IMPD.

Sponsors have reporting obligations for suspected unexpected serious adverse reactions, where applicable based on reports received regarding adverse events.

Medical devices

Clinical investigations of medical devices are subject to the general rules on experiments and to specific provisions in the medical devices decrees. In addition to obtaining research ethics committee approval, the manufacturer must notify the FAMHP before the conduct of a clinical investigation involving a non-CE-marked medical device or a CE-marked device tested for another indication than covered by the CE-mark. For Class III devices and

18 The amending act is the Royal Decree amending the Royal Decree of 9 October 2017 implementing the Law of 7 May 2017 on Clinical Trials of 3 November 2019. Among others, the Royal Decree of 3 November 2019 delegates to the FAMHP the power to set up appropriate procedures for clinical trial inspections and to establish a surveillance quality system.
implantable or long-term invasive devices of Class IIa and IIb, the notification must be made 60 days before commencement of the trial, and the FAMHP can raise objections during that period. There are also obligations to report adverse events and reactions.

There is a different process for performance evaluation of a non-CE-marked in vitro diagnostic medical device (IVD). Manufacturers must draw up a declaration and follow the procedure set out in Annex VIII of the Royal Decree on IVDs, and must keep the documents available for inspection.

iv  Named-patient and compassionate use procedures for medicines

The Medicines Act and the 2006 Decree allow for different ways to make a medicine available outside the marketing authorisation system.

Magistral preparation: pharmacists can prepare medicines for an individual patient or a group of patients on the basis of a medical prescription. For certain types of products and under specific conditions, the preparation can be subcontracted to a licensed manufacturer. This allows a higher level of quality and GMP compliance.

Compassionate use: a non-approved medicine can be used under the compassionate use provisions laid down in Article 83 of Regulation (EC) No. 726/2004. Compassionate use programmes are defined in the Regulation as:

- making a medicinal product belonging to the categories referred to in Article 3(1) and (2) [i.e., products covered by the centralised EU procedure] available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product.

The product concerned must either be the subject of an application for a centralised marketing authorisation or must be undergoing clinical trials. The specific procedure to be followed in Belgium is set out in Article 106 of the 2006 Decree and was amended in 2014. The applicant must submit an application for a compassionate use programme to the FAMHP, which includes a review by an ethics committee. The Decree sets out what information is required in the application, including a standardised informed-consent form for the patient. The applicant must specify whether it requests the intervention of the compulsory health insurance for reimbursement purposes. The FAMHP forwards the application to the European Medicines Agency (EMA) and may request, in consultation with the EMA and the applicant, an opinion from the Committee for Medicinal Products for Human Use. The Minister of Health must adopt a decision on the compassionate use programme within 55 business days from the decision on the admissibility of the request, failing which, the decision is deemed positive. Decisions are published on the website of the FAMHP and are regularly reassessed. Under certain conditions and for certain diseases, products available under a compassionate use programme may benefit from (limited) reimbursement under the so-called ‘early temporary reimbursement’ regime (see Section III below).

In emergency situations, an unauthorised medicinal product can be used without requesting a compassionate use programme if a number of conditions are met, in particular:

- the urgency is motivated by the fact that a patient is in immediate risk of dying or that the risk from non-treatment is higher than the inherent risks of the treatment;
- informed consent was obtained from the patient;
- the medicinal product is not being used in clinical trials;
it does not concern a medicinal product that does not need a registration or marketing authorisation; 
d there is no other available treatment on the market, under hospital exemption or as a magistral preparation; 
e there are no authorised products in other countries worldwide; and 
f it is impossible to submit a request for a compassionate use programme.

g While it is recommended to notify the FAMHP and the ethics committee of the site concerned, this is not a legal requirement to start the treatment. Treatment is provided under the responsibility of the healthcare professional and the entity arranging the supply.

Medical need: a medical need programme can be put in place by the marketing authorisation holder for an approved medicine but in an indication that is still under clinical development or regulatory review, or that is approved but for which the product is not yet marketed. The specific procedure is set out in Article 108 of the 2006 Decree and was amended in 2014. The procedure is somewhat similar to this for compassionate use programmes. The applicant must submit a request to the FAMHP, including the specified information. An opinion from an ethics committee is also required. The decision on the medical need programme is published on the FAMHP website.\textsuperscript{19} Under certain conditions and for certain diseases, products available under a medical need programme may benefit from (limited) reimbursement under the so-called ‘early temporary reimbursement’ regime (see Section III, below).

Imports: named-patient imports of medicines that have a marketing authorisation in the country of origin are allowed for patients who cannot be adequately treated with authorised and available medicines. This option is available for specific patients and for groups of patients, and the imports are made by a pharmacist.

In addition, the Medicines Act excludes specific products from the marketing authorisation requirement, including certain blood products, certain radiopharmaceuticals, and certain advanced therapies that are prepared in accordance with an individual prescription.

\textbf{v Pre-market clearance for medical devices}

The Belgian rules on marketing authorisations for medicinal products and on CE-marking for medical devices closely follow the EU rules. The procedures are administered by the FAMHP.

\textbf{vi Regulatory incentives}

\textit{Medicines}

The Medicines Act and the 2006 Decree implement periods of eight years of regulatory data exclusivity (during which generic and biosimilar applicants cannot file) followed by two years of market protection (during which regulators may review generic or biosimilar applications, but generic or biosimilar manufacturers cannot launch) under Directive 2001/83/EC for products for which qualifying national applications were submitted after 30 October 2005. For complete free-standing applications submitted on or before that date, holders of Belgian

\footnote{The distinction and relationship between medical need programmes and compassionate use programmes are not always clear, and the FAMHP updated its guidance in May 2017 in an effort to clarify the rules.}
marketing authorisations would benefit from 10 years of data exclusivity protection, during which generic applicants cannot file. These regulatory exclusivity periods begin when the product is first approved anywhere in the EEA, not necessarily in Belgium.

The additional data exclusivity provisions for ‘orphan medicinal products’ and for products with paediatric indications developed in accordance with an approved paediatric investigation plan under Regulation (EC) No. 141/2000\(^20\) and Regulation (EC) No. 1901/2006\(^21\) apply directly.

The Belgian Office for Intellectual Property is responsible for granting supplementary patent certificates for medicinal products that meet the criteria under Regulation (EC) No. 469/2009\(^22\) and for the paediatric extensions. There is no patent linkage under Belgian law (i.e., no linkage between the regulatory approval process and patent expiry). The Medicines Act contains a Bolar provision, making it possible to perform any necessary trials for approval during the patent protection period.

**Medical devices**

Belgian legislation does not provide specific regulatory exclusivity periods for medical devices. A device may be protected by a patent if it satisfies the requirements for patentability under the relevant rules.

- **vii Post-approval controls**

Post-approval controls over marketing authorisation holders for medicines and manufacturers of medical devices in Belgium closely mirror the EU requirements subject to the following of local requirements and procedures.

- **viii Manufacturing controls**

The substantive requirements governing the manufacture of medicinal products, including the need for a manufacturing or import authorisation, a qualified person and compliance with GMP, are discussed in the EU chapter.

The FAMHP regulates pharmaceutical manufacturing operations within Belgium and conducts inspections of manufacturing facilities pre-authorisation and periodically thereafter.

Changes to the manufacturing authorisation require variations to be submitted to the FAMHP.


Advertising and promotion

**Medicines**

Key principles on advertising are set out in the Medicines Act. They are supplemented by the 1995 Royal Decree on Information and Advertising for Medicines for Human Use and a 1993 Royal Decree on samples, which implement the EU advertising rules into Belgian law. These include the general requirements that advertising must not be misleading, and that it must be substantiated and accompanied by appropriate prescribing information. There is also a prohibition on pre-approval or off-label promotion of medicines, advertising of prescription-only medicines to the general public, and illegal inducements to prescribe (for further details on the latter, see Section V below). Some provisions go beyond what is required under EU law. Some forms of advertising media are prohibited (such as billboards or via telephone or SMS). Advertising to the public (of non-prescription drugs; advertising to the public is not allowed for prescription drugs) must be notified in advance to the FAMHP and, for radio and television advertising, prior approval must be obtained. This takes the form of a visa, granted by the Minister of Health, upon advice of the Control Commission of Medical Advertising.

The statutory scheme is supported by a self-regulatory system based on the pharma. be practice code. The code is enforced through an ethics commission within pharma.be. For non-interventional studies, the code also requires prior approval from the Visa Bureau of pharma.be. The visa procedure is intended to check compliance of the study with the legal and ethical requirements.

The rules restricting benefits to healthcare professionals, including a review of scientific meetings and hospitality, are discussed in Section V below.

**Medical devices**

The rules on advertising for medical devices are much less elaborate. The key provision is that non-CE-marked medical devices cannot be promoted (subject to an exception for showing the devices at fairs with an indication that they are not yet in compliance with the rules). Advertising of implantable medical devices to the public is prohibited. Advertising of medical devices is also subject to general advertising rules, requiring that advertisements be substantiated, factual, balanced and not misleading.

The Belgian medical devices industry association beMedTech (formerly known as UNAMEC) operates a code of conduct that is enforced through an ethics commission. The rules restricting benefits to healthcare professionals, including a review of scientific meetings, and hospitality and disclosure requirements (‘sunshine’ rules), are discussed in Section V below.

---

23 Royal Decree of 7 April 1995 on Information and Advertising for Medicines for Human Use, as amended.

24 Royal Decree of 11 January 1993 establishing the Conditions under which the Supply of Medicinal Products for Human Use in the Form of Samples can be Performed, as amended.
Distributors and wholesalers

Medicines
As under EU law, Article 12 ter of the Medicines Act provides that distributors of medicinal products must hold a wholesale distributor’s authorisation and specific obligations are laid down in the 2006 Decree. In particular, wholesale distributors must operate appropriate facilities and staff under the supervision of an appropriately qualified responsible person. They must comply with good distribution practices and maintain appropriate batch records.

Wholesale distributors are also subject to supply obligations that are aimed at ensuring adequate availability of medicines throughout Belgium. While strict, these obligations do not prevent distributors from exporting part of their supplies outside of Belgium. These obligations have also been invoked by parallel exporters.

The FAMHP is responsible for issuing, suspending and revoking wholesale distributors’ licences in Belgium. It conducts inspections before the grant of such a licence and periodically thereafter.

Medical devices
Belgium operates a fairly closed distribution system of medical devices in that certain medical devices may only be sold to final users via public pharmacies, hospital pharmacies or dental clinics (the list is set out in Annex XIII.1 to the Royal Decree on Medical Devices). This may change in the near future (as we explain in Section VIII below).

In addition, distributors (and exporters) of certain medical devices need to notify their activities to the authorities. Some aspects of the notification system were changed recently, in an effort to simplify the procedure. The FAMHP and beMedTech also issued guidance on good distribution practices. Brokers must also register with the FAMHP. Since February 2015, distributors of certain medical devices (and hospitals) must put in place a ‘contact point for materiovigilance’, responsible for reporting incidents to the FAMHP. The requirements were updated in December 2017.

Classification of products

Medicines
The Belgian rules on prescription status for medicines are based on the EU provisions.

Medical devices
Some medical devices are subject to restrictions in the distribution chain (e.g., via pharmacists or dentists).

26 Royal Decree of 18 March 1999, also cited above.
27 Royal Decree of 15 November 2017 on the Notification of a Contact Point for Materiovigilance and the Registration of Distributors and Exporters of Medical Devices.
xii Imports and exports
The Belgian regulations governing the import and export of medicinal products reflect those at the EU level.

xiii Controlled substances
Belgium implemented the UN Single Convention on Narcotic Drugs 1961 and the UN Convention on Psychotropic Substances 1971, and has recently consolidated and updated its legislation.29 The licences for manufacturing, distributing, importing or exporting such substances are issued on a national basis by the FAMHP and are subject to renewal. As a rule, specific authorisations must be obtained for the import or export of narcotic or psychotropic substances. Close collaboration also exists with Luxembourg.

xiv Enforcement
Medicines
Breaches of the medicines rules are often investigated by inspectors of the FAMHP. They can result in administrative fines or a referral to the public prosecutor. The latter can propose a settlement or bring the case before the criminal courts. There are not many criminal court cases for infringement of the medicines rules.

Competitors or non-profit organisations can also bring cases before the commercial courts, typically with a request for an injunction.

Finally, enforcement through the self-regulatory system operated by pharma.be is possible.

Medical devices
The enforcement mechanisms for medical devices are very similar to those for medicines.

III PRICING AND REIMBURSEMENT
Belgium operates strict controls on the prices of certain classes of medicines and medical devices and on their reimbursement status. The controls have a cumulative effect as, for many products, marketing is only viable when they are at least partially reimbursed.

29 See in particular: Royal Decree of 6 September 2017 on Narcotic and Psychotropic Substances, repealing Royal Decree of 31 December 1930 Regulating Soporific and Narcotic Substances, and on Risk Reduction and Therapeutic Advice; and Royal Decree of 22 January 1998 Regulating certain Psychotropic Substances, and on Risk Reduction and Therapeutic Advice.
Belgium

i  **Medicines**

Pricing\(^{30}\) and reimbursement\(^{31}\) rules are very complex in Belgium. The competent authority for price determination is the Federal Public Service for Economic Affairs, encompassing two specialised commissions: the Commission for Price Regulation and the Commission for Pricing of Medicinal Products.

The applicable procedure for price determination depends on the type of medicine\(^{32}\) and whether it is considered new. Price determination will either require notification to the Federal Public Service for Economic Affairs (e.g., for generics) or prior approval from the Minister for Economic Affairs (e.g., for innovative medicines). Price increases are also subject to either authorisation or notification requirements, and price decreases must be communicated. Decisions by the Minister for Economic Affairs can be challenged before the Council of State (see Section IV). The price approval process is based on an application dossier that comprises a justification for the requested price (including production cost, a copy of the company’s annual accounts for the past three years and a description of the market). A simplified pricing procedure applies for medicines approved on the basis of an abridged, bibliographical or hybrid application. In addition, margins applied throughout the distribution chain are subject to control and limitations.

Reimbursement is decided upon by the Minister of Social Affairs, following a recommendation by the Medicines Reimbursement Committee, which forms part of the National Institute for Health and Disability Insurance (NIHDI). The decision process and the dossier to be submitted depend on the category of medicine. There are three main categories, depending on whether the medicine represents added therapeutic value over existing products and whether it is innovative or generic. As a rule, the Medicines Reimbursement Committee adopts a proposal based on the elements submitted by the company and the medical and therapeutic value of the product. The proposal is then presented to the Minister of Social Affairs, who takes the final decision. The reimbursement decision fixes the reimbursement price (which may be lower than the price initially approved by the Minister for Economic Affairs) and the category of reimbursement (which determines the level of co-payment required from the patient). Decisions by the Minister of Health can be challenged before the Council of State (see Section IV below). In addition, specific procedures apply for amending

---

30 Pricing rules are set in a number of instruments, including the Code of Economic Law of 28 February 2013; Royal Decree establishing the Conditions, Time Frames and Practical Modalities regarding Pricing and Price Increases Requests, Pricing Notifications and Communications of the Price of Medicinal Products, Objects, Appliances, Substances assimilated to Medicinal Products and Raw Materials, as referred to under Title V of the Code of Economic Law of 10 April 2014; Ministerial Decree determining the Objects, Appliances, Substances assimilated to Medicinal Products referred to under Title V of the Code of Economic Law, and determining the Maximum Prices and Maximum Margins for Medicines, Objects, Appliances and Substances assimilated to Medicinal Products of 17 June 2014; Ministerial Decree of 20 April 1993 laying down Specific Provisions on Pricing; the Law on Economic Regulation and Pricing of 22 January 1945, each as amended.

31 Reimbursement rules are primarily set out in the Law on the Compulsory Health Insurance of 14 July 1994, as amended; and the Royal Decree establishing the Procedures, Time Frames and Conditions for the Intervention of Mandatory Health Insurance in the Cost of Pharmaceutical Specialties of 1 February 2018, as amended.

32 Namely, whether the product is an innovative medicine (and, within this category, whether the medicine is reimbursable or not) or whether the product is approved on the basis of an abridged, bibliographical or hybrid application.
the reimbursement modalities of a medicine (or group of medicines), which can be initiated by the marketing authorisation holder, the Medicines Reimbursement Committee or the Minister of Social Affairs.

Since 2010, the rules also allow for managed entry agreements to be concluded between the company and the Federal Health Insurance Service. These are commonly known as Article 81 agreements, although that term is no longer accurate in light of a recent overhaul of the Royal Decree on Reimbursement.33 The agreements allow for risk-sharing mechanisms between the company and the government. They are used primarily when there are uncertainties (e.g., as to the budgetary impact, the therapeutic value or administration specifics) and typically contain a financial mechanism to address these uncertainties, such as rebate schemes. An Article 81 agreement leads to a temporary reimbursement for three years, possibly renewable. That period of time is typically used to gather further information on the product. An Article 81 agreement must contain a number of elements, including details on the price and reimbursement basis of the product, tools to control the budgetary risks (for instance, by controlling the volume of products prescribed), follow-up measures and details on the financial risk-sharing mechanism.

In addition, since 2014, a system of early temporary reimbursement is in place for products that have not yet obtained a marketing authorisation but that are made available via an early access programme (namely a compassionate use or a medical need programme; see Section II.iv above). This system only applies for products that are used to treat certain diseases that reflect an unmet medical need. The diseases are identified in a list that is regularly updated and published on the website of the NIHDI. We understand that, in practice, the system has not been widely used so far.

Since July 2019, there is a 'linked' reimbursement procedure in place for personalised medicines and companion diagnostics. Under this system, medicinal products and their biomarkers are evaluated jointly as a package, and the Minister of Social Affairs takes a reimbursement decision on both products. This new procedure aims to prevent delays in the reimbursement of a test in comparison with the reimbursement of the related medicinal product.34

ii Medical devices

The pricing and reimbursement of medical devices in Belgium is quite complex, and the applicable reimbursement level and procedures depend on the type of device. Certain implantable devices and hearing instruments require price approval by the Minister for Economic Affairs, on the basis of an opinion from the Commission for Pricing of Medicinal Products. Maximum margins may also apply. Some devices (such as implants) can be

---

33 The above-cited Royal Decree of 1 February 2018 replaces the former Royal Decree of 21 December 2001. Articles 81 and 81 bis of the Decree of 2001 have now become Articles 111 and 112 of the Decree of 2018. In addition, Article 113 allows the Minister to take the initiative for negotiating a managed entry agreement even if the NIHDI has not proposed the start of such negotiations.

34 For the rules on companion diagnostics, see Article 33 ter of Royal Decree Establishing the Nomenclature of Health Benefits in the field of Compulsory Healthcare and Compensation of 14 September 1984, as amended. For the provisions on personalised medicines, see Chapter VIII of Annex 1 to new Royal Decree establishing the Procedures, Time Frames and Conditions for the Intervention of Mandatory Health Insurance in the Cost of Pharmaceutical Specialties of 1 February 2018.
Belgium

reimbursed as such, while others may be covered by the general expenses of the hospitals where they are used. There are also detailed rules on the levels of payment or co-payment by patients.35

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

In Belgium, the decisions of authorities, including the FAMHP, the Minister of Health and the Minister of Social Affairs, can be challenged before the highest administrative court, the Council of State. The procedure allows for interim relief but the standards are very high.

When the administrative decision also infringes civil rights, an action before the civil courts may be possible.

Each court may refer a question under EU pharmaceutical or medical devices law to the Court of Justice for a preliminary ruling. Such referrals are not infrequent.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Article 10 of the Medicines Act contains a broad prohibition on the provision of benefits to wholesalers; healthcare professionals who can prescribe, dispense or administer medicines; and institutions (such as hospitals) where medicines are prescribed, dispensed or administered. Article 10 contains specific exceptions, including:

a benefits of negligible value and that are relevant for the exercise of a healthcare professional;

b invitation to and hospitality at meetings, if the meeting is purely scientific in nature, hospitality is limited, the timing and location do not trigger doubts as to the scientific nature, and the support is limited to attending healthcare professionals and to the duration of the meeting. If the event takes place on several consecutive calendar days, the programme must be approved by the Minister of Health or an officially recognised body. The non-profit association Mdeon is recognised and operates the review procedure; and

c reasonable compensation for scientific services, in particular for clinical trials.

These rules, including the Mdeon review, also apply to medical devices.

Article 10 of the Medicines Act has been further implemented by the Belgian pharmaceutical industry association, pharma.be, in its code of conduct. The rules are fairly restrictive, more so than the EU-wide European Federation of Pharmaceutical Industries and Associations Code: maximum expenditure limits for meals and drinks offered to healthcare

---

35 See in particular: the Code of Economic Law of 28 February 2013; Royal Decree establishing the Conditions, Time Frames and Practical Modalities regarding Pricing and Price Increases Requests, Pricing Notifications and Communications of the Price of Medicinal Products, Objects, Appliances, Substances assimilated to Medicinal Products and Raw Materials, as referred to under Title V of the Code of Economic Law of 10 April 2014; Ministerial Decree determining the Objects, Appliances, Substances assimilated to Medicinal Products referred to under Title V of the Code of Economic Law, and determining the Maximum Prices and Maximum Margins for Medicines, Objects, Appliances and Substances assimilated to Medicinal Products of 17 June 2014; Law on the Compulsory Health Insurance of 14 July 1994; and the Royal Decree establishing the Procedures, Time Frames and Conditions regarding the Intervention of the Compulsory Health Insurance in the Costs of Implants and Invasive Medical Devices of 25 June 2014, each as amended.
professionals during scientific events apply, and gifts to healthcare professionals in relation to prescription-only medicines are prohibited (even if of negligible value), subject to limited exceptions. The Belgian medical devices association, beMedTech, also further implements the rules on interactions with healthcare professionals and other stakeholders.

Belgian legislation also contains a general prohibition on agreements between healthcare professionals and pharmaceutical or certain medical devices companies when the agreements provide benefits to the healthcare professionals.\(^{36}\) The scope of the prohibition is unclear and, in many instances, is superseded by Article 10 of the Medicines Act.

Healthcare professionals, hospital staff and payer representatives can be officials, in which case, the official bribery rules may apply. In the private sector, more limited private bribery rules can also be relevant.

Belgium recently introduced legal transparency obligations (the Sunshine Act), via the Law of 18 December 2016. The new rules largely repeat the existing voluntary transparency obligations set out in the pharmaceutical and medical device industry codes of conduct published by pharma.be and beMedTech. Pursuant to a Royal Decree of 14 June 2017, the Sunshine Act entered into force on 23 June 2017. The Act obliges pharmaceutical and medical devices companies to disclose details on their financial interactions with various healthcare professionals, healthcare organisations and patient associations. Certain interactions, such as gifts of limited value, are excluded. Companies must submit their information on a yearly basis. The reporting deadline for all transfers done within a given calendar year is 31 May of the following year.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

In addition to the general product liability principles, based on liability for defective products, Belgium has a special regime for compensation for medical damage, outlined in the Act of 31 March 2010.\(^{37}\) The regime covers compensation for damage caused as a result of healthcare treatment (other than non-reimbursable aesthetic treatment and experiments) where there is no liability of the healthcare provider and the damage is not the result of the condition of the patient. The compensation covers damage that is ‘abnormal’ (i.e., goes above what could be expected based on scientific knowledge, the status of the patient and the normal evolution) and that is sufficiently serious (at least 25 per cent permanent incapacity; at least six months’ temporary incapacity; particularly heavy impact on living conditions, including economic conditions; or death). Compensation is paid by a special fund. In addition, the fund can cover certain cases where the healthcare provider may be liable, but his or her liability is not sufficiently covered by insurance or the liability is disputed. In those cases, the fund is subrogated in the rights against the provider and the insurer.

The terms of the Act do not exclude cases where the damage is caused by a defective product, such as a medicine or medical device, but it does not seem to be the legislator’s intention to include these cases within the regime. As explained in Section II.iii above, Belgium has a specific no-fault liability system in relation to experiments on human beings, including clinical trials.

---

37 Under the Act on Compensation for Damage caused by Healthcare of 31 March 2010, as amended.
VII COMPETITION ISSUES

Belgian competition law is heavily based on EU competition law and in particular the principles laid down in Articles 101 (anticompetitive agreements) and 102 (abuse of dominant market position) of the Treaty on the Functioning of the European Union. It is enforced through by the Belgian Competition Authority, an administrative body composed of the Investigation and Prosecution Service and the Competition College. Occasionally there are complaints concerning practices in the pharmaceutical sector and, much more rarely, in the medical devices sector. The complaints cover similar types of problems that are reviewed at EU level, such as restrictions on supplies to competitors, restrictions on supplies to wholesalers who wish to engage in parallel export activities, and alleged abuse of patent or other exclusivity rights.

VIII CURRENT DEVELOPMENTS

As Belgium is an EU Member State, many developments in the Belgian regimes governing medicines and medical devices are driven by developments at EU level. In particular, Belgium will need to further adapt its clinical trials rules and procedures to the new Regulation (EU) No. 536/2014 on clinical trials (it has started doing so, with the law and Royal Decree discussed in Section II.iii above) and also to the new EU Regulations on medical devices.

At the purely national level, several initiatives are ongoing. Some key examples are provided below.

In January 2019, the system of distribution of medical devices was changed. Under the previous ‘closed system’ rules, the distribution and sale of a defined number of medical devices (such as implantable medical devices) was delegated exclusively to healthcare professionals and healthcare organisations. Pursuant to the Royal Decree Liberalising the Distribution Channel of Medical Devices of 19 December 2018, any medical devices company having a distribution activity is able to reach end users through a wider range of intermediaries, provided that these intermediaries comply with the legislation on medical devices distribution (and the upcoming Regulation (EU) 2017/745 on Medical Devices). This ‘liberalisation’ is part of a broader series of measures designed to implement Regulation (EU) 2017/745 on Medical Devices.

Shortage of medicines is also at the forefront of Belgian policy. In April 2019, the Belgian legislature introduced an export prohibition for full-line wholesalers. While the measure was later annulled by the Belgian Constitutional Court, in December 2019 the federal House of Representatives adopted new legislation aimed to prevent medicine shortages. Among other measures, the new legislation empowers pharmacists to dispense an alternative medicinal product where the prescribed one is not available. The legislation is expected to enter into force in January 2020.

As in previous years, there has been a strong emphasis on limiting the expenditure for healthcare coverage. This emphasis is in line with the position set out in the ‘Pact on the Future’, a policy document signed in July 2015 by the Minister of Social Affairs and the national industry associations pharma.be (representing the innovator industry) and Febelgen (representing the generic industry), which still serves as a basis for several policy developments. This document provides a high-level overview of policy priorities in Belgium.

38 These are discussed in the European Union chapter.
The document emphasised, for example, the importance of the continued and improved use of the Article 81 contracts between the industry and the government (see Section III above). The Pact on the Future stated that Article 81 agreements must be used more as ‘pay-for-performance’ tools instead of more traditional rebate mechanisms. This explains the current trend of an increasingly frequent use of Article 81 agreements, which have become a central tool in the reimbursement policies.

In addition, several projects relating to healthcare expenditure are currently ongoing. The Benelux countries, Austria and Ireland continue to jointly negotiate with the pharmaceutical sector on the reimbursement of medicines, with the overall purpose of alleviating the pressure of the most expensive medicines on public healthcare budgets. While the mechanism has only been used for a handful of products, the Belgian government has expressed its commitment to this initiative. The initiative, known as ‘Beneluxa’, has also served as a platform to create a common horizon scanning initiative and to incentivise the use of joint HTA reports.39

Also linked to healthcare expenditure, the Minister for Social Affairs continues to adopt measures to incentivise the uptake of biosimilars in Belgium, which continues to be very low compared to many other EU countries. These measures (including circulars), which provide guidance on the application of the public procurement rules to biosimilars, build on the agreement reached between the Minister and the industry in January 2016, which sets targets for the uptake of some of the biosimilars that are currently available for the hospital sector in Belgium. In April 2018, the ‘biocliff’ entered into force. Building on these initiatives, in 2019 the NIHDI put in place a pilot project to incentivise the prescription of biosimilar anti-TNF medicines.40

We also understand that the NIHDI and other authorities in the Belgium are exploring ways to increase the use of the temporary reimbursement system. As explained above (see Section III), this mechanism allows partial reimbursement of products that are made available before marketing authorisation, but in practice the mechanism is not widely used. The Minister for Social Affairs is working on several initiatives to reform the healthcare landscape in Belgium. For instance, the hospital landscape and the financing of hospitals is under revision in Belgium.

In addition, digital health continues to be a focus area for Belgian policy makers, and various stakeholders are working together to find ways to improve and streamline the use of patient data, including real-world data, in the Belgian healthcare sector. For instance, since January 2020 healthcare professionals must use electronic prescriptions in outpatient treatment, except in limited situations (e.g., the patient is older than 64 years). This change is the first stage of a Belgian strategy for a switch to paperless prescribing.

Moreover, Belgian policymakers continue to incentivise the development of digital health initiatives. In January 2019, the Interministerial Conference on Public Health approved the eHealth Action Plan 2019–2021.41 The plan, which builds on the eHealth Plan 2013–2018, aims to create synergies with international and European eHealth initiatives.

---

39 For complete information on the initiative and its procedures, see www.beneluxa.org.
40 Under the project, accredited physicians were rewarded with a premium for the prescription of a certain amount of anti-TNF medicines.

© 2020 Law Business Research Ltd
Finally, 2019 has seen an uptake in competition-related enforcement activities. Among others, the Belgian Competition Authority focused its efforts on restrictive and exclusionary measures hindering competition between pharmacists with regard to the market of non-pharmaceutical products.
I  INTRODUCTION

Regulation of pharmaceutical products and medical devices started to take form in Brazil during the 1970s: Law 5,991/1973 and Decree 74,170/1974 covered sanitary control of sales of drugs, pharmaceutical inputs and related items; Law 6,360/1976 established rules for production, marketing and sanitary surveillance of products; and Law 6,437/1976 defined sanitary violations and relevant penalties.

Later, as part of an economic and legal modernisation during the 1990s, the National Health Surveillance System and the National Sanitary Surveillance Agency (ANVISA) were created by Law 9,782/1999.

Included in the long list of ANVISA’s duties are:
a  coordinating the National Health Surveillance System;
b  establishing rules;
c  proposing, keeping track of and enforcing policies, guidelines and actions for sanitary surveillance;
d  authorising the activities of companies that manufacture, distribute and/or import products regulated by the law;
e  issuing import and export permits for the same products;
f  granting marketing authorisation to products;
g  issuing infraction notices and enforcing penalties; and
h  establishing, coordinating and monitoring the systems for toxicological and pharmacological surveillance.

State and municipal governments also have sanitary surveillance bodies, whose competence involves inspection and licensing of facilities, as well as local surveillance of health products and compliance with sanitary legislation.

II  THE REGULATORY REGIME

Medicines in Brazil are subject to stricter regulation than medical devices. For example, medicines are subject to price controls, while medical devices are not.

---

1 Alexandre Einsfeld and Joaquim Augusto Melo de Queiroz are partners and Ivan Cunha is a senior associate at Fialdini Einsfeld Advogados.
Medical devices are regulated by ANVISA under Resolution RDC 185/2001, Resolution RDC 36/2015 and Resolution RDC 40/2015. Restrictions on the advertising of medical devices are not as strict as those applicable to medicines (Resolution RDC 96/2008).

Activities related to the manufacture, import, export and distribution of products that are subject to sanitary control (including medicines and medical devices) require authorisation by ANVISA and licensing by local sanitary authorities.

### Classification

According to Law 9,782/1999, the products submitted to the control and surveillance of ANVISA are:

- **a** medicines for human use, their active substances and other inputs, processes and technologies;
- **b** foods and beverages;
- **c** cosmetics, personal care products and fragrances;
- **d** disinfectants meant for cleaning, disinfection or disinfestation of homes, hospitals and public places;
- **e** kits, reagents and inputs used for diagnosis;
- **f** medical and hospital, dental and hemotherapy equipment and materials, as well as equipment and materials for laboratory and image diagnosis;
- **g** immunobiologicals and their active substances;
- **h** blood and blood products;
- **i** human and animal organs and tissues to be used in transplants or reconstructions;
- **j** radioisotopes for use in in vivo diagnosis and radiopharmaceuticals, and radioactive products used in diagnosis and treatment;
- **k** cigarettes, cigarillos, cigars and any other smoking products, whether derived from tobacco or not; and
- **l** any products that may result in the possibility of risk to health, obtained by genetic engineering, or by any other procedures, or submitted to radiation sources that may result in potential risk to health.

There are legal definitions of medicines and medical products. Article 4 of Law 5,991/1973 defines a medicine as a pharmaceutical product, technically obtained or prepared, for prophylactic, curative, palliative or diagnostic purposes. In turn, Article 25 of Law 6,360/1976 defines medical devices as appliances, instruments and accessories used in medicine, dentistry and medical-related activities, as well as in physical education, beautification or aesthetic correction.

Based on these definitions, to correctly classify a product under these categories, it is important to study its characteristics and uses.

### Non-clinical studies

Law 11,794/2008 establishes rules for animal testing in science. It also created the National Council for the Control of Animal Experimentation (CONCEA), a body linked to the Ministry of Science and Technology (currently Ministry of Science, Technology, Innovations and Communications), responsible for coordination of the procedures for animal testing in trials.

Articles 11 to 16 of that law contain specific rules regarding protection of animal welfare: any entity involved in the breeding of animals for educational or scientific purposes
must be licensed by the Ministry of Science and Technology, and for that purpose it must establish an internal ethics committee with the participation of veterinary surgeons, biologists, professors and researchers in the specific area of interest and one representative from an animal protection society legally established in Brazil.

### iii Clinical trials

The rules that govern clinical trials in Brazil are ANVISA’s Resolution RDC 9/2015 and Resolution RDC 10/2015, and the National Health Council (CNS) Resolution CNS 466/2012. No federal law has been enacted regarding this matter yet; however, there is a bill of law pending in the House of Representatives (formerly PLS 200/2015, currently PL 7.082/2017).

The National Research Ethics Committee (CONEP/MS), a body linked to the Ministry of Health, is responsible for deliberation, surveillance, follow-up and monitoring of public policies for health. It evaluates the ethical aspects of the studies; the research protocol is scrutinised to ensure its correctness, clearness and compliance with ethical standards). This is followed by an analysis by ANVISA, focusing on the technical and health aspects.

### iv Named-patient and compassionate use procedures

According to Resolution RDC 81/2008, pharmaceutical products for which marketing authorisations have not been granted can be imported by individuals for personal use only. A request should be presented to ANVISA with documents that allow for an assessment of (1) whether the product has had marketing authorisation issued in its country of origin, and (2) the efficacy and safety of the drug.

Resolution RDC 203/2017 establishes criteria and procedures for the importation, on an exceptional basis, of products subject to sanitary surveillance without registration in Brazil, intended exclusively for use in public health programmes by the Ministry of Health and its related entities.

In addition, Article 24 of Law 6,360/1976 establishes that new medicines, exclusively for experimental use but under medical control, are exempt from registration, and may also be imported with the express authorisation of the Ministry of Health. This exception is valid for up to three years.

Brazilian legislation also allows patients, under compassionate use programmes, to have access to medicines that are still in the clinical development phase. Finally, under the expanded access programmes, patients may have access to medicines during and after Phase III clinical trials.

### v Pre-market clearance

The first step to obtaining marketing authorisation for a pharmaceutical product is to obtain the proper licence from ANVISA. The bureaucratic process and technical requirements for these licences vary depending on the applicant’s activity (i.e., whether manufacturer, distributor, importer or exporter).

The applicant must be Brazilian; foreign companies cannot apply directly, but they can do so through local distributors.

The applicant must then file the request for marketing authorisation. Along with the necessary forms, documents regarding the product, its composition, trade name (brand), pharmaceutical form, presentation, sanitary restrictions, validity term and instructions for storage must be presented. The same goes for reports on production and quality control.
and reports on experiments (including clinical trials) conducted by the company. A draft of the product’s proposed instruction sheet or insert, a sample of the label’s layout, proof of payment of the sanitary fee and the suggested price must also be submitted.

Issuance of marketing authorisation still takes a year. Law 13,411/2016 rationalises the analysis and establishes strict time limits based on how urgently patients need the drug and how complex the drugs are.

For medicines, this law establishes an examination procedure that takes into consideration the technical complexity of the matter and the clinical, economic and social benefits derived from use of the product, subject to the request. Processes are classified as prioritised (120 days for a decision, starting from the request for priority examination) or ordinary (365 days for a decision, starting from the date of the market authorisation request). These deadlines can be extended by one-third, once only, by ANVISA.

Law 13,411/2016 was followed by Resolution RDC 204/2017, which sets forth the products to which prioritised analysis applies.

According to ANVISA’s regulations, the fees for obtaining marketing approval vary according to the size of the company and are measured by annual gross revenue – the amount may be as much as 157,416 reais for a new product that is part of a large group. For generic and branded generic medications, the costs are lower.

Medical devices are subject to either simply being listed by ANVISA or a registration process, depending on the level of risk attributed to the product. The listing process is simpler, since no registration examination is required. For some technical and more specific products, further certification by a technical agency (National Institute of Metrology, Quality and Technology (INMETRO), linked to the Ministry of Development, Industry and Foreign Trade) may be necessary.

vi Regulatory incentives

Intellectual property rights, including patents, trademarks and industrial designs, are considered fundamental rights, as per Article 5, Paragraph XXIX, of the Brazilian Constitution.

Brazil is also a Contracting State of the Paris Convention for the Protection of Industrial Property, the Stockholm Act, the Patent Cooperation Treaty and the TRIPS Agreement.

Law 9,279/96 regulates the rights and obligations related to industrial property, establishing the procedure for granting patents, the requirements placed on patent holders, and the extent of the rights granted by a patent. It also encompasses the procedures for granting trademarks and industrial designs. Copyrights and software are subject to separate laws.

Patents are valid for a period of 20 years starting on the filing date. It usually takes more than 10 years after an application is filed for a pharmaceutical patent to be granted, mainly because of the backlog faced by the National Industrial Property Institute (INPI). According to the Sole Paragraph of Article 40 of Law 9,279/1996, a patent of invention is valid for a minimum period of 10 years from the date it is granted (or seven years for utility model patents), thus ensuring that the patent owner has a minimum protection period. The Sole Paragraph of Article 40 of Law 9,279/1996 is the subject of an action for alleged unconstitutionality, awaiting judgment by the Supreme Court.

There is no specific link between marketing authorisations and patent protection. According to Article 43, Paragraph VII, a patent violation is not deemed to have occurred in connection with ‘acts practised by unauthorised third parties, related to the invention protected by a patent, for the sole purpose of producing information, data and test results,
aiming at obtaining marketing authorisation in Brazil or abroad for the exploitation and commercialisation of the patented product, after expiration of the time limits set out in Article 40’.

Article 195 of Law 9,279/1996 defines the types of criminal unfair competition, among which is to ‘divulge, exploit or use without authorisation the results of tests or other undisclosed data whose preparation involves considerable effort and that have been submitted to government entities as a condition for approving the marketing of products’. However, there is no specific legal provision for the protection of dossiers (which are necessary for marketing authorisation requests, or contain data about clinical trials of reference drugs). These documents are considered confidential by ANVISA.

vii Post-approval controls

Post-registration alterations are regulated by Resolution RDC 73/2016.

Among the obligations of a marketing authorisation holder is the need to report to ANVISA any incidents, adverse effects or technical complaints related to the product. Periodic safety reports are mandatory, and proof of their submission is one of the conditions to be met when renewing a marketing authorisation.

After marketing authorisation is granted, the holder can make requests for alterations, from simple to complex ones. For requests of a simple nature, with no repercussions on safety, quality of efficacy of the product, the procedure is equally uncomplicated, with little or no analysis of documents. For complex topics (such as changes in formula or the ingredients of a product), technical evidence must be submitted to facilitate a thorough examination.

viii Manufacturing controls

Companies involved in the activity of extracting, producing, manufacturing, processing, packing or repacking pharmaceutical products or ingredients must have an operating permit (AFE) from ANVISA. For certain controlled drugs, applying for special authorisation (AE) is necessary. Additionally, authorisations from municipal and state health surveillance bodies may be necessary, depending on the where the facilities are located.

In addition to general information regarding the legal entity itself, the request must consider appropriate technical information. Demonstration of the adequacy of facilities and equipment, an established quality system, clear validation policies and qualified human resources, among other things, is a condition for obtaining an AFE. If an AE is necessary, submission of additional information, such as a copy of the guidelines on good manufacturing practices (GMPs) and a list of all controlled pharmaceutical substances that will be produced at the facility, is mandatory.

Inspections for issuance of AFES and AEs for manufacturing are conducted by municipal, state and national bodies.

ANVISA is responsible for the issuance of GMP certificates. These apply to production facilities, covering production lines, pharmaceutical forms, therapeutic or product risk classes for which companies have been inspected. GMP certificates are valid for two years, starting from the date of publication in the official federal gazette. In August 2019, Resolution RDC 301/2019 was issued by ANVISA with changes to the General Rules for GMP.

According to Resolution RDC 102/2016, provided that the technical characteristics inspected at the time of issuance remain the same, GMP certificates only need to be updated
in the case of a commercial or corporate transaction, to reflect the new situation of the certificate holder. According to the same regulation, management of AFEs and AEs depends on the nature of the operation.

ix Advertising and promotion

There are several instruments concerning the promotion and marketing of pharmaceutical products in the Brazilian legal framework, such as Law 6,360/1973, Law 9,294/1996 and Decree 2,018/1996.

The Brazilian Association of the Research-Based Pharmaceutical Industry (Interfarma) has a code of conduct for pharmaceutical product advertisements. The Brazilian Self-Regulatory Advertising Code, issued by the National Self-Regulatory Advertising Council (CONAR), also applies to drug advertising. However, the major guidelines for promotion of pharmaceutical products to both healthcare professionals and the general public are Resolution RDC 96/2008 and Normative Ruling 05/2009, both issued by ANVISA.

Promotion of prescription medicines is limited to media directed exclusively at healthcare professionals who are qualified to prescribe or dispense them. Advertisements must contain certain technical information, such as the number of the marketing authorisation, indications and counter-indications, possible adverse reactions and interactions with other medicines, food and alcohol. For specially controlled products, promotion is limited to publications of exclusively technical content, referring to diseases and medications, destined exclusively to healthcare professionals qualified to prescribe or dispense specially controlled medication. Advertisements citing scientific information must refer to data extracted from academic journals, with bibliographical data and an indication of the origin of the study.

Additionally, advertisements for specially controlled medicines can cite technical-scientific articles related to the active principle of the medication. Full bibliographical references must be disclosed.

Over-the-counter drugs (OTCs) can be advertised to the general public, through different media, but promotions must observe some limitations. Advertisements for OTC medicines must not:

a contain expressions mentioning ‘scientifically proven’ or ‘demonstrated through clinical trials’;
b suggest that a product is the only means of treatment, or that healthy habits or visits to a doctor are superfluous;
c employ celebrities or people known to the public stating that they use the product or recommending its use;
d employ direct or indirect language relating the use of the product to alcoholic or gastronomic excesses;
e relate the product to physical, emotional or sexual attributes or beauty of a person, except when these are properties approved by ANVISA;
f present abusive, deceitful or frightful images of diseases; or
g include messages, symbols or images directed at children or teenagers.

Medical devices are not subject to any specific guidelines but, according to Law 6,360/1973, health surveillance authorities may intervene if an advertisement for a specific product is considered harmful to public health.
Distributors and wholesalers

Distributors, importers and exporters (as well as companies performing the activity of storage and transport) of medicines, health products, cosmetics, personal hygiene products, perfumes and sanitisers must obtain a licence from ANVISA to operate, under Resolution RDC 16/2014. Depending on the activities to be performed, further state and municipal authorisations may be necessary.

The request must be submitted to ANVISA, comprising both general aspects (acts of incorporation, taxpayer identification number, activities performed by the company, local authorisations, service agreements or similar documents signed with companies licensed by competent authorities, proof that the technical manager is a qualified professional, GDP manual if applicable) and technical aspects (proof of technical capacity, demonstration of qualified personnel, hygiene conditions, statements of purpose for reception, identification, stock control and storage of finished, returned or withdrawn products, proven quality system, among others). Official fees for licensing are variable, linked to the company’s size and revenue.

Classification of products

There are five categories in Brazilian law regarding medicines, determined according to dispensation and restriction of access:

- **OTCs**;
- drugs sold with medical prescription (without retention of the prescription);
- drugs sold with medical prescription, in which the prescription must be retained by the pharmacist or drugstore (no refill without another prescription);
- drugs subject to special control; and
- drugs exclusively used in hospitals.

OTCs can be advertised to the public, under limitations specified by Resolution RDC 96/2008. Advertising of prescription medicines (including those subject to special control and exclusively used in hospitals) is limited, and should be aimed at medical professionals only.

Imports and exports

The importation of medicines and medical devices is regulated by Resolution RDC 81/2008, issued by ANVISA. The holders of the marketing authorisation for a product, and third parties authorised by the marketing authorisation holder, can import and export it. In 2018, Resolution 228 brought a few changes to rules regarding the importation. The new rules require differentiated treatment for products subjected to ANVISA’s inspection by creating four types of channels that consider the type of product and its risk. In addition, Resolution 228/2018 created nine criteria for managing the sanitary risk of imports, which include the history of the company, the existence of problems regarding the use of the product and the result of laboratory analyses.

Prior authorisation must be granted by ANVISA for the importation of medicines and medical devices, which can be granted either when the relevant shipment leaves its port of origin abroad, or when it arrives in Brazil.
Importers in general must be enrolled with the Integrated Foreign Trade System (SISCOMEX) and obtain authorisation for their activities from the Federal Revenue Service (i.e., an ‘Ambient for Registration and Tracking of Activities of Customs Agents’ licence).

### xiii Controlled substances

If a company intends to manufacture, manipulate, distribute, import or export certain controlled pharmaceutical products, it must apply for special authorisation from ANVISA.

When applying for it, further information and structures are required by ANVISA, such as a list of all controlled pharmaceutical substances to be distributed or transported and the existence of a separate, restricted area for these products.

Pharmaceutical products that contain controlled substances can be sold, but ANVISA’s regulations require a pharmacist to retain the medical prescription and record every sale.

### xiv Enforcement

Law 6,437/1977 defines the infractions of sanitary regulations in the activities of manufacture, distribution, import and export, marketing and advertising of products subject to sanitary surveillance, as well as the relevant penalties.

Infractions are classified according to their importance, and penalties are applied accordingly, ranging from 2,000 to 1.5 million reais (which may be doubled in the event of recidivism).

As well as fines, sanitary authorities may impose one or more additional measures on the offender: warning, product apprehension, product destruction, product interdiction, suspension of sales or manufacture of the product, cancellation of marketing authorisation, total or partial interdiction of the company, prohibition to advertise, cancellation of sanitary authorisations, intervention in cases where the company receives public funds of any nature, and corrective advertisement.

The Brazilian Penal Code also contains a specific provision involving violation of sanitary rules: falsification and adulteration of therapeutic or medicinal products is considered a crime against public health, as is the sale of such products without marketing authorisation or with incorrect information.

### III PRICING AND REIMBURSEMENT

Drug prices are subject to analysis by the Drug Market Regulation Chamber (CMED), following the criteria of CMED Resolution 2/2004. A company intending to commercialise a product in Brazil must submit documents demonstrating the category of the product (from I to VI, with I applying to a new product with a molecule that is subject to a patent and that brings improvement for treatment in relation to medications already used for the same therapeutic indication, and VI referring to a generic drug).

The price established by the CMED is the maximum price that can be charged for the product in the private market and to public entities. In addition, in view of the typically large volume of sales to public-sector entities, CMED Resolution 4/2006 created the Price Adjustment Factor (CAP), a linear and compulsory discount applicable on all sales to public entities under certain circumstances (e.g., sales by court order of pharmaceutical products not otherwise supplied at no charge by the National Health System – SUS). The current CAP discount rate is 20.09 per cent, according to CMED’s Rule 11, of 19 December 2019.
For medical devices, prices are overseen by ANVISA through the Nucleus for Economic Assistance in Regulation (NUREM).

According to Article 196 of the Brazilian Constitution, health is a fundamental right of all citizens and a duty of the government. The government is thus obliged to provide the means necessary to supply medicines to all Brazilians. This is done through the Single Health System (SUS). Care and medicines are dispensed by public hospitals and clinics.

There are no legal provisions for reimbursement of costs incurred by patients to buy medicines. The list of drugs provided by the SUS is not comprehensive, and does not include expensive medicines or those for treating rare diseases, syndromes or conditions; the supply of these is generally sought through judicial measures with preliminary injunction requests.

In August 2018, CMED issued Resolution 02/2018, which regulates the general rules concerning administrative proceedings related to infractions in the drug market, and defines the sanctions to those infractions.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Law 9,784/1999 regulates the administrative procedures at federal level, including those related to ANVISA. However, ANVISA has a number of its own regulations that encompass varied procedures that it conducts as part of its day-to-day activities. It is ANVISA’s Resolution RDC 255/2018 that dictates the general rules concerning all administrative proceedings.

In February 2019, ANVISA issued Resolution RDC 266/2019 regarding rules concerning administrative appeals. As a rule, with some specific exceptions, every decision issued by ANVISA is subject to an administrative appeal that stays the effects of the challenged decision.

Also, because the Brazilian Constitution contains the fundamental principle of access to justice, any final decision made by ANVISA (similar to any administrative act performed by any public entity) can be subject to judicial review through different means (ordinary suits, mandamus actions, declaratory suits, among others). Preliminary injunctions to stay the effects of harmful administrative acts can be sought through all these legal mechanisms.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The limits involving relationships between prescribers and payers are specified by self-regulation and regulations issued by ANVISA.

Interfarma’s Code of Conduct states that any gifts to professionals must be related to medical or educational practice, and must not exceed one-third of the Brazilian minimum monthly wage. Additionally, gifts are limited to a total of three per year.

Resolution RDC 96/2008 also applies to the relationship between prescribers and payers, stating that it is forbidden to give, offer, promise or distribute gifts, benefits or advantages to healthcare professionals, although exceptions are made for institutional items (not related to a specific product) and technical literature (scientific articles and journals, technical books and the like, aimed at professional development).

Companies must also observe limitations when (1) sponsoring the participation of healthcare professionals in scientific events, which is allowed, but must never be conditional on the prescription or promotion of a medicine, and (2) establishing relationships and interacting with patient associations or organisations. Any support given to such entities,
according to Interfarma’s Code of Conduct, must be based on a written agreement, not be conditional on any perquisite other than institutional promotion of the company, and not suggesting any degree of exclusivity.

Brazil’s anticorruption law (Law 12,846/2013) holds companies civilly and administratively liable for acts against the public administration, either national or foreign. Such acts include offering, promising or giving illicit advantages to a public agent or related third party, sponsoring the practice of any illicit acts defined by Law 12,846/2013, performing fraudulent acts involving public bidding and administrative contracts or hampering investigations related to illicit acts. Administrative penalties range from 0.1 to 20 per cent of the company’s gross revenue in the previous year (or a fine of up to 60 million reais if this criterion cannot be used), as well as publication of the relevant decision in the press, paid for by the offending company. Additional penalties may be sought by the federal, state and municipal governments through the relevant public prosecution services, aiming at forfeiture of gains resulting from the infraction, suspension or interdiction of the company’s activities, compulsory dissolution of the company and prohibition to receive public incentives, loans or donations for a period of up to five years.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There is no special system or mechanism to compensate persons injured by medicines or medical devices in Brazil. These cases are subject to the general liability and compensation rules of the Civil Code and Consumer Defence Code.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Brazilian legislation defines several situations that violate competition law. The most important ones are described in Article 36 of Law 12,529/2011 (which includes harming free competition and free initiative by any means, dominating a relevant market for products or services, increasing profits arbitrarily, and abusively exercising a dominant position, among others).

Some important cases have been decided by Brazilian courts regarding anticompetitive activities in the life sciences industry.

In 2005, the Administrative Council for Economic Defence (CADE – the antitrust authority) found several pharmaceutical companies guilty of forming a cartel (an alleged attempt to prevent generic medicines from entering the market). Lawsuits were filed by the companies and a first-level decision was rendered in 2011 declaring CADE’s decision null. Appeals were filed, but the lower court’s decision was upheld at the second instance. There are currently pending appeals to the Superior Tribunal of Justice (the highest non-constitutional court in Brazil). Another important case was a decision rendered by CADE in 2015 against a pharmaceutical firm for sham litigation.

There is no settled jurisprudence from the courts addressing pay-for-delay agreements related to the pharmaceutical industry. However, there are legal scholars who advocate that pay-for-delay agreements cannot be accepted under Brazilian legislation.
ii Transactional issues

INPI Normative Instruction 70/2017 came into force on 1 July 2017, covering the administrative procedure for recordation of IP licensing and assignment agreements. The main aspect of this new regulation is that the INPI may no longer interfere in – and limit – the percentage of royalties paid by the licensee to the licensor, when the companies have any corporate relationship. Previously, irrespective of the agreement between the parties, the INPI interfered in the contract to limit royalty payments, imposing caps that applied only to tax deductibility (from 1 to 5 per cent depending on the relevant industry, according to their essentiality degrees). Certificates of recordation now must contain a disclaimer that reads: ‘The INPI did not analyse the contract in light of laws on taxation and remittance of payments abroad.’

VIII CURRENT DEVELOPMENTS

In 2019, ANVISA issued over 70 new Resolutions. These new regulations deal with several topics, such as importation of products, administrative appeals, good distribution, storage and transportation practices and the regulation of cannabis-based medicines.

A few of the most relevant regulatory changes are as follows:

a. RDC 262/2019 updates regulation of importation of products;

b. RDC 266/2019 establishes procedures for administrative appeals challenging decisions rendered by ANVISA;

c. RDC 301/2019 updates General Rules for Good Manufacturing Practices for medicines;

d. RDC 304/2019 establishes rules for good distribution, storage and transportation practices for medicines; and

Chapter 7

CHINA

John Balzano and Aaron Gu

I INTRODUCTION

China continues with drug and device regulatory reform. Since 2015, China has embarked on a reform effort to fully restructure its drug and medical device regime to promote innovation. This departs from the previous 10 years during which incomplete regulations, a smaller drug and device regulatory agency, and long wait times for approval of development and marketing applications made the launch of innovative drugs (i.e., drugs approved based on full data and/or approved first in China), particularly those that were imported, a difficult and multi-year process.

Beginning in earnest in 2017, and in particular with the issuance of the Opinion on Deepening the Reform of the Review and Approval System and Encouraging the Innovation of Drugs and Medical Devices (Innovation Opinion) (No. 42 of 2017), the central government established a reform plan to create a true research-based, innovative industry for drugs and devices. These reforms included a notification system for clinical trials, acceptance of foreign data, expansion of clinical trial sites, and a marketing authorisation holder system that permitted smaller companies with research (but no manufacturing) capability to hold and reap the benefits of product approvals. As will be discussed herein, the prior system tied one product licence to a specific manufacturing facility and made contract manufacturing and supply chain diversification difficult.

Since the Innovation Opinion, China has been implementing many of the changes in its policy blueprint for innovation via regulatory fiat or pilot programmes, as opposed to principled amendments to its laws and regulations. For example, in 2015 the legislature and the chief drug and device regulator, the National Medical Products Administration (NMPA), worked to implement a pilot marketing authorisation holder programme (MAH Pilot) in 10 provinces and municipalities. A similar device MAH programme was adopted on a limited scale and expanded to 21 provinces and municipalities in August 2019. In 2019, the National People’s Congress passed the first full-scale revision of its Drug Administration Law (DAL) since 2001. At the same time, it issued its first specialised statute governing various aspects of the life cycle of vaccine products, the Vaccine Administration Law (VAL), prompted by a scandal related to the manufacturing of vaccines that emerged during the summer of 2018. On that basis, the NMPA and its Centre for Drug Evaluation began to issue new implementing rules and guidance documents rapidly starting from August, a process that will continue throughout 2020 and the years to come.

---

1 John Balzano is a partner and Aaron Gu is an associate at Covington & Burling LLP. This chapter is based on the ‘China’ chapter in previous editions of The Life Sciences Law Review, which was authored by John Balzano and Andrew Shaoyu Chen.
At the time of this writing, many of these reforms are ongoing for drugs, so the text below combines the existing reforms and legislation completed to date with the elements of the current system that remain, noting when possible (and credible) how existing draft proposals could change that.

For devices the evolution is more complete in some ways. Although the Regulation for Supervision and Administration of Medical Devices (RSAMD) has not yet been amended since the Innovation Opinion in late 2017, the State Council and NMPA restructured that regulation more recently with a full revision in 2014 and a minor revision in early 2017. The NMPA only finished the implementing regulations for the 2014 regulation in 2018 as multiple new draft amendments for the RSAMD were appearing. Therefore, in some respects, such as with their more detailed good clinical practice and well-developed adverse event reporting and monitoring regulations, device regulations are further ahead of drugs. The sections below explore the device changes since 2014 with notes as to when the pending drafts of the RSAMD could particularly change the system.

II THE REGULATORY REGIME

i Regulatory agencies and their jurisdiction

As of the full government reorganisation in March 2018, the NMPA is now the primary pharmaceutical and medical devices regulatory agency in China. It is a subordinate bureau of the State Administration for Market Regulation (SAMR) – a super-ministry that covers company registration, product and consumer protection regulation, advertising, antitrust, standardisation and intellectual property, among other areas. Previously, since 2013, the China Food and Drug Administration – a stand-alone ministry – regulated this area, but the reorganisation reshaped it into a smaller, specialised product regulator under SAMR. The reorganisation also removed food from its jurisdiction.

The NMPA enjoys power over most aspects of pre-market approval and a substantial part of post-marketing activities. Under the current arrangement, the NMPA is organised into departments and affiliated centres. The departments have responsibility for administration and enforcement functions, while the affiliated centres are responsible for scientific review and recommending product approval decisions for the departments to adopt and implement.

For drugs, the primary departments include the Department for Drug Registration, which is subdivided into departments for research and development, traditional Chinese medicine, chemically synthesised drugs and biological products, and the Department for Drug Supervision, which is subdivided by the type of manufacturing that each subdivision supervises (e.g., chemically synthesised, biologic) and a subdivision in charge of pharmacovigilance activities. The affiliated centres include the Centre for Drug Evaluation (CDE) and the Centre for Drug Re-Evaluation (CDR). The CDE evaluates clinical trial and marketing authorisation applications, and approves subsequent amendments and renewals. The CDR includes the National Centre for Drug Adverse Event Monitoring, which is also responsible for device adverse event monitoring.

The NMPA similarly has registration and supervision departments for medical devices. The registration department is subdivided by whether the devices use electrical power or not, as well as including a subdivision for supervising research and development. The supervision subdivision is divided into divisions responsible for regulating manufacturing, distribution, and monitoring and evaluation. The Centre for Medical Device Evaluation (CMDE) is the affiliated centre responsible for organising the technical evaluation of medical devices.

© 2020 Law Business Research Ltd
With an official headcount of 216 at the national level (not counting contract personnel),\(^2\) the NMPA relies on provincial counterparts, which are merging with local administrations for industry and commerce to become ‘market supervision bureaus’, and similar device and drug regulatory authorities in the municipalities\(^3\) to carry out various activities, including accepting applications, conducting on-site checks and inspections, collecting samples, and issuing manufacturing and distribution licences. These provincial agencies receive their budget and their personnel allocation from the provincial governments, and they can vary in terms of capacity. State-accredited laboratories and clinical trial sites (e.g., in state-owned hospitals) also play a role in drug and device regulation in China.

China has worked since 2015 to provide the affiliated centres (CDE and CMDE) with more reviewers. Real numbers are difficult to determine, but the NMPA's announcement on the CDE's hiring\(^4\) and the CDE’s annual reports indicate that it continues to add reviewers, and that the number of personnel has grown to around 800, from 60 to 70 a few years ago.\(^5\) The CMDE has similarly been adding reviewers but has fewer than the CDE.\(^6\) The increases in staff have been and will continue to be an important step in resolving delays.

Although the NMPA is the primary agency for pre-approval, other government agencies also play important roles in the pharmaceutical regulatory framework. Many of these other agencies that had some hand in regulating drugs and devices have also changed names or merged with other agencies. For example, a division previously under the National Development and Reform Commission (NDRC) that is now within SAMR has a key role in articulating drug and device pricing policy. The SAMR has a significant role in enforcing advertising and promotion and other consumer protection and fair competition and antimonopoly laws that intersect with the drug and device industries. The National Health Commission (NHC, formerly the National Health and Family Planning Commission (NHFPC)) oversees all aspects of the medical profession and hospitals (which include NMPA-accredited clinical trial sites for drugs and devices), and plays a part in determining the essential drugs that may be reimbursed under China's state insurance plans. The National Healthcare Security Administration also plays a part in setting the reimbursable drugs for these insurance plans. For imported drugs, the China Customs Administration is involved in product-quality inspections and customs clearance. This sharing of responsibility creates a complex system in many respects.

ii Primary statutes and regulations

Unlike in the United States, there is not one law covering foods, drugs, devices and cosmetics. There is a law or an administrative regulation governing each of these areas. The primary statute regulating drugs (including biologics) is the DAL, which was enacted by the national legislative body, the National People’s Congress, in 1984 and then substantially amended in

\(^3\) While varying from year to year, the local drug agencies and affiliated organisations at provinces and municipalities have a total approximate headcount of 80,000 (direct and affiliated).
\(^4\) The NMPA's announcement on CDE's hiring in 2018 indicates that the CDE plans to recruit 40 more staff in 2018, including 21 reviewers. See www.nmpa.gov.cn/WS04/CL2146/318508.html.
\(^6\) Statistics compiled by reviewing many hiring announcements on CMDE’s website, www.cmde.org.cn.
Small amendments were made to the DAL in 2013 and 2015 to support what China considered to be more pressing regulatory reforms, such as drug pricing. The State Council has enacted one general set of implementing rules for the DAL, referred to as the DAL Implementing Regulations (DALIR), which were last amended in 2019, before the passage of the DAL. The latest DAL amendment is potentially game changing in that the MAH of all drugs approved for marketing authorisation will be primarily responsible for development, quality and safety and effectiveness monitoring and reporting over the course of its life cycle with contract manufacturers and distributors sharing various responsibilities.

The NMPA administers several agency rules under the DAL and the Regulations for Implementation of the DAL to govern various activities, such as development, registration, manufacturing and marketing of drugs. These include good practice on manufacturing, distribution, clinical development and laboratory work. The core regulations governing clinical trials and small molecule drug and biologic registration are the Drug Registration Regulations (DRR), for which the NMPA has not finalised a comprehensive amendment since 2007, despite releasing drafts in 2014, 2016 and 2017, and three in 2019. China is expected to finalise a substantial revision of the DRR shortly to implement the DAL.

However, the NMPA has made changes to the policies reflected in the DRR via shorter regulatory documents. For example, it implemented the more recent reference product and MAH reforms through these documents. In October 2017, the NMPA issued a document entitled Adjustment of Several Matters Regarding the Registration of Imported Drugs (CFDA No. 35 of 2017) (Document 35). Document 35 removes certain restrictions on the development and registration of imported drugs that are in the DRR. These reforms may be incorporated into the DRR (or guidance documents) as the implementation of the DAL and process of regulatory reform progresses.

The CDE also issues its own rules and guidance documents related to drug development and registration, priority pathways and supplemental applications. It has issued many proposed rules and guidance documents to implement the 2019 DAL.

The framework legislation for medical devices is a regulation (not a law) enacted by the State Council, namely the RSAMD. As with drugs, the NMPA has enacted a number of implementing rules covering registration, production and distribution. The State Council revised the RSAMD in 2014 and 2017, and another amendment is very possible in 2020.

Reform of the NMPA’s rules and guidelines on various aspects of medical devices and drugs continues on a regular basis. As the NMPA ventures into new and more cutting-edge areas it continues to release a number of specialised guidance documents, including those governing digital health, artificial intelligence and cybersecurity.

---

9 These regulations cover in vitro diagnostic reagents (IVDs), but IVDs are regulated separately under a specialised set of implementing regulations. Throughout this chapter, references to medical devices refer to non-IVD devices, unless otherwise indicated.
iii Classification

Drugs

The general structure and classification of drugs is governed by the DAL. The newly revised DAL defines ‘drugs’ broadly as:

any substance used for preventing, treating and diagnosing human diseases as well as purposely regulating human physiological functions with specified indications or functions, usage and dosage, including traditional Chinese medicines . . . chemical drugs and biological products.10

As will be discussed below, the NMPA does recognise some category overlap. When products may be considered drug and device combination products, the NMPA and a combination of experts from either the CDE, CMDE or both will make a decision as to whether to regulate the product as a drug or as a device. This concept of combination products is being incorporated into mainstream regulations with the drafts of the DRR.

Once determined to be a drug, the regulatory requirements applicable to a product will be determined by its pathway and its features. Previously the location of manufacturing determined the primary pathways, with different requirements for domestically manufactured drugs or imported drugs. The revised DAL now leaves the distinctions between domestic and imported pathways in doubt as all products will receive a marketing authorisation and there is no ‘imported drug licence’ provision as existed in the prior DAL.11

Under the 2019 drafts of the DRR, drugs will still be classified into three types: traditional Chinese medicines and natural drugs, chemical drugs and biological drugs. Within each classification, drugs are again placed into registration categories. These registration categories determine the non-clinical and clinical data and other requirements necessary for registration.

In 2015 and 2016, pursuant to authorisations from the National People’s Congress and the State Council, the NMPA restructured the registration categories for chemically synthesised drugs. These new categories were intended to reduce confusion about the registration process, integrate the new reference product system for generics and encourage innovation. The five categories under this system are:

a Category 1: innovative drugs. These drugs have an active ingredient that has a clear structure and is clinically valuable. The ingredient must be new to the world, not just new to China.

b Category 2: improved innovative drugs. These drugs have an improvement that is clinically valuable and new to the world, such as certain structural changes, dosage forms, routes of administration, strengths and indications.

c Category 3: generics with foreign reference products. This category is for generic drugs that use fully evaluated drugs (typically originator drugs) that are marketed abroad but not in China as their reference products.

d Category 4: generics with domestic reference products. The opposite of Category 3, this category is for generics that use fully evaluated drugs that are marketed in China as their reference products.

10 Article 2 of the DAL. Translation provided by LexisNexis.
11 Article 38 of the DAL.
China

Category 5: imported drugs already approved for marketing abroad. Following on from the separation between imported and domestic drugs described above, this category is either for original drugs that are already marketed abroad (5.1) or generic drugs marketed abroad (5.2). These drugs use the import licence pathway.12

Biologics have not undergone a similar reform, and at present under the 2007 DRR consist of 15 unwieldy and overlapping categories (e.g., one for monoclonal antibodies and one for biologics not marketed inside or outside of China). By means of a guidance document, China adopted a structure for biosimilars that was similar in certain respects to the guidance issued by the World Health Organization in terms of setting forth a method for a comparative evaluation typically against an innovative therapeutic biologic. That guidance defined biosimilars as those biologics that have demonstrated similarity to a reference product, and in 2019 China approved its first biosimilar under that framework.

Although not in force, the draft DRR now proposes even more simplified categories. For example, for chemically synthesised drugs, those categories are: (1) innovative drugs, (2) modified new chemical drugs, and (3) generic drugs. For biologics, they are (1) innovative biologics, (2) modified new biologics, and (3) a more mysterious category referred to as ‘marketed biologics’, which includes biosimilars but is otherwise unexplained. The 2019 draft DRRs eliminate the complex appendices and promise to replace them with more detailed guidance documents that the CDE will issue. The meaning and content of these categories remain unclear at present, including whether innovative drugs that are first approved in other countries can qualify as innovative drugs in China. Since 2016, that has not been the case.

Certain types of drugs may also be subject to separate and heightened requirements and require additional special permissions. The most prominent example is now vaccines, which are subject to various requirements under the 2019 Vaccine Administration Law, but other examples are ‘narcotic drugs’ and ‘psychotropic drugs’, which are subject to, among other restrictions, stringent limits on research, manufacturing and distribution depending on their active ingredients and further classification.

Devices

Medical devices are also defined via regulation and then further sub-classified. The RSAMD defines ‘medical devices’ broadly as:

the instruments, equipment, appliances, in vitro diagnostic reagents and calibrators, materials and other similar or related articles directly or indirectly used with human bodies, including the computing software required. Their effectiveness is primarily achieved by physical or other similar means and not by pharmacological, immunological or metabolic means, although it may be assisted in its function by such means, the purpose of which is to achieve the following objectives:
(1) diagnosis, prevention, monitoring, treatment or mitigation of diseases;
(2) diagnosis, monitoring, treatment or mitigation of injuries or the functional compensation thereof;
(3) inspection, replacement, adjustment or support of the physical structures or physiological processes;
(4) life support or sustaining;

The RSAMD then defines three classes of medical devices:

Class I medical devices means medical devices with low risks, and those for which safety and effectiveness can be ensured through routine administration; Class II medical devices means medical devices with moderate risks, which must be strictly controlled and administered to ensure their safety and effectiveness; Class III medical devices means medical devices with relatively high risks, which must be strictly controlled and administered through special measures to ensure their safety and effectiveness.

The NMPA and its relevant divisions have discretion to determine what constitutes a medical device and what class it fits into. Every device in the 200-page Medical Device Classification Catalogue released in August 2017 is a device, however, and the NMPA does not exercise enforcement discretion to treat them otherwise.

Applicants for a device registration may make their own determination as to classification and then submit their application to the NMPA or they can treat their device as a Class III and ask the NMPA to make adjustments. They can make that determination with reference to the Classification Catalogue and general rules and principles of classification. The NMPA also oversees an online platform, run by the National Institute For the Control of Pharmaceutical and Biological Products (NICPBP, formerly known as National Institutes for Food and Drug Control (NIFDC)), through which manufacturers can submit applications for a predetermination of device classification.

The current RSAMD and the Administrative Measures on Medical Device Registration classify a medical device as either a domestic device or an imported device, depending on whether the finished device is manufactured inside or outside of China. If it is an imported device, the NMPA reviews and approves a registration application for Class II and Class III devices. Class I imported devices go through a notification system, which the NMPA also administers. For domestic devices, the review and the reviewing authority depend on the classification. Class I device manufacturers must notify municipal authorities before marketing their products; a provincial-level device regulatory authority approves Class II medical device registration applications; and the NMPA reviews and approves Class III medical device registration applications.

Most in vitro diagnostic reagents are considered medical devices. The NMPA maintains a separate body of regulations for devices that meet this definition, including different rules on development, registration, and licence amendment and renewal. The primary NMPA

13 Article 76 of the RSAMD. This is an edited version of the translation available on www.chinalawinfo.com.
14 Article 4 of the RSAMD.
15 Article 16 of the RSAMD.
rule for IVDs is the Measures on the Registration of In Vitro Diagnostic Reagents (IVD Measures), which set out a similar classification and registration scheme for IVDs. Under the IVD Measures, IVDs are defined as:

In vitro diagnostic reagents managed as medical devices refer to reagents, reagent kits, calibrators, quality control products and other products for in vitro testing of human samples used in the process of predicting, preventing, diagnosing, monitoring the treatment of, and observing the prognosis of disease and evaluating a state of health. They can be used alone or in combination with other devices, appliances, equipment or systems.

In vitro diagnostic reagents for blood screening and radionuclide indicators are not considered device-type IVDs and are regulated as drugs. The IVD Measures also divide IVDs into three classes (I, II, III), III being the highest risk and I being the lowest.

**Combination products**

The NMPA issued a notice in 2009 on review of drug and device combination products. If the primary mode of action of a product is medicinal, the CDE will review it as a drug, or lead a joint and parallel review by both the CDE and the CMDE. If the primary mode of action of a product is not medicinal, the CMDE will review it as a device, or lead a joint and parallel review by the CMDE and CDE. One example of a product that the NMPA may treat as a combination product is a tissue-engineered product, which may be considered a medical device that would also have to meet certain requirements particular to the development of a biological product. The 2019 draft DRR reinforces this framework, and notes that where a drug-device combination product has been approved as a drug, subsequent products will also be approved. It also makes it clear that the CMDE must review device data for drug-dominant combination products prior to the NMPA conducting a final review for approval.

**iv Non-clinical studies**

Both drugs and devices require various non-clinical and clinical testing to support marketing. Non-clinical studies for drugs must comply with the NMPA Drug Good Laboratory Practice Regulations, and must be conducted by institutions and laboratories that have been certified by the NMPA. The NMPA also accredits laboratories that conduct pretrial type testing for Class II and III devices.

**v Clinical studies and data**

Under the regulations, the default requirement for a permission to market a drug or Class II or III device in China is to conduct a clinical trial. As we explain below, the NMPA will permit some flexibility in this arrangement in certain cases. Some devices are exempt from clinical trials based on existing data and the safety record of predicate devices, and drug applicants

---

can apply for an exemption from all or part of the clinical trial requirement based on existing data. For both drugs and devices, the NMPA has adopted a more structured mechanism to accept foreign data to support marketing applications in China.

The revised DAL and device proposals also include a conditional approval programme, under which a foreign-approved drug for an orphan indication or a drug for preventing or treating life-threatening diseases can be approved based on early-stage data. In October 2018, the NMPA and NHC implemented an earlier variant of this programme when they jointly issued procedures under which a drug designated by the CDE and approved in the United States, EU or Japan can receive approval in China conditioned on a post-market study and risk mitigation plan on a special expedited basis.20

**Drugs**

Before a clinical drug trial can be initiated in China, the sponsor must submit a clinical trial application (CTA) to the NMPA (specifically to the CDE), which the CDE must approve. Under the revised DAL, China has implemented an ‘implicit approval system’ in which the applicant submits a dossier or materials and then may begin the trial according to its protocol if the CDE has not objected within 60 business days of the date of filing. There is a separate system of notifications for bioequivalence studies to support generic drugs.

Currently for new drug trials (the practice under the new DAL is not yet clear), the NMPA will permit an umbrella review of all three phases of a trial following a pre-CTA meeting. Also, an expedited review is potentially available pursuant to three programmes: breakthrough approval, conditional approval, and priority review and special approval. These programmes accelerate approval for marketing based on various criteria, including the severity or rare nature of the illness and the clinical need for the drug. These programmes build upon various earlier expedited programmes that the NMPA has run to reduce the timeline for approval.21 As discussed below, the NMPA has also recently adopted a filing system for bioequivalence studies for generic drugs that is less onerous than the CTA process.

The NMPA requires that investigational drugs (regardless of the imported or domestic pathway) be manufactured at good manufacturing practice (GMP) facilities and comply with GMP standards, that government-certified laboratories conduct quality testing to confirm conformity with the quality standards,22 and that the sponsor seeks review and approval of the clinical trial by a qualified ethics committee. Ethics committee approval must take place before CTAs are submitted to the NMPA. If the institution has one, another approval by a clinical trial management committee may be required.

Clinical trials can be conducted only at institutions that have been inspected and accredited by the NMPA with departments that have been certified for that type of clinical investigation. Under the Innovation Opinion and the newly revised DAL, this certification process has now changed from a pre-approval to a filing. Clinical trials in China are governed

---


22 Articles 35 and 36 of the DRR. Also see the NMPA clinical trial flow chart: http://eng.sfda.gov.cn/WS03/CL0769/61658.html.
China

by pharmaceutical good clinical practice (GCP) regulations,\textsuperscript{23} which follow similar GCP regulations in other countries in some respects. The GCP regulations and the DRR set out sponsor and investigator obligations, including for serious adverse events. The NMPA, or ethics committee, can hold or terminate a study for safety reasons.

Once a clinical trial protocol is approved by the NMPA, historically information associated with it (including the protocol) can be difficult to amend, even for small changes, but the draft DRR will permit various amendments which may require an approval, notification, or mention in an annual report depending on the degree to which the change affects safety or effectiveness. In the past, this shortcoming has led to applicants having to file an entirely new CTA when making changes to their approved CTA, even if those changes are not safety-related.

In some cases the DRR still specifies the following minimum numbers of study subjects for different phases, and the trial must have sufficient statistical power.\textsuperscript{24} The NMPA has been revising the application requirements for chemically synthesised drugs,\textsuperscript{25} but the following requirements for biologics remain on the books at least until the draft DRR is finalised.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Therapeutic biologic</th>
<th>Preventive vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Phase II</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Phase III</td>
<td>300</td>
<td>500</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

A central difference between the imported and domestic approval pathways is the requirement of prior foreign approval for imported drugs, whereas no such foreign approval is required for domestically produced drugs. As of 2017, if the drug has been approved abroad, China’s drug regulations generally require submission of proof of approval in the form of a certificate of pharmaceutical product prior to submitting the CTA for an imported drug. In the event that the drug has not been approved elsewhere, an application for an imported drug can include submission of a CTA without proof of foreign approval. It is unclear whether this requirement will remain under the draft DRR.

Foreign manufacturers can choose to apply for permission to conduct part of an international multi-centre trial (IMCT), and China has lifted the restriction that an applicant must show that it has begun Phase II or the drug has been approved abroad.\textsuperscript{26} Once the IMCT is complete, the applicant can apply directly for marketing approval.

China further embraced the idea of multi-centre clinical trials by adopting special guidance on these types of trials in early 2015, and has pledged to encourage domestic drug manufacturers to participate in these trials.\textsuperscript{27}

In June 2018, the NMPA released guidance on the acceptance of foreign data, including early stage data, to support marketing applications in China. The data must be generated

\textsuperscript{24} Appendixes 2 and 3 of the DRR.
\textsuperscript{25} New Chemical Drug Registration Category Application Material Requirements (Trial Implementation) (CFDA No. 80 4 May 2016), available at www.nmpa.gov.cn/WS04/CL2182/300157.html.
\textsuperscript{26} Article 44 of the DRR.

© 2020 Law Business Research Ltd
according to China’s requirements including related to design and human subject protection, and proper attention must be given to whether there are concerns about ethnic differences in the subject population abroad that could be meaningful for China. The NMPA has also taken steps to permit acceptance of real world evidence, releasing a guideline and joining the trend of other agencies around the world in exploring this new area. It is currently unclear how real world evidence may be applied.

**Devices**

Clinical data are used to establish the safety and efficacy of medical devices that are registered for marketing in China. In general, manufacturers must submit clinical trial data to register Class II and Class III medical devices (including in vitro diagnostics). No clinical trial is required for Class I devices.

The revised 2014 RSAMD broadened the exemptions from clinical trials for certain devices and for IVDs. The exemptions for devices include: (1) devices for which there is an identical type of device on the market with a well-established safety record following many years of clinical use; (2) devices that can be evaluated effectively through non-clinical data; and (3) devices that can be evaluated through pre-existing data on the same types of devices. To further define these categories, the NMPA issued multiple catalogues of exempt devices, ultimately issuing one unified catalogue in 2018 with an update in 2019, and guidance on how to determine whether a device falls under one of these broad exemptions. Exemptions similar to (1) and (2) also exist under the revised IVD regulations. A proposed amendment to the RSAMD would remove the requirement for a clinical evaluation for Class II devices and potentially broaden the exemption for Class III devices to cover those that present a lesser degree of risk.

Clinical trials of Class II and most Class III medical devices do not require NMPA approval. However, the NMPA has issued a catalogue of a subclass of high-risk Class III devices for which pre-approval of the clinical trial is required. This catalogue has not been updated since 2014 and includes eight different types of products that NMPA deems to pose higher risks to human bodies, such as nano orthopedic implants.

---

28 Article 17 of the RSAMD.
29 id.
30 id.
31 id.

© 2020 Law Business Research Ltd
All trials for both medical devices and IVDs must take place at hospitals and other healthcare institutions that the NMPA has accredited to conduct device trials. In 2017, the State Council amended the RSAMD to permit hospitals to qualify as clinical trial sites after completing a filing process. While no pre-approval from the NMPA is required (unless the device is designated as a high-risk Class III device), all medical device clinical trials must be approved by the institution’s ethics committee and notified to the provincial-level government where the clinical trial sponsor is located. The NMPA issued procedures to implement this provincial notification requirement in July 2015. In addition, under the revised RSAMD, device trials must comply with medical device GCPs. The NMPA issued new GCPs for medical device trials to support registration with the NMPA in 2016 and new GCP inspection principles in 2018. These GCPs added to the provisions on informed consent (including those on consent from children and others who lack the capacity to consent), requirements for agreements between sponsors and the site, and the coordination of multi-site trials. The GCPs set forth a set of reporting requirements for adverse events that occur during the trial. In vitro diagnostics are subject to a separate set of GCPs for their trials. Like with drugs, the NMPA has always permitted stakeholders to rely on foreign-generated data to support applications in China. However, in 2018, the NMPA issued guidance on the acceptance of foreign data to support device registration applications. The guidance focuses on design, human subject protections and attention to ethnic differences.

**Human genetic resources**

Foreign companies that sponsor clinical trials in China and collect human biospecimens must apply for approval or notification to do so jointly with the Chinese clinical trial site (i.e., the hospital) from the Office of Human Genetic Resource Administration within the Ministry of Science and Technology. This approval or notification is required regardless of whether the foreign company is conducting genetic tests and covers any sample that contains human DNA. In 2019, the State Council revised the HGR regulations. Among several other changes, the new regulations introduced a notification pathway if the study would be used to support marketing approval of the drug or device in China and if no samples associated with the study are exported outside of China. The amendment also introduced a data notification requirement under which the Chinese party must notify the Office of Human Genetic Resource Management and upload the data to be transferred prior to transferring data associated with the samples to a third party outside of the collaboration. The regulations on human genetic resources also include controversial provisions on the sharing of intellectual property, including patent rights to any invention related to the samples. The

---

36 Article 18 of the RSAMD.
37 id.
38 See the Announcement on the Notification of Medical Device Clinical Trial (CFDA 2015), available at www.nmpa.gov.cn/WS04/CL2138/300025.html.
Office of Human Genetic Resource Administration reviews the agreements associated with a clinical trial to determine whether these requirements have been met and has significant discretion to delay or reject an application.

In December 2019, the Ministry of Science and Technology issued a special notice where it required, among other things, all entities that had submitted HGR applications in 2018 conduct a self-inspection regarding their compliance with HGR regulations by early January 2020, and the agency is also arranging regular and random inspections of national and provincial science and technology agencies in 2020.41

vi Named-patient and compassionate use procedures

Under the DAL, China has committed to create an expanded access pathway under which a company sponsor can apply for permission for an expanded access treatment programme for patients with life-threatening illnesses that otherwise cannot qualify for the trial. In addition, the DAL permits provincial governments to approve one-time imports of drugs that are urgently needed, a power that used to belong to the NMPA and was rarely used. Implementing regulations and guidelines associated with these new programmes do not exist yet.

Currently, the NMPA permits limited drug compounding by medical institutions for use on their own patients, sometimes without having to receive NMPA clinical trial approval or marketing authorisation.42 In addition, Chinese drug regulations provide for the importation of unapproved drugs to satisfy urgent clinical needs or in the case of national emergencies. The urgent clinical need standard is a significant one, which is difficult for individual patients to meet, but may be used rather more commonly when the drug is necessary to treat a specific group of patients to prevent the spread of serious contagious disease.43

In the absence of a finalised compassionate use pathway, the Bo’ao medical tourism zone in Hainan Province has emerged as a place that provides earlier access to unapproved drugs and medical devices. Medical institutions can assess patients for a treatment plan in the zone and apply for importation of unapproved medicines and medical devices. Recently Bo’ao obtained approval to make those decisions for itself instead of obtaining NMPA approval. The drugs or devices are then imported specially into Hainan for this purpose and used there. This has become a fairly efficient process for obtaining access to unapproved medicines on an expedited basis.

vii Pre-market clearance

Drugs

As discussed, the NMPA has different requirements for drugs depending on the registration category that they fall under. The registration categories are currently in flux, but this section addresses current requirements. These are likely to change in the coming years.

42 Article 76 of the DAL.
43 Article 36 of the DALR.
**Imported drug application**

If manufactured abroad and by a qualified foreign manufacturer, the application is for an imported drug. If approved abroad, typically the foreign manufacturer holding the relevant approval for the foreign regulatory health authority is the applicant before the NMPA and will be required to present a certificate of pharmaceutical product to show marketing abroad. If the drug for import is not yet approved abroad, the NMPA can approve the imported drug as a Category 1 innovative drug (see above) and no foreign approval is required.

In addition, the foreign manufacturer must submit drug samples from three batches to be tested by the NICPBP for conformity with product specifications and quality standards. The draft DRR introduces requirements for inspections of development sites in some cases, as well as registration inspections, including manufacturing sites for certain types of drugs and for-cause inspections to verify application materials, including those related to suppliers.

The manufacturer (or now under the new DAL the MAH) must also appoint a local entity in China to act as the agent for the imported drug registration. Agents may be drug distribution entities that hold distribution licences, which allow them to book sales and promote the drug. Agents bear joint responsibility with the MAH and liability for quality, safety and other regulatory obligations and related violations.

**New drug application**

Domestic drugs and biologics submit new drug applications. For chemically synthesised drugs, a new drug is now considered to be one that is new to the world in the ways specified in registration Categories 1 and 2 described in Section II.iii. The DRR provide that all biologics must proceed through the new drug pathway.

For this pathway, the NMPA requires that a manufacturer obtains a drug manufacturing licence after a facility inspection demonstrating GMP compliance. Under the DAL, the manufacturing licence and the GMP certification has been merged.

Previously, domestic manufacturers would file a new drug application or a generic drug application. However, for domestically made products the only licence the NMPA issued was a manufacturing facility licence. Therefore, once the drug was approved the NMPA would issue a new drug certificate which would become linked to the site and, subsequently, an official drug approval number. A domestic drug would then be permitted to go on the market. All biologics, regardless of whether they were innovative or follow-on products, had to use the new drug application pathway, and any additional indications required a new drug application, although they would become part of the same licence. For imported drugs, there was a separate imported drug licence application that resulted in an imported drug licence being granted.

Going forward, the NMPA will receive registration applications for all drugs whether domestically made or imported. Once development is complete, an applicant will file a marketing authorisation application under one of the registration categories described above (innovative product, modified new product, or a follow-on (i.e., generic or biosimilar)). The draft DRR permits applications for first-time APIs and packaging (previously separate from the product application) to be filed and reviewed together, including underlying data for these new APIs and materials. The NMPA is also implementing the equivalent of a master file system through which others can access the data underlying the APIs and packaging materials.

---

44 Articles 84 to 95 of the DRR.
China

without obtaining the data itself. During the registration process there can also be a variety of registration inspections, including an inspection of the clinical data site, a manufacturing site inspection (separate from that for a manufacturing licence), potentially inspections of suppliers or other third parties, or other for-cause inspections if needed to verify application materials.

**Generic drug application**

With the exception of original drugs manufactured abroad, drugs that are not new to the world are generic drugs and go through an abbreviated process through which they establish therapeutic and quality equivalence to a reference product marketed in China or abroad. Equivalence is established either through a bioequivalence study, an in vitro study, if the drug qualifies for an exemption, or a clinical trial to show efficacy in some cases. In most cases, the reference product will be an original product, but the NMPA will also permit an ‘internationally recognised’ generic product to serve as a reference product.45

Generics on the market that are on the Essential Drug List (2012 version) for reimbursement in healthcare institutions and in solid oral forms were required to demonstrate equivalence to reference products by the end of 2018. All other fixed oral dosage form generics can freely determine when they will demonstrate equivalence, but the first generic manufacturer to seek such approval will get three years of exclusivity during which equivalence applications for other generics of the same type will not be accepted.46

The NMPA has developed and implemented a new set of guidelines for demonstrating bioequivalence. Under this new system, bioequivalence studies may begin after the applicant has notified the NMPA through an electronic platform.47 The CDE review of a generic drug application proceeds in parallel with manufacturing site inspection and collection of drug samples by the provincial drug regulatory authority, as well as drug quality testing by the NICPBP. If results are satisfactory, the NMPA will approve the application and issue a drug approval number to the applicant, which should already have obtained a drug manufacturing facility permit.48

The pathway for biosimilars is somewhat different; that is to say, biologics for which there is an existing standard may be brought on the market. Under the current DRR, biologics for which there is a pre-existing national standard typically only need to conduct Phase III studies in China and for others, Phase I may be waived.49

The CDE’s guidance document on biosimilars (2015), intended to strengthen the methods for research and development of similar biologic products and their stepwise characterisation and comparison to reference originator products, including a quality comparison, and non-clinical and clinical evaluations. This guidance also includes some

---

45Opinion on Developing Therapeutic and Quality Equivalence Evaluation for Generic Drugs (State Council General Office No. 8 of 2016), available at www.gov.cn/zhengce/content/2016-03/05/content_5049364.htm.


48Chapter 5 of the DRR.

49Appendix 3 of the DRR.
provisions on labelling and pharmacovigilance.\textsuperscript{50} As discussed, the new category under the draft DRR of ‘marketed biologics’, including biosimilars does not yet play a clear role in this system.

\textit{Approval timelines}

In 2015, the NMPA began examining what had become a huge application backlog for both drugs and devices. The agency had tens of thousands of applications pending, with thousands more being filed each year. The State Council and the NMPA committed to significantly reducing this backlog by the end of 2018. The CDE's annual report, released on 3 March 2016, indicated that the drug backlog had been reduced from approximately 22,000 to 17,000 applications, which is a reduction of around 22 per cent,\textsuperscript{51} and by 2017, the NMPA touted reducing the backlog to only 4,000.\textsuperscript{52} The NMPA also committed to increasing the speed of the reviews and the criteria for review and approval by adding review personnel and creating review guidelines. By 2019, the NMPA claimed that the backlog had all but disappeared.\textsuperscript{53}

With these reforms still progressing, the total time for review, site inspection, drug sample testing and final approval of an imported drug licence, a new drug application or a generic drug application is in flux, but it can still take one to two years. Most of this time continues to be occupied by the CDE review process. The DRR provide for 150 business days for CDE review of new or imported drug applications (200 business day limit under the draft DRR), and 160 business days for CDE review of generic drug applications (200 business day limit under the draft DRR). In practice, the CDE’s review often takes longer, although the draft DRR appears to set an overall cap and may improve timing. If the CDE needs additional information, it can issue a request to the applicant, and the review clock stops. The applicant will have four months to provide the additional information, and the CDE will have an additional 40 days to review the additional information. Requests for additional information are common in all applications, and sometimes repeated, although the CDE is required to avoid repeated requests. Reviewers may meet with the applicant upon request and the NMPA has implemented a new set of meeting guidelines that permit more structured and frequent interactions when issues arise in the development or the registration process.

Priority review is available for certain drugs that treat serious or life-threatening conditions, including new drugs for the treatment of HIV, cancer or orphan diseases, and new drugs that treat unmet medical needs. The NMPA’s new priority categories over the past three years include drugs that treat diseases prevalent among children and elderly people, drugs that are on national scientific research plans, foreign innovative drugs that transfer manufacturing to China, and drugs that are being developed simultaneously in the United


Priority status facilitates applications by allowing the applicant better access to CDE reviewers for their marketing applications and in some cases for questions about their clinical trials. Publicly available information suggests that the fast-track mechanism has, in fact, shortened review times. The timelines for review for expedited programmes under the draft DRR range from 70 to 130 business days.

Renewal application

Under both the revised and prior DAL, the registration for a drug is valid for five years. Six months before expiry of the registration, the applicant must submit a renewal application to the NMPA if it is an imported drug or to the local provincial drug regulatory authority if it is a domestic drug. Renewal applications generally do not require new clinical data, though new testing or data from the required Phase IV study may be a condition of renewal (as discussed above, the NMPA can set conditions as part of the new conditional approval expedited programme). The relevant regulatory authority must complete the review and either approve or deny the application within six months of accepting the filing. If the renewal application is not approved, drugs manufactured after expiry of the existing marketing or manufacturing authorisation may not be marketed in China. The NMPA has now transferred the decision-making power relating to renewal applications for imported drugs to the CDE.55

Supplemental drug application

Certain post-approval changes to a drug, whether imported or domestic, require NMPA approval of a supplemental drug application. Certain changes may require a new drug application, such as a new indication or route of administration. The applicant must be the company that holds the existing marketing or manufacturing authorisation. Under the draft DRR, there would be three pathways for changes, depending on the degree to which they affect the safety and effectiveness of the drug. Major changes would require affirmative agency approval before moving forward, but other changes with less impact would require only a notification or reporting in an annual report.

Devices

Some form of pre-market review and approval is required for domestic production or importation of all three classes of medical devices. Domestic and imported Class I devices must be notified to either the municipal food and drug regulatory authority where the manufacturer is located or the NMPA, if manufactured abroad, before being placed on the market. Once the applicant submits the notification, the authorities will make an ‘on-the-spot’ determination to issue a notification certificate, provided that the materials are complete.

As noted above, domestically manufactured Class II devices must be reviewed and approved by a provincial-level device regulatory authority. Class III medical devices, as well as Class II and III imported medical devices, must be approved at NMPA level. For imported devices, the applicant must appoint a regulatory agent in China.


For all Class II and III devices, government-certified laboratories first verify conformity with the device’s ‘technical requirements’, which the applicant must formulate in advance, and applicable standards through testing. This testing is often referred to as registration testing or type testing. For Class I devices, the applicant may submit its own internal test results. While self-biocompatibility testing has been available for some time, it is not clear whether the revision to the RSAMD will do that more broadly.

The statutory time frame for agency decisions on the different types of devices depends on the class of the device and the type of technical review required. For Class I devices, either the municipal device regulatory authority or the NMPA (if an imported device) will make an immediate determination of the completeness of materials and, if complete, accept the notification. In the case of a Class II or III device, the relevant agency will make a determination as to whether the application is complete and appropriately filed (i.e., the agency has jurisdiction). Within three business days of acceptance of the application, the materials are sent on to a technical review institution, which under normal circumstances has 60 business days to complete its review. If outside expert help is required or the institution decides that it needs to conduct an inspection of the applicant’s quality management systems, then the time may be extended beyond the 60 business days. Similarly, the technical review institution may make a one-time request for any supplementary materials required. It then has another 60 business days from the time of receipt of those materials to make its decision. Once the technical review is complete, the NMPA has 20 business days to make a decision.

The NMPA already gives priority to innovative devices (described below) and, in 2016, as part of its effort to reduce delays and focus its resources on key areas, it issued new procedures on priority review for devices associated with national scientific initiatives, those with orphan indications, those that treat children or elderly people, and other devices that serve urgent clinical needs. Those accepted to these pathways get priority access to CMDE reviewers regarding the design of their application. Similar conditional approval procedures are available for devices that treat orphan indications or meet urgent clinical needs.

After approval, a medical device registration certificate is issued that is valid for five years. Like with drugs, six months before the expiry of the five-year period, the manufacturer must submit a medical device renewal application. If the renewal application is not approved by the time the licence expires, the application will be deemed approved.

Changes to certain elements of the registration require amendments or updates. The type of amendment and the length of review depends on whether it is a ‘licensing matter’ or a ‘registration matter’. Licensing matters include the non-proprietary product name, its model, its specifications, its structure, its composition, its scope of use (indications), its technical requirements and the foreign site of a manufacturer. Registration matters include the name of the applicant, the name of the agent and their addresses. In the case of a domestic manufacturer, the address of the manufacturing site is also a registration item. For

registration items, the original licensing agency will issue a revised licence in 10 business days. Licensing items require another technical review before a modified registration certificate will be issued.\footnote{Articles 49 to 53 of the Measures on the Medical Device Registration (CFDA 2014), available at www.nmpa.gov.cn/WS04/CL2186/300660.html.}

\section*{viii Regulatory incentives}

Chinese regulation is designed, in some respects, to encourage innovation and development and manufacturing of products for which there is a particular clinical need and value through expedited pre-market approval pathways. By contrast, effective post-approval regulatory incentives are weaker and their implementation is incomplete. China has established a system of patent protection for drugs and devices, although recent statistics show that the invalidation rate for those patents is fairly high.\footnote{‘Over 75\% Patents are Invalidated? New Drug Research and Development is Afraid to Fall into the Paradox of Chine Style Innovation’, Zhouhuang Lu, China Intellectual Property Magazine, Issue 137, available at http://www.phirda.com/artilce_18053.html?cId=1.}

Non-patent intellectual property protection does not exist in China. There is no implemented regulatory or market exclusivity, no patent term restoration, and it lacks IPR enforcement mechanisms present in other markets such as patent linkage or early resolution of patent disputes through effective interlocutory relief in the form of injunctions. Until recently, there were patent certification and weak leakage mechanisms in some drug regulations, but the draft DRR removes those protections and, in any event, they have gone unenforced recently.

Under the Innovation Opinion, China committed to implement new incentive systems, including regulatory data protection, patent linkage and patent term extension. The remainder of this section describes the existing system, and the progress that the NMPA and other agencies have made on the other reforms. Similar commitments have now been made in the US–China Phase One Trade Deal.

The promised reforms have slowed significantly since 2017. The new DAL and the draft DRRs contain no mention of these measures, and the explanation to the draft DRRs essentially states that the government is putting those measures on hold for another time. Before this slowdown the following progress was made: under regulatory data protection, innovative drugs (undefined term), innovative therapeutic biologics, orphan drugs, paediatric drugs, and drugs that have achieved a successful patent challenge would receive a certain period of protection for their original undisclosed clinical test data. This would prohibit follow-ons from using that data to apply for marketing permission. As described below, in April 2018, the NMPA released a draft regulatory data protection regulation,\footnote{Draft on the Implementing Measures for the Protection of Trial Data of Drugs (for Interim Implementation) (NMPA 2018), available at www.nmpa.gov.cn/WS04/CL2051/227856.html.} but has done nothing since.

Pursuant to the Innovation Opinion and documents that preceded it, patent linkage will describe a system for resolving patent disputes before the approval of a potentially infringing drug. An applicant would prepare a statement of relevant patents. The applicant would need to give the holder of a relevant patent notice of its application, permitting the...
holder to file a suit within a certain period of time. During that suit or for a certain period, the NMPA would continue its review, but would not issue its approval. To date, no real progress has been made in developing a linkage system.

In early 2019, the National People's Congress issued a proposal for patent term extension as part of a proposed amendment to the Patent Law. Under this proposal, the State Council may decide to grant an additional five years of patent protection to compensate for delays in the review process for innovative drugs that are applying for marketing both in China and abroad. The extension can be up to five years on an invention patent, but in no event amount more than 14 years of protection post-marketing. It is not clear when this will be finalised.

**Drugs**

**Patent protection**

China gives 20 years of patent protection. An applicant is required to provide information on patent status in China as part of its drug registration application. Although the regulations require that if there are relevant third-party patents in force, the applicant must make a declaration of non-infringement, this does not result in patent enforcement because the innovator is given no notice of the declaration and the NMPA does not allow potential patent infringement to halt regulatory approval. This provision is removed in the draft DRR with nothing equivalent in its place. Technically there are also provisions on the books that a follow-on applicant cannot file its registration application two years before the patent's expiry, but this is viewed as in conflict with the equivalent of a Bolar Exemption in the Patent Law, which permits development during the term of patent protection. Therefore, the NMPA does not implement these provisions rigorously, which is part of the reason why the patent linkage reforms set forth above are important.

**Marketing exclusivity**

China does not have true regulatory marketing exclusivity. The DRR provide that the NMPA can set a 'new-drug monitoring period' of up to five years when it approves the manufacturing of a domestic drug that is first in its class. The monitoring period is not available for imported drugs and, within the revised chemical drug registration categories, the monitoring period only applies to innovative new drugs and improved new drugs, which means it only applies if the drug (or its innovation) is new to the world. The monitoring period does not apply to generic drugs. During the monitoring period, the drug is under enhanced adverse event monitoring requirements, and the NMPA is not allowed to approve the clinical trial, manufacturing or importation of another domestic or imported drug in the same class for the same indication. If, however, the approved domestic drug is not manufactured within two years of approval, the NMPA can approve another domestic or imported drug application. The monitoring period does not provide complete exclusivity, however, because if the NMPA

---


62 Article 18 of the DRR.

63 Article 19 of the DRR.
has approved the CTAs of other applicants for the same drug, those applications may proceed to registration. The draft DRR removes the provisions on the monitoring period leaving its continued enforcement in doubt.

**Proposed regulatory data protection**

China issued a draft regulation on regulatory data protection (RDP), which has not yet been finalised. Under this regulation, RDP would run from the time of approval and prevent the NMPA from approving marketing applications from other applicants for the same type of drug that rely on the data of the protected drug, unless there is consent.64

The RDP draft proposed to grant six years of RDP for innovative small molecule drugs and 12 years for therapeutic biologics for which there were trials in China. However, full terms would be further limited to drugs for which the marketing applications are submitted in China before or simultaneously with those in other countries. Applications submitted later in China than in the rest of the world would only receive between one to five years of data protection, and applications relying on foreign data would receive only one-quarter or half of the degree of protection depending on whether they submitted supplementary ‘China clinical trial data’.

**Devices**

The regulations for the registration of medical devices do not require patent certification or contain provisions on data or market exclusivity, and they are not covered by the aforementioned reforms. The revised Measures on Medical Device Registration in 2014 expressly state that any patent disputes will be handled under the relevant laws (i.e., the Patent Law).65 There are procedures for expedited review and approval of medical devices when there is a public health emergency and the same kind of device is not marketed in China, or is marketed but is in short supply. Medical devices undergoing expedited procedures also benefit from assistance from the NMPA during development and registration.66

As discussed above, the NMPA has also created an expedited pathway for review of applications for ‘innovative devices’ in 2014 and amended it in November 2018. To qualify as an innovative device:

a the patent for the technology must be held in China;

b the application for innovative device is within five years after the date of patent authorisation, or if the patent is not granted yet, the National Intellectual Property Administration should issue a research report showing that the core technology has innovation and creativity;

c the primary work on the product’s design and use mechanisms must have been the first of its kind in China;

d its safety or functionality must be a fundamental improvement over comparable technology;

e it must be leading technology internationally;

f the device must have clear clinical value;

---


65 Article 48 of the Measures on Medical Device Registration.

preliminary research must be complete, traceable and there must be a basic product model; and

the data must be complete and traceable.67

The innovative device pathway does not entitle applicants to marketing exclusivity, however. It provides the applicant with priority in terms of access to communication with the NMPA regarding its application and the ability to hold a licence without a manufacturing facility. As noted above, the NMPA has recently released procedures on additional priority pathways, which are based on more on clinical needs and not other IP-related criteria. Conditional approval is also available for certain devices.

ix Post-approval controls

Adverse events

Drug and medical device manufacturers are obligated to establish systems to report and analyse adverse reactions and events and product complaints, and meet any conditions imposed as part of the product approval.68 In 2011, the NMPA issued detailed regulations on adverse reaction and event reporting for drugs and devices. The Measures on the Administration of Adverse Drug Reaction Reporting and Monitoring (2011) require drug regulatory authorities at national, provincial and municipal levels to set up adverse event collection systems, and impose reporting and monitoring obligations on not only the drug manufacturer, but also drug distributors and healthcare organisations. Specific reporting time frames and follow-up actions are set out for handling individual cases, clusters of cases, periodic accumulative reporting, enhanced monitoring and imported drug reporting.69

For medical devices, the NMPA issued revised Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation in August 2018,70 and the ADR Centre subsequently issued multiple guidance documents for comment shortly thereafter.

The reporting obligations under the new regulations remain similar (albeit with different timelines for reporting), serious adverse events and group adverse events. However, the new regulations also introduced a category of innovative medical device events. For ‘innovative devices’ (a term that is not yet clearly defined, but may mean those devices that have not yet been approved anywhere in the world), licence holders are required to report all adverse events for the first five years of the their device licence. The new regulation also requires biannual reports of events for innovative devices.

The new regulations also include various other new individual and periodic reporting obligations. Some of these require reporting in a matter of hours after becoming aware of the event. For example, they require yearly risk assessments for devices. If there is a group event, it must be reported within 12 hours and each individual event must be reported within 24 hours of awareness. If a licence holder takes action to control a device event abroad (e.g.,

68 See, e.g., Articles 41 to 44, 67 to 68, 121 and 169 of the DRR, and Article 47 of the RSAMD (requires manufacturer to establish device AE reporting system).

© 2020 Law Business Research Ltd
recall, market withdrawal, re-labelling), they are expected to notify the NMPA of an action plan for devices in China within 24 hours. These and other new, more intense requirements colour this new regulation, which went into effect on 1 January 2019.

The licence holders are obligated and the NMPA has the authority to order recalls of drugs and medical devices because of serious adverse reactions or events or other safety issues. Under new device recall regulations released in 2017, the NMPA can order a mandatory device recall for both safety and non-safety related issues, including if the device presents a risk of unreasonable harm, does not meet mandatory national standards or its own technical requirements (i.e., specifications), or violates good manufacturing or distribution practices in a way that causes unreasonable harm. This and other similar triggers have expanded the scope of recallable products.

Manufacturers and distributors also have different obligations, in varying circumstances, to cooperate with, report on or implement recalls. For example, for medical devices, the manufacturer is required to conduct an investigation and evaluation of adverse event and other safety-related information to determine whether they reveal a ‘defect’. The manufacturer must also classify the recall into one of three classes – the first class being the highest risk and the third being the lowest. The class will determine reporting obligations and timelines. If a manufacturer does not conduct a recall voluntarily, the NMPA may order one if it disagrees with the manufacturer. The manufacturer must report on the progress of the recall and its final results.

The new DAL stresses various aspects of post-market surveillance on the part of the obligations of MAHs, contract manufacturers and distributors. The DAL promises a more stringent regime for reporting and evaluating adverse drug reactions, and pulling products off the market for which there are serious reactions. MAHs are also required to develop post-market risk mitigation plans and file annual safety reports. Although the draft DRR does not cover adverse event reporting, the NMPA and CDE will likely soon develop implementation rules and guidance documents.

**Transfer of licences**

Transfer of licences may be more difficult to achieve in China than it may be in other countries. Part of the reason is that NMPA regulations give limited guidance on this issue and regulatory changes have created further uncertainty. Another reason at least for domestic products is because of the connection between the product permission and the manufacturing facility permissions. The revised DAL now expressly states that the transfer of marketing authorisation is permitted, provided it is approved by the NMPA and the transferee agrees to assume obligations for safety, effectiveness and quality.

Previously, for domestically manufactured drugs, licences were issued to the specific manufacturer for the specific manufacturing site. As a result, any transfer required a transfer of ownership of the site because the two were bundled together. This was usually done via an equity acquisition of the holder of the two licences, because NMPA regulations had specifically prohibited any ‘purchase and sale, rental, or other loan of the licences’. Under the pilot MAH system, the marketing authorisation was transferrable as it now is in the DAL.

---

71 The Measures on the Administration of Drug Recalls were promulgated in 2007, and the Measures on the Administration of Medical Device Recalls (Interim) were promulgated in 2011 and amended in 2017.
For imported licences, the situation was somewhat different because there was no manufacturing licence. Thus, the licence was permitted to be transferred by a procedure to change the name of the holder, and the manufacturing site could be changed via a supplemental application to the licence.

These issues are somewhat different regarding devices. The facilities still require manufacturing licences but, in contrast to drugs, the NMPA also issues product licences for domestic devices. Therefore, for both imported and domestic devices, the NMPA has permitted the Class II and Class III device product licences to transfer between entities using an application to amend the name of the applicant on the licence. For Class I devices, the new applicant is likely to submit a new filing, which could be accomplished relatively quickly. The applicant may have to make other changes to items on the licence, such as the registration agent and the manufacturing site, through product licence amendment procedures, depending on the details of the deal.\(^72\)

There are more specific provisions on the transfer of device manufacturing licences. Under the revisions to the Device Manufacturing Regulations, the manufacturing licence travels with the entity. If the entity survives a merger or split, then the licence need only be modified. If the original entity is dissolved, then the licence will not be transferred and any new entity must apply for a new licence.\(^73\)

**Suspension or revocation of approvals**

The NMPA has broad authority over licences, their approval, their renewal every five years and their cancellation on the basis of safety concerns or fraud. This discretion extends not only to product licences but also to facility licences, accreditations and clinical trial approvals. For example, the NMPA has a number of grounds for revoking or refusing to renew a product licence under the current and draft DRRs as follows:

\(^{72}\) Articles 49 to 50 of the Measures on Medical Device Registration; Article 15 of the Measures for the Supervision and Administration of Medical Device Manufacturing (CFDA 2017), available at www.nmpa.gov.cn/WS04/CL2186/300702.html. For imported devices, a change of a manufacturing address abroad is a more complex process that requires the submission of more information and a longer timeline.

\(^{73}\) Article 18 of the Measures for the Supervision and Administration of Medical Device Manufacturing (CFDA 2017).
For devices, a renewal will not be granted if: (1) the filing of the application is not timely; (2) compulsory standards for the medical device have been revised and the device fails to meet the new standards; and (3) specific conditions related to medical devices needed for treating rare diseases or for public health emergencies are not met.  

Second, there are several types of non-compliance that can trigger licence suspension or revocation in China. For example, the revised DAL provides for the revocation of drug approval licences on various grounds, including:

- production or sale of counterfeit or substandard drugs;  
- obtaining a licence through fraud, including the submission of false materials;  
- conducting a clinical trial without approval;  
- producing a drug with ingredients or packaging materials that have not been reviewed; or  
- non-compliant labels.

The RSAMD provides for the re-evaluation and potential revocation of medical device licences when:

- new developments in science and technology raise questions about the safety and effectiveness of the device;  
- adverse event reporting raises questions about the safety and effectiveness and indicates that there is a defect; and  
- any other circumstances that the NMPA determines warrant a re-evaluation.

These grounds are echoed in the new adverse event reporting regulation for the devices discussed above. The revised RSAMD provides that obtaining a licence via fraudulent or corrupt means is a basis for revocation of the licence. Other activities that constitute impermissible marketing of devices or marketing of devices known to be unsafe or not in compliance with standards may result in fines, seizures, disgorgement and, in certain circumstances, blacklisting from the industry.

In September 2017, the Supreme People’s Court issued an interpretation as to certain provisions of the PRC criminal law to apply them to circumstances in which a drug or medical device application is procured by making fraudulent misrepresentations or using fabricated data. This allows for the criminalisation of data integrity violations that are the result of intentional misconduct.

---

74 Article 55 of the Measures on Medical Device Registration.  
75 Articles 116 and 117 of the DAL.  
76 Article 123 of the DAL.  
77 Article 125 of the DAL.  
78 id.  
79 id.  
80 Article 51 of the RSAMD.  
81 Article 64 of the RSAMD.
x Manufacturing controls

As discussed above, drugs and Class II and III device manufacturing facilities located in China must hold a manufacturing licence, and observe drug or device GMP. Class I device facilities submit a notification to local food and drug regulatory authorities before proceeding with production.

Upon completion of the facility construction, the facilities must obtain a manufacturing licence and pass GMP inspection before they can be issued a drug or medical device manufacturing licence.

Class II and Class III device facilities must be verified as device GMP-compliant before a local authority will issue a manufacturing licence. This requires a compliance inspection.82 If any manufacturer is found to be non-compliant with the rules, and does not correct the violation, it can be fined or shut down.83

Contract manufacturers must be similarly GMP-compliant and hold the requisite manufacturing licence. In some circumstances, in which the NMPA has determined that the products present heightened risk, such as in the case of psychotropic drugs or narcotic drugs, the agency will not permit contract manufacturing.84 Under the revised DAL, contract manufacturers and MAHs must execute supply and quality agreements meeting the obligations of each. The NMPA will release guidance on these agreements and their content, which it will have the power to inspect. In addition, the DAL creates a class of separate obligations for CMOs: establishment of a quality system, implementation of quality control and release procedures, supplier verification, traceability, storage, product labeling, adverse drug reaction monitoring and reporting and recall implementation.

Import manufacturers are also required to comply with GMPs for drugs or devices, as the case may be. The NMPA monitors compliance with all facilities that support the products that it licenses through inspections. Inspections may be for cause and announced or unannounced. In some cases, the regularity of inspections is risk-based. For example, for device manufacturers, the NMPA and its local counterparts set a risk level that determines the number of inspections during a specific period. The NMPA also conducts inspections of facilities abroad for compliance with China drug and device GMPs, although it is not entirely clear what determines the need for these inspections. The NMPA finalised new regulations on overseas inspections for drug and device manufacturers in late 2018. As the draft DRR now abolishes distinctions between imported and domestic products in many ways, the imported products may be subject to the manufacturing site inspections that are part of the registration inspection chapter.

82 Article 10 of the Measures for the Supervision and Administration of Medical Device Manufacturing.
83 Article 67 of the RSAMD; Article 67 of the Measures on the Supervision and Administration of Medical Devices Manufacturing.
**Advertising and promotion**

**Drugs**

**Advertising**

The NMPA must pre-approve all drug advertising and prohibits any direct-to-consumer advertising of prescription drugs. The term ‘advertising’ is broadly defined under the general Advertisement Law and can include any published media that directly or indirectly introduces the product (or service). As a result of amendments to the Advertisement Law in 2015 and the interim regulation on internet advertising in 2016, the legislature has made it clear that the definition of advertisement includes websites, mass emails and postings on microblogs and other social media sites.\(^{85}\) Other rules have indicated that various media and promotional activities as examples, including product samples. Therefore, there is ample authority on which agencies can enforce against sponsors. Promotion or advertising of a drug before NMPA approval is prohibited, although some limited scientific exchange may be permissible.

The SAMR issued an agency-level advertising rule covering all drugs, medical devices, health foods and foods for special medical purposes (new Advertisement Rule) in December 2019,\(^ {86}\) which replaced but adopted the principles of the drug-specific advertisement requirements and prohibitions previously provided in a number of laws and regulations, including the Measures for Review of Drug Advertisement (the Advertisement Measures) and the Standards for Drug Advertisement Review and Release (the Advertisement Standards), both of which will be repealed when the new Advertisement Rule becomes effective in March 2020.

The provincial drug regulatory authority where the advertiser is located must review and approve all drug advertisement materials. Article 2 of the new Advertisement Rule provides that advertisements of prescription drugs can only run in NMPA and NHC-approved medical journals (of which there are over 500). The prohibition on consumer advertising of prescription-only drugs also prevents many indirect advertising activities, such as sending journals or reprints to the public, or any other means of advertising to the public.

Upon approval, drug advertisements are given an approval number, which appears on the advertisement. Advertisement approval is valid consistent with the shorter of the validity period of the product registration/filing or manufacturing licence, or for two years if there is no validity period for the product registration/filing or manufacturing licence. Upon the approval’s expiry, or if any change is needed to an approved and unexpired advertisement piece, a new advertisement application must be filed and new advertisement approval should be obtained. The NMPA has posted on its website all advertisements that have been approved and those against which there has been enforcement.

China prohibits advertising outside the content of the approved scope of use of the product in the registration documents and label or package insert (off-label promotion). The prohibition against off-label advertising is set out in Article 6 of the Advertisement Standards and Article 5 of the new Advertisement Rule:

---


The drug advertisement relating to the indications or the primary therapeutic functions . . . must not exceed the scope of the drug instructions.

The DAL also technically prohibits off-label promotion through its anti-counterfeiting provisions. The Anti-Unfair Competition Law (AUCL) contains prohibitions on false or misleading promotion that have been used to limit or penalise off-label conduct.

Some penalties for an unapproved advertisement include hefty fines in the hundreds of thousands of dollars, immediate revocation of the advertisement approval, and rejection of any advertisement application for the subject drug for one year. Heavier penalties would apply in the event that an illegal advertisement expands the scope of the indications or primary therapeutic function, exaggerates efficacy or seriously deceives and misleads consumers. Heavier penalties include the provincial authority suspending the sale of the subject drug within the province that has jurisdiction, and ordering the drug company to run corrections regarding the advertising concerned. Criminal penalties may be available in extreme cases.

Promotion
The term ‘promotion’ is not defined under Chinese law. Any activity related to a drug is promotional, if, objectively, the intent is promotional as the term is commonly understood (i.e., where it is intended to further the acceptance and sale of the drug). This includes a broad array of product launch activities and associated materials. China has other laws that govern promotion and require that it be generally truthful and non-misleading. As discussed, these include the AUCL and the Law for the Protection of the Rights and Interests of Consumers (Consumer Protection Law). The AUCL is often a basis for enforcement by the new Market Supervision Bureaus, which have been combined with the drug regulatory authorities and investigate promotional violations, including violations of off-label promotion. There is no clear distinction between what constitutes promotion under these laws and what constitutes advertising under the Advertisement Law, even though the AUCL does appear to indicate that there is a distinction.

As noted above, scientific information exchange, including exchange of off-label information, may be viewed as non-promotional with somewhat less risk when conducted appropriately, because the intent is to advance science and medicine through the exchange of scientific information between medical professionals, rather than to further the acceptance or sale of a drug.

Devices
Device advertisements also require pre-approval. Regulation of advertising and promotion of medical devices is similar to that for drugs, as described above. The rules for advertising and promotion of medical devices are set out in several regulations, such as the RSAMD, the Measures on the Examination of Medical Device Advertisements (2009) and the Standards on the Examination and Release of Medical Device Advertisements (2009), both of which, like the drug standards, will be repealed as a result of the new Advertisement Rule in March 2020. Device promotion is also subject to the AUCL and the Consumer Protection Law. A recent proposal to amend the RSAMD would eliminate the device advertisement approval requirement, but has not yet been finalised.
Distributors and wholesalers

China requires a company to have a licence to engage in the retail or wholesale distribution of drugs that are manufactured by other companies. No distribution licence or other permission is required for a drug MAH or drug or device manufacturer to distribute the products that it manufactures for itself, provided that it is not for retail and specified distribution conditions are met. Both drug and device distributors must meet respective sets of good supply practices.87

The system of device distribution licences also exists for Class III medical devices. Distributors of Class II devices no longer need a licence, but those distributors must submit a notification to their local municipal governments – a recent proposed amendment to the RSAMD would eliminate even this notification requirement. In either case, the entity must certify that it has appropriate premises, storage conditions and quality management systems, and personnel for its scope of operation.88 Class I device distributors do not require any licence or filing. Under proposed legislation, distribution of certain Class II devices (which include many everyday items, such as condoms) may no longer require a filing.

In 2017, China released a policy for drugs called the Two Invoice System. The aim is to curb corruption in the drug supply chains, and the system limits those supply chains to two invoices. In other words, once the product leaves the manufacturer or the manufacturer’s agent, there may be only two invoices, one from the manufacturer to the distributor and one from the distributor to the end user hospital. Those in the supply chain are required to check the invoices, and failure to observe the policy can result in blacklisting from important procurement processes or loss of distribution credentials. There are some limited exceptions to this system, such as for transfers between entities in the same corporate group or to exclusive distributors, or under some provincial rules, registration agents. Certain provinces have expanded the system to devices. In November 2019, the Leadership Group for Deepening the Medical and Health System Reform of the State Council issued a notice that further encourages some pilot provinces to implement a One Invoice System from 2020, which means there will only be one invoice from the manufacturer to the medical insurance administration agency for certain drugs that fall into the scope of the centralised procurement programme, which is discussed below.89

Prescription status

The NMPA classifies drugs as prescription drugs or over-the-counter (OTC) drugs, and requires the NMPA’s review and pre-approval for both. For the purposes of distribution and sale, the NMPA further classifies OTC drugs into Type A or B, where Type A drugs can be sold only by pharmacies or distributors that have received drug wholesale or retail distribution licences, and Type B drugs can be sold at most retail outlets, such as convenience or grocery stores, if approved by provincial governments. The NHC regulates prescribing behaviour for physicians, including a requirement that physicians use the non-proprietary names of drugs. The NMPA has not set up prescription or non-prescription classifications for medical devices, but pursuant to their approvals some devices may only be sold to and used in medical institutions.

---

88 Articles 29 to 31 of the RSAMD.
Imports and exports

In addition to the product licences for imported drugs and devices, there can be a variety of additional requirements and formalities at the ports. For example, special import or export permits are required for certain narcotic or psychotropic substances.\textsuperscript{90} Drugs that are imported for processing and re-export may not require NMPA pre-approval; only provincial drug regulatory authority notification is required for such products provided they will not be sold or used in China.\textsuperscript{91} Additional testing at the border is required, except in the case of oncology drugs pursuant to a special policy by the State Council from 2018.\textsuperscript{92}

Under the revised DAL, importation of unapproved drugs has been removed from the definition of counterfeit drugs. Later provisions reduce penalties for the importation of small amounts of unapproved drugs. This was seen by many as providing flexibility for individuals to import low-cost generics for personal use from other countries.

The NMPA generally does not impose the same requirements for exporting drugs or devices and relies instead on the regulatory oversight of the country of destination. Manufacturers of exported drugs and certain devices must still obtain a manufacturing licence and comply with good manufacturing practices and standards. There are exceptions for nine types of drug\textsuperscript{93} and two types of device,\textsuperscript{94} which the NMPA has placed into the catalogue of drugs and devices subject to full NMPA supervision.\textsuperscript{95} In addition, special export permits are required for exporting some narcotics or psychotropic substances. In most cases, drug and device manufacturers must also submit a filing to their local government before export.\textsuperscript{96} Certificates of free sale for foreign import authorities may be available from provincial governments, provided that the China manufacturer meets the relevant requirements.

Controlled substances

China exercises heightened control over narcotic and psychotropic drugs. The State Council promulgated the Rules on the Administration of Narcotics and Psychotropics, which provide separate rules on these products. The NMPA, the Ministry of Public Security, and the National Health Commission recently jointly issued the revised Catalogue of Narcotics and the revised Catalogue of Psychotropics. Special heightened control is exercised by several government agencies regarding the growing of plants from which narcotics or psychotropics are extracted, and the clinical trialling, manufacturing, transportation and distribution of narcotics and psychotropics. For example, government agencies set the total amount of narcotics and psychotropics needed annually, and the NMPA then sets the annual production plan based

\begin{itemize}
\item Article 66 of the DAL.
\item Gentamicin, atorvastatin, sildenafil, oseltamivir, cefoperazone, glycerine, heparin, artemisinin and traditional Chinese medicine in finished dosage form and indicated for erectile enhancement.
\item Glucose-testing strips and condoms.
\item Article 3 of the Administrative Regulations on Filings for Contract Manufactured Drugs for Foreign Enterprises (CFDA 2005), available at www.nmpa.gov.cn/WS04/CL2196/323528.html; Article 70 of the Measures on the Supervision and Administration of Medical Devices Manufacturing.
\end{itemize}
on the current supply and stockpile. The NMPA and the department of agriculture jointly set
the annual growing plan. Special permits are given only to limited entities to study, produce
and distribute narcotic and psychotropic drugs.

**xvi Enforcement**

Overall the enforcement environment has become stricter. New legislation has raised
penalties significantly and the NMPA and the local MPAs have come to expect significantly
more sophisticated regulatory compliance systems and activities from drug and device
manufacturers. The NMPA has also introduced provisions into regulations that make
enforcement easier, such as requiring strict compliance and demanding recalls for
non-compliance with thousands of mandatory standards.

Enforcement against violations of drug or medical device requirements is undertaken by
the drug regulatory authorities at national, provincial and lower local levels, with cooperation
from other government agencies such as the SAMR, NHC and the public security bureau
(China’s police force) at all levels of government. Routine and for-cause inspections and
investigation of complaints by competitors and individual consumers are the primary means
of detecting actual or suspected violations, and complaints from competitors are often the
triggers for for-cause inspections. The NMPA has also adopted comprehensive regulations on
unannounced inspections for drug and device manufacturers.

The focus of inspections can include many compliance requirements and activities, such
as those targeting good practice (laboratory, clinical, manufacturing, storage), data integrity,
conflicts of interest, bribery, violative advertisement and off-label promotion. The penalties
include revocation of licences and certificates, which can be imposed (see Section II.vii) on
post-approval controls in many more situations than in the United States. Other penalties
include administrative fines, seizure of products, disgorgement of profits and blacklisting of
companies and individuals. Monetary penalties are increasingly high. Criminal liability can
be imposed for many violations, and disbarment from engaging in drug or device work is
possible. Production or distribution of counterfeit medicines as defined by the DAL may be
subject to life in prison or the death penalty if the violation causes death or especially serious
harm.97

Increasingly, the NMPA has been requiring manufacturers, distributors and clinical trial
sponsors to conduct self-evaluations into good practice compliance and report on the results
to the NMPA. For example, in mid-2016, all holders of device distribution licences were
required to take stock of compliance with device distribution regulations and good storage
practice (GSP) over a two-year period and report back to the NMPA on any non-compliances
and plans for remediation. Failure to comply risked the holder’s distribution licence.98 The
NMPA required similar self-evaluation for drug clinical trials in 2015 and has continued
rigorous self-evaluation and trial inspection requirements to the present. Holders of CTAs
are required to review for compliance with GCP. The original self-evaluation resulted in the
withdrawal of nearly 80 per cent of the trial approvals for non-compliance.99

97 Article 141 of the Criminal Law of the People’s Republic of China.
98 Notice on Regulating Distribution Activities in Medical Device Circulation (CFDA No. 112 of
99 Eighty Percent of New Drug Data is Fraudulent, Where are the Flaws in the Research Environment?
In 2018 and 2019, the NMPA also issued notices reinforcing its ability under various drug, device and cosmetic regulations to enforce fines and debarment sanctions against individuals. In a growing trend, legislation, including recent drafts of the RSAMD and the revised DAL, has included provisions against responsible individuals in addition to increased fines for entities. This included holding individuals accountable for falsification of clinical data as discussed above. Both the revised DAL and the proposed drafts of the RSAMD include greater penalties against individuals, such as lifetime debarment for serious violations.

III PRICING AND REIMBURSEMENT

China has recently begun to reform its system for drug pricing. Specifically, it has abolished the ‘maximum retail price’ for drugs, and is now implementing a plan to permit those prices to be set more by the market and by reimbursement standards negotiated more openly by stakeholders. Specifically, for drugs that are reimbursed on China’s state insurance plans (discussed below), the price will be determined by reimbursement rates. For patented drugs produced exclusively by one manufacturer, the price will be set through transparent negotiations between the manufacturer, government and healthcare industry representatives. Prices will still be set or guided by the government for certain types of drugs, such as narcotic drugs and psychotropic drugs. For all other drugs, however, the prices may be freely set by the manufacturers, provided that they accurately reflect costs.

Most insurance is through state plans. The government operates three basic insurance programmes: one for urban employees, one for urban non-state-employed residents and one for rural residents, covering nearly 90 per cent of the nation’s population. Covered drugs for the urban plans are included in the National Reimbursement Drug List (NRDL), which has a total of 2,709 drugs in its most recent version, which the government revised in November 2019 and will update once a year. Newly approved drugs are eligible to be included in the NRDL of the next year, which will be effective from 1 January of the following year. For example, to be included in the NRDL of 2019, which will be effective from 1 January 2020, the drug must be approved prior to 31 December 2018.

The National Healthcare Security Administration makes the decision to include a drug in the NRDL. In doing so, it will seek public comment, organise an expert review, select the drugs and vote on inclusion. It will then negotiate with drug companies for partial candidate products. Drug companies cannot apply to be included in the NRDL, although they will need to submit documents when their products are selected as candidates. The covered drugs for the rural plan may vary by province. In 2018, the State Council announced that it would fast-track inclusion of imported oncology drugs into reimbursement catalogues.


102 id.
Seventy drugs were newly added in 2019, through successful negotiation of an average price cut of 60.7 per cent by the National Healthcare Security Administration with the various drug companies.\(^{103}\)

The NRDL is categorised into two lists. Drugs on List A are the National Essential Drug List and are fully reimbursable in any province. Drugs on List B are only partially reimbursable under various insurance schemes at provincial level. Reimbursement rates for the drugs on the NRDL are determined by government agencies based on various factors, including cost of production, clinical need, and supply and demand. Pricing and reimbursement decisions are now taken primarily by the new National Healthcare Security Administration, as well as the Ministry of Human Resources and Social Security. In early 2019, for the purpose of reducing drug prices, the State Council started a pilot programme in four municipalities and seven cities that requires centralised procurement through a bidding or negotiation process of certain selected drugs for which the generic drugs have proven their therapeutic and quality equivalence to corresponding reference products.\(^{104}\) The winning product, normally the one with the lowest price offered, will take 60 to 70 per cent of the volume of such type of product purchased by state-owned hospitals for the following year. The pilot programme continued to evolve and was later expanded to the entire country with the winning products taking 50 to 80 per cent of the market share in state-owned hospitals (depending on how many products won the bidding). Although currently this centralised procurement programme does not apply to new drugs with valid patents, Wuhan is conducting a pilot programme to expand it to those drugs as well.\(^{105}\)

By contrast, the commercial insurance sector is smaller, but steadily developing.\(^{106}\) For example, the government has been trying to promote critical disease insurance for individuals who have exceeded their coverage level under the state plans. Individuals with qualifying diseases that obtained critical disease coverage would be eligible for 50 per cent reimbursement under those plans. The government has encouraged the commercial insurance sector to play a strong role in providing this type of coverage.\(^{107}\)

A pricing system also exists for medical devices, but its features may differ depending on the locality. In some localities, the government will set a maximum retail price for devices. The manufacturer reports information about its costs to the government and is then permitted a certain mark-up that is set by the government.

As with drugs, coverage by the national plans and reimbursement rates for medical devices are set by a combination of central and local government agencies. Medical institutions (i.e., hospitals and clinics) acquire devices through restricted procurement processes.

---


105 See https://med.sina.com/article_detail_103_1_74900.html.


IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Administrative and judicial remedies are available in China to appeal agency decisions and redress illegal government practices. Administrative regulations are rarely challenged in the courts for alleged defects in the underlying authority or rule-making procedures because China’s Administrative Litigation Law prohibits ‘abstract’ challenges of this sort to the validity of administrative rules. Most efforts to formally challenge the NMPA focus on challenging concrete NMPA administrative decisions instead. Processes are available for both administrative reconsideration and judicial review of administrative decisions, but it may be difficult to win controversial cases in court in the absence of a clear violation by the agency of laws, regulations or its own rules.

i Administrative reconsideration

When an applicant is not satisfied with a government agency’s decision, the applicant may file an administrative reconsideration request for review by either the government agency itself or its supervising ministry or department within 60 days.108 To file an administrative reconsideration request challenging a NMPA decision, the applicant must have legal standing to do so. The complaint must name the respondent and the specific decision the applicant is challenging.109 Permissible grounds for reconsideration are:

- the agency’s fact-finding on major issues is incorrect and evidence is inadequate to support the decision made;
- the law was erroneously applied;
- the agency violated relevant statutory procedures;
- the agency exceeded its authority or abused its power; or
- the decision was obviously inappropriate.

A special division within the NMPA is responsible for handling administrative reconsideration requests (the Administrative Reconsideration Office (ARO)) to challenge decisions made by the NPMA itself or its local offices. For complex cases and cases involving a challenge to underlying laws or regulations, the Administrative Reconsideration Committee (ARC), which consists of the commissioner and deputy commissioners of the NMPA and ranks higher than the ARO, will hear the case.

The ARO or ARC will examine the request and decide within five days whether it meets the requirements for reconsideration.110 If so, it will be accepted for review and the ARO or ARC is obliged to render a decision within 60 days. If the situation is complicated, the time for review may be extended by a maximum of 30 days. The ARO or ARC may affirm the administrative decision, or overturn it and remand the matter to the government agency with instructions to take either a specific or an alternative administrative act. The decisions made

---

by the ARO and ARC are legally effective upon the signature of the head of the NMPA. The applicant can appeal an ARO or ARC decision to the State Council, whose decision is final, without the availability of judicial review.

The draft DRR has proposed a new dispute resolution mechanism related to drug applications. When an applicant disagrees with the CDE’s rejection of its application, the CDE will organise an expert committee within 50 business days to review the conclusions and make a recommendation. If at any time during the registration period the applicant believes that a decision has not been objective or impartial, the applicant can file a complaint to the entity involved or its acceptance and complaint centre, which will handle that complaint according to internal procedures. Applicants have access to standard administrative reconsideration and litigation procedures thereafter.

**ii Judicial lawsuit**

If an applicant decides not to appeal the ARO or ARC’s decision to the State Council, it may bring a judicial lawsuit in the People’s Court against the ARO. If the People’s Court finds that any of the following conditions are met, then the administrative act must be annulled or partially annulled, or the defendant must be ordered to take another alternative administrative act:

- the major evidence was inadequate;
- the administrative agency erroneously applied the law or regulations;
- the administrative act violated legal procedures;
- the administrative act exceeded authority;
- administrative power was abused; or
- the administrative act was obviously inappropriate.

**V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS**

China has enacted laws and regulations to prohibit bribery, kickbacks or other inappropriate financial relationships or sponsorship. The revised DAL still contains these provisions, and penalties for violations could include revocation of the drug or medical device approvals, civil fines and criminal penalties. In addition, the SAMR administers the Anti-Unfair Competition Law and regulations against commercial bribery. Bribery cases may also be handled through the criminal justice system. Scrutiny of these activities has grown substantially in the past few years since the government launched anti-bribery investigations of foreign drug manufacturers.

---

111 Article 17-20 of the Administrative Reconsideration Measures of the CFDA.
The fallout from those investigations has resulted in much more significant scrutiny of the relationships between drug companies and healthcare providers by regulators in China. The NHC issued a policy of ‘Nine Prohibitions’ (or bad acts in the healthcare system) that would be the focus of government scrutiny and enforcement resources, as well as blacklisting rules meant to curb ethical abuses in the healthcare sector. The Nine Prohibitions are:

- no linkage between healthcare provider incomes and profits from drug sales or medical services;
- no rebates for prescribing medicine or referrals for services or drugs;
- no overcharging of patients;
- no acceptance of illegal donations;
- no illegal advertisements or promotion of drugs, devices, food or other products by medical institutions or healthcare providers;
- no collation of statistics for commercial purposes or personal gain by healthcare providers;
- no private buying or selling of drugs, devices or other equipment by healthcare providers;
- no acceptance of kickbacks or commissions from healthcare companies or engagement in entertainment activities provided by those companies; and
- no solicitation or acceptance of financial benefits from patients.  

In late 2013, nine agencies, including the NHC and NMPA, issued a joint opinion (a blueprint of sorts) intended to create higher standards for ethical conduct by physicians and other hospital personnel in their dealings with the drug industry. The opinion also mentioned higher standards for safety for medical devices but singled out corruption associated with drugs as the primary target.

Scrutiny in this area continues to be very significant and regulatory reform is continuing. In late 2014, the NHC issued measures on clinical research projects at medical and other health institutions, which, among other things, called for stronger clinical research and ethics committee management of these projects, and guidelines for financial management intended to prohibit payments directly to investigators.  

To further control improper incentives given by the drug industry to Chinese hospitals, in 2015, the NHC released regulations further circumscribing donations to healthcare institutions, emphasising that all such donations must have an acceptable charitable purpose and that charities (all donations must flow through approved charities) must conduct a thorough review of the donor and the plan for the donation itself. Anti-corruption investigations and physician kickbacks continue to be significant issues in China.

As discussed above, the NMPA and other agencies have been taking measures to curb corruption in other ways. These include the Two Invoice System, discussed above, aimed at

---

reducing corruption by slimming down distribution chains. There are also new measures on medical representatives, which require a separation between medical affairs representatives and salespeople, and a registration system that makes that separation more visible.

In 2017 and 2019, China revised the AUCL, and the 2017 revision contains a new and arguably expanded concept of what constitutes commercial bribery and increased penalties. This adds another tool to combat corruption in this space.

In December 2017, building upon the Innovation Opinion and other related policies, the NMPA issued proposed rules on medical representatives. These proposed rules were an effort to separate sales from what the NMPA called ‘academic promotion’. This appears to have been intended to reduce corruption and illegal forms of promotion in medical institutions. To date, the rules have not been finalised.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Compensation can rely on provisions specifically on drugs and devices in the Tort Liability Law, and perhaps on provisions in other laws, such as the Consumer Protection Law, the Product Quality Law and the Regulations on Medical Disputes. The Regulations are currently under revision. For example, a draft amendment of the Consumer Protection Law was released in 2016 and the Product Quality Law has just been amended in December 2018. Compensation is available when the product is defective or not made in accordance with compulsory national standards. Drugs or medical devices can still cause injuries in the absence of product defects or medical malpractice, but no special strict liability has been set up for compensation under such circumstances.

The newly revised DAL adopts a principle of joint liability common to other areas of Chinese law under which a patient can bring suit against the MAH, the manufacturer, the distributor or the hospital and those entities must accept responsibility and defend the suit regardless of fault. They can later be indemnified by the true responsible party.

VII CURRENT DEVELOPMENTS

Since the Innovation Opinion China has gradually revised its framework laws and regulations for drugs and devices. The newly revised DAL and subsequent implementation proposals were the central developments in 2019, and that implementation will continue throughout 2020. A newly revised RSAMD is also expected in early 2020.

China also continued to expand its place internationally with respect to drug development. The NMPA joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017 and was elected as a representative of its Management Committee of ICH in June 2018. The CDE continued with its programme to train reviewers and translate and adopt ICH guidance documents.

China continued to approve a number of innovative products, including over 50 innovative small molecule drugs and therapeutic biologics, slightly more than the US FDA approved the same year. Stakeholders can expect that China will continue to expand its policies to encourage innovation and to bring clinically needed drugs to China.

I  INTRODUCTION

The Czech Republic’s pharmaceutical market value (Rx, OTC and food supplements) increased by 5 per cent in 2019. The pharmaceutical industry in the Czech Republic is dominated by foreign global players such as Novartis, Sanofi, Roche, Pfizer and Teva.

The Czech pharmaceutical market is strongly dominated by large pharmacy chains which are often combined with wholesale operators within one business group, such as the Dr. Max chain, with more than 400 pharmacies, and the wholesaler ViaPharma, both of which are controlled by Penta Investments, and the BENU chain of pharmacies, which is part of Phoenix Group.

The Czech Republic, as an EU Member State, has implemented the relevant EU regulation related to medicinal products, namely Directive 2001/83/EC on the Community code relating to medicinal products for human use, and the rules and regulations governing medicinal products included in EudraLex. In domestic law, medicinal products are, in particular, regulated by Act No. 378/2007 Coll., on pharmaceuticals (the Pharmaceuticals Act) and by related implementing regulations and guidelines.

The rules governing medical devices are newly set out in Regulation (EU) No. 2017/745 (MDR) and in Regulation (EU) No. 2017/746 on in vitro diagnostic medical devices (IVDR), which will apply from 26 May 2020 and 26 May 2022 respectively. As both the MDR and the IVDR constitute EU law directly applicable in individual Member States, no further legal transposition into Czech law is necessary. Nevertheless, a new Medical Devices Bill implementing the MDR is currently being prepared, while in future the existing Medical Devices Act (Act No. 268/2014 Coll.) will regulate only in vitro diagnostic medical devices. Simultaneously, new regulation on the advertising of medical devices, similar to the regulation concerning medical products, is being introduced.

On 1 January 2019, a new regulation on the reimbursement of medical devices prescribed by public health insurance took effect. The crucial date was 1 June 2019, when the relevant medical devices had to be reapplied for under the new reimbursement system.

The main supervisory body for both human medicinal products and medical devices in the Czech Republic is the State Institute for Drug Control (the Institute). The Institute supervises all aspects of how human medicinal products are handled. The activities of the Institute include monitoring the quality, safety and efficacy of medicines at all stages of their development and use, including how they are advertised. Similarly, the Institute monitors

---

1 Kamila Seberová is counsel at Wolf Theiss.
the use of medical devices. The Institute also maintains a registry of medical devices. The second instance body supervising the Institute is the Ministry of Health. The Institute is also involved in price and reimbursement procedures for medicinal products and medical devices.

Veterinary medicinal products intended for administration to animals are supervised by the Institute for State Control of Veterinary Biologicals and Medicines.

Food supplements are particularly regulated by Act No. 110/1997 Coll. on food and tobacco products and Decree No. 58/2018 Coll. on food supplements and food composition. This Decree provides and regulates the requirements for the composition, labelling and use of food supplements. The Czech Agriculture and Food Inspection Authority is in charge of overseeing compliance with food supplements regulation. Before marketing a food supplement, the producers and distributors are required to send the Ministry of Agriculture a notification containing the text that will appear on the packaging of the product.

II THE REGULATORY REGIME

i Classification

Medicinal products

The Pharmaceuticals Act contains two separate definitions of ‘medicinal product’. A medicinal product is understood to be either:

a a substance or combination of substances presented as having therapeutic or preventive properties in the case of human or animal diseases (presentation-based definition); or

b a substance or combination of substances which may be used in or administered to humans, or used in animals or administered to animals, either to restore, modify or affect physiological functions through pharmacological, immunological or metabolic action or to make a medical diagnosis (function-based definition).

Therefore, any product that is specifically described or recommended for the treatment or prevention of a disease, whether on its packaging or a package insert, is a medicinal product.

Medical devices

Unlike medicinal products, medical devices do not achieve their principal intended function in or on the human body by pharmacological, immunological or metabolic effects (however, their function may be supported by these effects). A medical device is an instrument, apparatus, aid, device, software, including software designed by its manufacturer for specific use for diagnostic or medical purposes and necessary for the correct use of a medical device, material or other item, intended by the manufacturer for human use for:

a the diagnosis, prevention, monitoring, treatment or alleviation of the disease;

b the diagnosis, monitoring, treatment, alleviation or compensation of injury or disability;

c the examination, replacement or modification of anatomical structure or physiological process; or

d conception control.
**Food supplements**

Food supplements are foodstuffs that are aimed at supplementing the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, contained in the foodstuff alone or in combination, and which are designed to be taken in measured small unit quantities.

**Borderline products**

The Institute has the authority to issue opinions and decisions where doubt exists as to whether a certain product is subject to marketing authorisation as a medicinal product or an active substance, a homeopathic product or another product. Similarly, the Institute decides whether or not a particular product is a medical device and under which class of medical devices it should be classified. Any product that falls under the definitions of both a medical device and a medicinal product should be considered a medicinal product.

**ii Non-clinical studies**

Clinical trials are preceded by preclinical testing carried out on animals or cell cultures. The use of experimental animals is regulated in the Czech Republic by Act No. 246/1992 Coll., on the protection of animals against cruelty, which includes an obligation to use a method other than animal testing whenever such a method is approved and available.

The Institute oversees the compliance with good laboratory practice (GLP) in the field of pharmaceuticals. This field is particularly regulated by Decree No. 86/2008 Coll., laying down good laboratory practice in the field of pharmaceuticals, and by the Institute-issued Guidelines. A translation of the OECD Principles of Good Laboratory Practice forms an annex to the above-mentioned Decree. A National GLP Programme has been introduced and the Institute maintains a list of the testing facilities that meet GLP requirements. Any testing facility that complies with GLP principles is granted a GLP certificate issued by the Institute.

**iii Clinical trials**

**Medicinal products**

Approximately 400 clinical trial applications are submitted each year in the Czech Republic. However, the number of clinical trial applications has stagnated, and even declined, in recent years. Most clinical trial applications concern oncological, rheumatological and neurological indications.

The conduct of clinical trials is currently governed by Directive 2001/20/EC as implemented by the Czech Pharmaceuticals Act and related decrees and guidelines. Once Regulation (EU) No. 536/2014, whose aim is to harmonise and simplify clinical trial regulation across the EU, enters into force, expected during 2020, clinical trials will be carried out for a transitional period either under Directive 2001/20/EC or under Regulation (EU) No. 536/2014. After the transitional period, clinical trials will be carried out in accordance with the requirements set out in the Regulation.

The sponsor of each clinical trial must obtain the approval of the Institute, the approval of at least one ethics committee and the patient’s consent (informed consent). As part of the clinical trial evaluation, all data from the preclinical studies and, where appropriate, any existing clinical trial are reviewed. Multicentre clinical trials must be reviewed by a specific
ethics committee for multicentre trials. The Institute publishes a list of all such committees set up in the Czech Republic, as well as a list of other standard committees set up at healthcare facilities.

To make it easier for patients to find a suitable clinical trial, the Association of Innovative Pharmaceutical Industry (AIFP) has set up a patient counselling centre.

**Medical devices**

A medical device conformity assessment typically includes a clinical evaluation. A clinical evaluation of a medical device is a process that aims to critically evaluate clinical data and to demonstrate the safety and efficacy of the medical device under study, while also adhering to the intended purpose established by the manufacturer under normal conditions of use.

Clinical data is obtained through clinical trials of a given medical device, clinical trials or other studies carried out on an equivalent medical device as referenced in scientific literature, from published and unpublished professional reports or conclusions on the use of a given device in clinical practice or of an equivalent medical device bearing the CE marking. Clinical trial data is transmitted to the European Database on Medical Devices (Eudamed).

iv **Named-patient and compassionate use procedures**

**Pharmacy exemption**

In the Czech Republic, medicinal products can only be prepared in pharmacies under the conditions set out in the Pharmaceuticals Act, in Directive 2001/83/EC and in accordance with the interpretation contained in the judgment issued by the CJEU in *Abcur AB v. Apoteket Farmaci AB* (C-545/13). This applies to products prepared in a pharmacy upon medical prescription made out to a specific patient (‘magistral formula’) and to pharmacopeial products supplied directly to the patients served by the pharmacy in question (‘officinal formula’).

The Institute sets the amount and conditions for the reimbursement of each individually prepared medicinal product, radiopharmaceutical, transfusion product and advanced therapy medicinal product. The Institute also maintains a list of all individually prepared medicinal products.

**Non-authorised medicinal products**

Non-authorised medicinal products may be used and prescribed for treatment in the Czech Republic under the following conditions:

a no authorised medicinal product composed of similar therapeutic properties is distributed in the Czech Republic;

b the medicinal product is authorised abroad (or is an advanced therapy product);

c the use of the medicinal product is sufficiently justified by scientific knowledge; and

d the medicinal product does not contain a genetically modified organism.

The physician must also notify the Institute immediately of any prescription or use of a non-authorised medicinal product. Non-authorised medicinal products are only reimbursed under health insurance if this reimbursement has been pre-approved by the health insurance provider.
Specific therapeutic programmes

If there are whole patient groups (e.g., with a rare diagnosis) for which authorised medicinal products are not available, the Ministry of Health may give consent to use non-authorised medicinal products within 'specific therapeutic programmes', subject to an opinion issued by the Institute. Such a programme can be initiated by a physician, hospital, the Ministry of Health, medical professional society, health insurance company, patient organisation or pharmaceutical company. Programmes are approved for a limited period, and are also usually restricted to a specific diagnosis or group of patients, or specific healthcare providers. Furthermore, the distribution method and the number of packages may be regulated. Medicines used in a specific therapeutic programme may be covered by health insurance.

Off-label use of medicinal products

Medicinal products can be used off label (i.e., for other therapeutic purposes or in a manner other than that indicated in the approved summary of product characteristics (SmPC) if no medicinal product with the necessary therapeutic properties is in distribution. However, this use must be sufficiently justified by scientific knowledge. Nevertheless, medicinal products are typically not covered by health insurance in these cases.

Hospital exemption for advanced therapy medicinal products

In accordance with Regulation (EC) No. 1394/2007, on advanced therapy medicinal products, and in accordance with the Pharmaceuticals Act, hospital exemptions are intended to ensure that non-authorised advanced therapy medicinal products may be used to meet the individual medical requirements of a given patient. Hospital exemptions are typically used where, due to the nature of a given medicinal product or indication, sufficient clinical data cannot be obtained for the authorisation procedure.

Medical devices

If no corresponding medical device is on the market that meets the requirements of the Medical Devices Act, the Ministry of Health may grant exceptional authorisation to use a medical device that does not meet these requirements.

Pre-market clearance

Medicinal products

Each medicinal product is subject to an authorisation procedure before being placed on the market in the Czech Republic (unless specific conditions for using non-authorised products apply). As an EU Member State, the Czech Republic recognises all standard types of marketing authorisations (national marketing authorisations, MRP/DCP procedures and centralised marketing authorisations carried out by the European Medicines Agency (EMA) valid throughout the EU).

According to the available statistical data on national marketing authorisations, the period for assessing applications was 150 days for generic products and 210 days for other types of national marketing authorisations. Applicants have 180 days to remedy shortcomings in the documentation submitted. This period is not included in the total duration of the registration procedure, and therefore the total duration of the registration procedure is often longer.
In addition to the marketing authorisation procedure fees, each marketing authorisation holder (MAH) is required to pay the Institute regular ‘annual maintenance fees’ as compensation for the costs of the Institute’s activities associated with maintaining marketing authorisations. These fees amount to 39,100 korunas where the Czech Republic is a reference member state (RMS) and 19,500 korunas in other cases.

Medical devices
All medical devices intended to be marketed in the Czech Republic must carry a CE mark (including a written declaration of conformity) and must be accompanied by information in the Czech language on its safe use. A device registered in the Czech Republic or in any other EU Member State can be freely marketed in all European Union countries. Medical device registrations in the Czech Republic and the EU are valid for five years. Any manufacturers intending to continue to market their device in the European Union after this period must apply for a renewal.

The Registry for Medical Devices was launched in 2015. The system was created in order to collect data on the medical devices marketed in the Czech Republic and is accessible both by the competent authorities and the general public. The publicly accessible part provides information on all medical devices, field safety notices and registered entities. The other part of the platform provides the competent authorities with information on products, importers, distributors and notified bodies, incident reports, and data on conducted clinical trials.

Under the current Medical Devices Act, the manufacturer, the distributor and the importer (for medical devices in risk class I and certain in vitro diagnostic medical devices, distributors and importers are exempt from the notification duty) must submit an application for notification of a medical device to the Institute no later than 15 days after it has been introduced or delivered to the market. From May 2020, the new requirements under the MDR will apply to new medical devices marketed in the Czech Republic.

vi Regulatory incentives

Patents within authorisation or P&R procedures
The Institute does not examine the industrial property rights of third parties during marketing authorisation or pricing and reimbursement procedures. Moreover, according to the decision-making practice of the Czech courts, the application for the maximum price and reimbursement of the medicinal product as such does not constitute a breach of patent rights.

The Czech Patent Act also acknowledges a ‘pharmacy exemption’, whereby the individual in-pharmacy preparation of medicinal products upon prescription is exempt from patent protection. Additionally, the Bolar exemption was also incorporated into the Czech Patent Act and the Pharmaceuticals Act. This exemption applies to activities performed with the invented product for experimental purposes, including the experiment and tests necessary before the medicinal product is placed on the market.

Supplementary protection certificates
The Czech Industrial Property Office grants supplementary protection certificates (SPCs) of up to five years for substances that are protected by a valid patent in the Czech Republic as long as these are active substances in preparations registered before being placed on the market. In addition, such medicinal products may also be protected by a paediatric extension, which extends the lifetime of the SPC by a further six months.
The new Regulation No. (EU) 2019/933 introduces a manufacturing exemption from the protection granted under the SPC. The Regulation authorises EU-based companies to produce generic or biosimilar versions of SPC-protected medicinal products during the period of validity of the certificate if they are manufactured either for export to an EU market where protection has expired or never existed or are for storage during the last six months of the SPC’s validity.

**Data and market exclusivity**

In the Czech Republic, the standard EU exclusivity regime known as the 8+2+1 rule applies. Current EU regulation grants eight years of data exclusivity for pharmaceutical products, which is followed by a two-year market exclusivity period. This cumulative 10-year period (eight years of data exclusivity plus two years of marketing exclusivity) may be further extended by one year for certain new indications which are proven to provide an additional clinical benefit compared with previous indications.

The market exclusivity period for orphan designated pharmaceutical products is 10 years. Each indication with an orphan designation confers 10 years of market exclusivity for the indication in question. Market exclusivity is extended by a period of two years if the orphan designation also relates to a paediatric indication.

**Post-approval controls**

**Medicinal products**

The obligations of marketing authorisation holders are included in the Pharmaceuticals Act and related decrees and guidelines. This regulation is to a large extent harmonised with Directive 2001/83/EC and EudraLex.

**Adverse drug reaction**

The EudraVigilance database was put into operation in 2017. As of that date, reports must be submitted to the EudraVigilance database directly within the time limits stipulated by law (i.e., serious reports within 15 days and non-serious reports within 90 days).

**Periodic safety update reports**

As part of their pharmacovigilance obligations, MAHs must send periodic safety update reports (PSURs) via the PSUR repository maintained by the EMA. Based on the assessment of the results of the PSUR evaluation, the MAH may submit an application to amend the marketing authorisation, including an updated SmPC and package leaflet.

**Pharmacovigilance system of the marketing authorisation holder**

To comply with its pharmacovigilance obligations, each MAH must operate a pharmacovigilance system through which it:

- collects information on the risks of medicinal products;
- evaluates the information referred to in (a) and considers options for risk reduction and risk prevention; and
- takes all necessary and appropriate measures.

Each MAH must carry out regular auditing of its pharmacovigilance system.
Qualified person responsible for pharmacovigilance

Each MAH must permanently have in place a qualified person responsible for pharmacovigilance. This qualified person is responsible for setting up and administering the pharmacovigilance system and should reside and carry out his or her pharmacovigilance tasks within the territory of the European Union. The Institute may ask a MAH to appoint a pharmacovigilance contact person in the Czech Republic, reporting to a qualified pharmacovigilance person.

Risk management plan

Each MAH must operate and update a risk management plan (RMP) for each medicinal product. RMPs must be proportionate both to the identified risks and the potential risks of a specific medicinal product and to the need for collecting post-authorisation safety data. This obligation does not relate to holders of marketing authorisations issued before 21 July 2012, unless the Institute imposes an obligation on these MAHs to introduce an RMP. The obligation to operate and update an RMP does not automatically imply an obligation to submit and update an RMP included in the registration dossier; for the majority of medicinal products, this obligation means carrying out standard pharmacovigilance.

Post-authorisation studies

There are several types of post-authorisation studies:

Post-authorisation safety studies (PASSs)

PASSs are implemented by MAHs at their own discretion or carried out following a decision of the EMA, the Institute or another agency, either imposing a duty during the authorisation process or afterwards in case of doubt regarding the safety risks of an authorised medicinal product.

Studies carried out in the Czech Republic are reported to the Institute. MAHs should also enter in the EU PAS Register all non-interventional PASSs conducted voluntarily in the EU or included in the RMP. At present, this function is fulfilled by the ENCePP Register.

Studies must not promote the use of a particular medicinal product, and MAHs must not provide HCPs with financial compensation other than for their time and expense spared for participating in these studies.

Post-authorisation efficacy studies (PAESs)

In its marketing authorisation decisions, the Institute may require MAHs to carry out a PAES if any doubts regarding certain aspects of a medicinal product’s efficacy cannot be rectified before it is placed on the market, or if they are to maintain their marketing authorisation in the event that new information that may require a substantial revision of the previous efficacy evaluation, or other new efficacy data, comes to light.

PAESs should be notified to the Institute. Information on PAESs should also be entered in the EU PAS Register to support their transparency, whether initiated, managed or financed by an MAH voluntarily or as an obligation.
Non-interventional post-authorisation studies (PASs)

A PAS is generally any study in which the authorised medicinal product is used in the standard way and in accordance with the terms of the marketing authorisation, and in which the use of the medicinal product is not determined by the patient’s inclusion in such a study but rather by the decision of the physician. Non-interventional PASs particularly include epidemiological, pharmacoeconomic and research studies.

PASs should not be used for advertising purposes (i.e., as supporting evidence for prescribing, supplying, selling, dispensing or consuming medicinal products). The Institute monitors how non-interventional PASs reported in the register are organised and assesses them in terms of whether they have any advertising nature. If the study is considered to be of an advertising nature, then further assessment will be undertaken as to whether the expert’s remuneration for participating in the study is more than the maximum statutory amount of 1,500 korunas per year.

Notification regarding the presence on the market

Each MAH has a statutory duty to report when a medicinal product is placed on the market in the Czech Republic, when it is suspended or terminated, and when its marketing subsequently resumes.

Sunset clause

A marketing authorisations expires if the medicinal product has not been placed on the market in the Czech Republic within three years of its effective date. For generic medicines, this period only begins to run on the date when market exclusivity expires. It follows from the above that the three-year period for placing a generic medicinal product on the market begins to run on 1 January of the year following that in which the market protection of the reference product has expired.

Under certain circumstances, namely if there is no corresponding product on the market or if it is the first generic on the market, and where this may lead to a reduction in the price of medicinal products with the active substance in question, consequently leading to savings to public health insurance, an exemption may be granted to the sunset clause. This applies where the marketing authorisation would otherwise be invalidated due to the medicinal product not being placed on the market within three years of authorisation being granted.

Medical devices

The Czech Republic has adopted a Medical Devices Vigilance System, which is a system for reporting and evaluating adverse events and safety remedies for medical devices. The purpose of this system is to improve the health and safety protection of patients, users and third parties by reducing the likelihood of the same type of adverse event recurring at different times and at different locations.

A manufacturer or its representative, or an importer, must report to the Institute in writing any adverse incident associated with its medical device. If the Institute identifies an adverse incident, then it should report that information to the manufacturer or its authorised representative. The Institute should inform the other Member States, and the European Commission, of such measures taken or considered to minimise the recurrence of adverse events.
The Institute publishes a list of Field Safety Notices (i.e., communications sent out by medical device manufacturers or their representatives in relation to the safety remedy taken) on its website, and instructs importers and distributors to provide and document the internal process control system for distribution and import activities as well as adopt corrective actions.

Post-market clinical follow-up studies are carried out after the medical device has been launched. It acts as a subsequent collection of clinical data using a medical device in normal clinical practice. These studies will be newly regulated by the MDR.

viii  Manufacturing controls

**Medicinal products**

Medicinal products must be manufactured by persons that are authorised to do so by the Institute and that meet the criteria of good manufacturing practice (GMP). The qualified person of the manufacturer is then responsible for ensuring that each batch of a medicinal product is manufactured and controlled in accordance with the Pharmaceuticals Act, its implementing legislation (including GMP), the marketing authorisation dossier and the marketing authorisation. The GMP guidelines issued by the Institute correspond to EudraLex – Volume 4 – Good manufacturing practice (GMP) Guidelines. The Institute maintains a list of approved manufactures and a list of GMP certificate-holding manufacturers of active substances.

The National Medicines Verification System of the Czech Republic (CZMVS) has been established based on Falsified Medicines Directive 2011/62/EU and Commission Delegated Regulation (EU) 2016/161. End users (i.e., all distributors and pharmacies) have access to this verification system. The National Verification Organisation (NOOL) was founded to create and operate the CZMVS and to provide individual entities with access to the CZMVS.

**Medical devices**

The conformity assessment usually involves an audit of the manufacturer’s quality system and, depending on the type of device in question, also involves a review of the technical documentation provided by the manufacturer on the safety and performance of the device.

ix  Advertising and promotion

**Medicinal products**

The Advertising Regulation Act defines the advertising of medicinal products as any information, persuasion or incentive intended to promote the prescription, supply, sale or consumption of medicinal products. Advertising activities include visits by representatives, the provision of samples and gifts, and the sponsorship of congresses, including travel and accommodation costs.

Advertising must only focus on authorised medicinal products, the information presented in advertising must not contradict the SmPC, and advertising must promote the rational use of the medicinal product by presenting it objectively.

Advertising rules differ depending on whether it is targeted at the general public or at HCPs (persons authorised to prescribe or dispense medicinal products, which is most often a doctor or pharmacist). Advertising targeted at the general public must only be carried out
for non-prescription medicinal products. No gifts, promises, offers or other incentives may be offered to HCPs in relation to the advertising, unless they are of negligible value (up to approximately €60 per year) and relate to their profession.

Pharmaceutical companies in the Czech Republic usually also adhere to the ethical codes of the professional associations which regulate marketing practices, such as the AIFP (innovative firms) or the CAFF (generic firms).

**Medical devices**

The advertising of medical devices is not currently subject to specific regulation, and therefore general rules on advertising apply.

However, in relation to the adoption of new local regulation supporting the MDR and IVDR, a new medical devices regulation is being introduced which is largely inspired by existing regulation on medicinal products advertising. The bill distinguishes between advertising targeted at the general public and that targeted at professionals, and prohibits advertising targeted at the general public to promote devices which the manufacturer’s instructions state must only be used by an HCP or which can only be dispensed upon prescription (voucher).

**Distributors and wholesalers**

**Medicinal products**

Authorisation must be obtained from the Institute for distribution activities concerning medicinal products. Operators authorised to dispense medicinal products (such as pharmacies) must also obtain distribution authorisation if they wish to onward distribute part of the medicinal products. Distribution may also be carried out by the medicinal products manufacturer, albeit of its own medicinal products only. Distributors must appoint a qualified person and must comply with the rules of good distribution practice.

If a distributor distributes only medicinal and auxiliary substances, then the existence of an authorisation requirement will depend on the type of customer distributed to. If it delivers to medicinal products manufacturers, it does not need to obtain distribution authorisation.

Distribution authorisation is granted in one Member State and, if carrying out distribution in other Member States, the competent authorities are notified only as long as the distributor does not have its own distribution warehouse in those other countries. Distribution authorisation does not cover the import of medicinal products from non-EU countries, for which specific manufacturing authorisation must be obtained.

**Medical devices**

Any distributor intending to operate in the Czech Republic must submit a notification to the Institute via the Medical Devices Register prior to commencing its activities (except for distributors of medical devices falling under risk class I and certain in vitro diagnostic medical devices). Distributors must comply with good distribution practice, which lays down the requirements for maintaining the safety and performance of the medical device.

**Classification of products**

**Medicinal products**

Medicinal products can be categorised by their dispensing method as follows:

- prescription medicinal products;
b prescription medicinal products with a blue strip (for narcotic or psychotropic substances);

c restricted prescription medicinal products (may be prescribed only by a doctor with specific competence);

d OTC medicinal products; and

e restricted OTC medicinal products (such as with an age limit, maximum quantity of packages per purchase, a ban on mail order dispensing; as currently applies to products containing pseudoephedrine).

In 2018, the Czech Republic introduced the ePrescription system. Prescriptions in electronic form are stored in the Central Repository of Electronic Prescriptions (CREP). Each e-prescription has a unique 12-digit identifier and a bar code that a pharmacist can scan. If the pharmacist finds a prescribed medicine in the CREP, they can dispense it to the patient.

**Medical devices**

Any medical device that may endanger human health or life if not used under the supervision of a doctor may be dispensed only on prescription (voucher). A list of these medical devices is set forth in an implementing regulation. Medical devices are also issued on prescription if the patient is entitled to have the device reimbursed under public health insurance.

**Imports and exports**

**Medicinal products**

Imports of medicinal products from EU countries is covered by distribution authorisation. Imports from non-EU countries can only be carried out by a person who has been authorised to manufacture medicinal products by importing from outside the EU.

Parallel import means the distribution of a medicinal product from another EU country to the Czech Republic, where the distribution is not arranged for by, or in cooperation with, the MAH. Parallel import may only take place if a parallel import permit has been granted by the Institute. Parallel distribution is a similar activity that relates to centrally authorised medicines. This activity must be reported in advance to the EMA.

**Medical devices**

Import means the placing on the market of a medical device that has been obtained outside the territory of the EU. Imports may only be carried out by an importer registered with the Institute. The MDR places new and more extensive obligations on importers.

**Controlled substances**

Medicinal products containing narcotic or psychotropic substances must only be dispensed against a specific prescription type bearing a blue strip. Pharmacies must report to the Institute concerning the status and movement of addictive substance stocks.

Addictive substances, preparations, precursors and auxiliary substances can only be imported or exported if an import or export permit has been issued by the Ministry of Health.
**Enforcement**

**Medicinal products**

State supervision of human medicinal products in all areas is carried out by the Institute. The activities of the Institute include monitoring the quality, safety and efficacy of medicinal products in all stages of their development and use. For this purpose, the Institute uses a system of preliminary reporting; licensing, authorisation and registration procedures; inspections; laboratory controls; and monitoring of the practical use of medicines. It also gathers all appropriate information. The Institute is entitled to take action where a risk to public health arises, to impose penalties, and to request necessary documentation.

The Institute also monitors compliance with regulations on medicinal product advertising. However, TV and radio advertising for medicinal products is supervised by the Council for Radio and Television Broadcasting.

**Medical devices**

The Institute is responsible for the comprehensive market surveillance of medical devices. This means that it can oversee how the obligations set out in the Medical Devices Act are met across the entire distribution chain. The Institute's oversight activities as regards medical devices is therefore targeted not only at manufacturers, importers and distributors of medical devices, but also at others including pharmacies that dispense prescription medical devices to patients and healthcare facilities that use medical devices in the provision of healthcare services. The Institute has issued a methodology for the oversight of distributors and importers of medical devices.

**III PRICING AND REIMBURSEMENT**

**i Medicinal products**

In the Czech Republic, most reimbursable medicinal products are price-regulated. On the other hand, non-reimbursable pharmaceuticals are not price-regulated. Regulated prices are set at ex-factory level or are regulated according to statutory prices (for individually prepared medicinal products, as well as parenteral nourishment, radiopharmaceuticals and transfusion products). The ex-factory price of a given medicinal product is set at the average of the three lowest prices based on the reference basket; reference basket states include all EU countries except Austria, Bulgaria, Cyprus, the Czech Republic, Estonia, Germany, Greece, Luxembourg, Malta and Romania. If the lowest price in the reference basket is extremely low (more than 20 per cent lower than the average of the next two lowest prices for the same product), then the price is set at the average of those next two lowest prices for the reference product. If a medicinal product (with the exception of highly innovative drugs) is not on the market in at least three reference basket states, the agreed price of the medicinal product can be used in the evaluation. If none of the above-mentioned procedures is applicable, the price is set at the maximum ex-factory price of the closest therapeutically comparable medicinal product available in the Czech Republic or in the reference basket countries. For highly innovative medicines, the ex-factory price can be set at the average manufacturer's price found in at least two reference basket states. MAHs can supply products for lower prices than the stipulated maximum ex-factory price so as to reduce or eliminate the difference between the price and the reimbursement.
Reimbursement is based on a system of therapeutic indication-based reference groups. Each reference group includes medicinal products that are similar in effectiveness, safety profile and clinical use, and which are considered to be therapeutically interchangeable. All products within the same reference group have the same reimbursement price based on the daily therapeutic dose. The Institute may award a bonification price for any product that has a better effectiveness, a better safety profile or a better compliance rate than the reference medicinal product. The reimbursement price is set according to the EU lowest price for a medicinal product within a reference group, which then becomes a reference product.

Wholesalers and pharmacies are remunerated under a margin scheme. This scheme is published by the Ministry of Health. Margins are applied jointly for both wholesaler and pharmacy, with the lesser margin being kept by the wholesaler, and the greater margin being applied by the pharmacy.

**Medical devices**

In 2019, a new regulation was introduced on the reimbursement of prescription medical devices under public health insurance schemes.

Reimbursed medical devices are classified into reimbursement groups. Each manufacturer or distributor determines which reimbursement group its medicinal product should be classified into in its notification to the Institute. The Public Health Insurance Act stipulates a reimbursement limit for each reimbursement group. Furthermore, a prescription restriction may be in place to determine which physician may prescribe the medical device, any indication restrictions and the quantity limit.

The reimbursement of non-categorised medical devices that are not included in any of the reimbursement groups and are approved by the Ministry of Health is capped at 50 per cent of their price (100 per cent reimbursement is provided only for non-categorised medical devices that are subject to risk-sharing agreements).

**IV ADMINISTRATIVE AND JUDICIAL REMEDIES**

Appeals can be filed against decisions issued by the Institute regarding medicinal products and medical devices. Appeals are decided by the Ministry of Health (if not remedied by the Institute itself).

A judicial remedy can be sought from the court by filing an administrative action. Actions against decisions on appeal must be filed no later than two months after a decision is delivered. Judicial reviews are undertaken by the regional court as the first degree court and by the Supreme Administrative Court as the court of cassation.

**V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS**

All state-owned or public entities (including hospitals and other healthcare providers) must publish all private law contracts in the Register of Contracts no later than three months after each contract has been concluded, otherwise the contract will be considered void. Contracts are exempt from the obligation to be published in the Register if the performance value of the contract is below 50,000 korunas. Moreover, certain documents do not have to be registered (e.g., contracts concluded with individuals that do not fall within the entity’s business activity, project documentation, drawings and contracts regarding the intelligence...
services or which affect the security of the Czech Republic). Additionally, the parties may redact or sanitise confidential data that cannot be disclosed under the laws governing free access to information, including trade secrets.

The Ministry of Health has introduced transparent management principles for organisations it directly manages, namely state-owned hospitals. Under these binding rules, bonuses are divided into addressed and unaddressed bonuses. An addressed bonus is provided in direct connection with a specific delivery of goods (a specific order, invoice, etc.) or a specific type of goods and is linked, for example, to the purchase volume at a particular time. It can be therefore divided by the unit price of the goods. The amount of unaddressed bonuses, on the other hand, cannot be linked to a specific supply of goods (order or invoice) or a specific type of goods, as this value is calculated separately or in aggregate. The Ministry recommends that the prices reported to health insurance companies should be adjusted to take into account any discounts or addressed bonuses received, or any invoice-related credits, refunds, and so on. Non-addressed bonuses cannot be reflected in the reported price because they cannot be allocated to a particular product or device. If a medicinal product is provided as a natural bonus, it should be provided free of charge in accordance with the price regulations. This medicinal product should also be reported to the health insurance company at no cost. Bonuses may only be accepted under a written contract, which must be published in the Register of Contracts. The organisation must use the revenues from the bonuses received solely for costs that are connected to the operation and upgrade of the medical facility.

The AIFP, a Czech association of innovative firms, has launched a transparency initiative based on the AIFP’s Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations (which implements a similar initiative by the European Federation of Pharmaceutical Industries and Associations (EFPIA)). The idea behind this initiative is for information on cooperation between HCPs and pharmaceutical companies to be published on a publicly available website. Most large generic firms have also acceded to this initiative.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

If an authorised medicinal product is used in the provision of healthcare and its use causes side effects not listed in the SmPC, the MAH is liable for any damage caused by those effects and cannot be relieved therefrom. If the side effects are listed in the SmPC, the MAH is held liable only if the MAH specifically caused the damage.

As regards off-label use or the use of a non-registered medicinal product, healthcare facility operators are liable for damage to the health or the death of any person resulting from that specific use of the medicinal product.

Regarding the use of medicinal products in clinical trials, the Pharmaceuticals Act places an obligation on both the investigator and sponsor to obtain liability insurance as a precondition for commencing a clinical trial.

The Czech parliament has recently approved the new Harm from Compulsory Vaccination Compensation Act, under which the state must compensate any vaccinated person who has suffered material and intangible damage from a vaccination. The state will also compensate the parents of any child who dies or has serious health disorders after a compulsory vaccination.
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law
A new protected distribution system that aims to ensure the availability of medicinal products for patients was approved by the Czech parliament in late 2019. The new system amends the existing emergency system, which was introduced in 2017. Under the new regulation, any distributor providing an MAH with a written representation that it requires medicinal products in order to ensure the provision of healthcare to Czech patients and that it will not export those products is entitled to request sufficient supplies of medicinal products so as to meet the average demand over a two-week period for the medicinal products distributed by this distributor from operators authorised to dispense medicinal products (i.e., pharmacies). This regulation therefore imposes a contractual obligation on MAHs and a ban on exporting medicinal products that should be distributed through the protected distribution system and disrupts existing DTP distribution models. In doing so, this regulation restricts competition and contradicts the principle of the free movement of goods. This new regulation was not supported by the Ministry of Health, which has prepared its own emergency system based on the Slovak model, and this is now going through the legislative process. Under this newly proposed regulation, MAHs will be required to set up and operate a specific emergency system for the supply of their medicinal products if the availability of the medicinal product to patients cannot otherwise be ensured. The pharmacy will then be under obligation to use any medicinal product delivered after ordering it through the emergency system by dispensing it to patients upon prescription only.

In relation to the pharmaceutical market, further competition concerns may arise in relation to bonus schemes (which may include loyalty bonus elements).

ii Transactional issues
In recent years, the Czech Competition Authority has dealt at a local level with competition clearance for mergers and acquisitions involving pharmacy and wholesale chains such as Dr. Max/ViaPharma and BENU/Phoenix.

VIII CURRENT DEVELOPMENTS

i New medical devices regulation
Following the adoption of the MDR and the IVDR, new local laws will be adopted, namely the new Medical Devices Act relating to general medical devices. The existing Medical Devices Act will be amended and will apply only to in vitro diagnostic medical devices. An entirely new regulation on the advertising of medical devices will be adopted. This will be combined with the new regulation on the reimbursement of the medical devices, which was introduced in 2019.

ii Clinical trials
It is anticipated that the EU Clinical Trial Regulation will enter into force during 2020. It depends on the completion and full functionality of the EU Clinical Trials Portal; the Regulation will become applicable six months after this is confirmed.
ePrescription
A new ePrescription system was introduced in the Czech Republic. One of the key functions of this system is a Shared Patient Record. It enables healthcare professionals to work with the data available in the central repository of electronic prescriptions. Patient participation is based on the opt-out principle.

Biosimilars
The entry of biosimilars into the Czech market has slowed lately. This is mainly due to a legislative change which imposed a 30 per cent reduction on the maximum price of biosimilars as compared to original products (instead of the previous 15 per cent reduction). Discussions are currently under way as to whether such a price reduction is appropriate.
Chapter 9

DENMARK

Karin Absalonsen

I  INTRODUCTION

The Danish life sciences industry contributes considerably to both R&D, economic progress and employment in Denmark. An analysis from the Danish Ministry of Industry, Business and Financial Affairs published in February 2019 shows that the value increment in the life sciences industry has increased by 88 per cent in eight years. By comparison, the value increment in the industry in Denmark as such has increased by 17 per cent during the same period. Furthermore, the productivity level is twice as high in the life sciences industry compared to the overall economy.

The regulatory framework for medicines for human use in Denmark is based on EU Regulation (EC) No. 726/2004 and Directive 2001/83/EC, which are implemented in national Danish law primarily in the Health Act, the Medicines Act, the Pharmacy Act and the Ethics Committee Act. The regulatory framework for medical devices is based on EU Regulation 2017/1745, which is implemented in the Medical Devices Act.

The requirements and procedures for marketing authorisation of medicines are partly covered by EU law, whereas national law regulates pricing and reimbursement. The competent authorities are the Danish Medicines Agency (DMA), the Danish Ministry of Health, the Danish Health Authority and the Danish Patient Safety Authority. In the decision-making with respect to regulation of medicines, a number of advisory bodies advise the DMA such as the Medical Products Committee, the Pharmacovigilance Council and the Reimbursement Committee.

1 Karin Absalonsen is a partner at Nyborg & Rørdam Law Firm P/S.
4 Health Act, Consolidated Act No. 903 of 26 August 2019.
6 Pharmacy Act, Consolidated Act No. 801 of 12 June 2018.
7 Ethics Committee Act, Consolidated Act No. 1083 of 15 September 2017.
II THE REGULATORY REGIME

i Classification

Medicines are defined as any product that (1) is presented as a suitable product for the treatment or prevention of diseases in human beings or animals, or (2) may be used in or administered to human beings or animals to restore, change or modify physiological functions by a pharmacological, immunological or metabolic effect or to make a medical diagnosis.10

Medical devices are defined as devices intended for diagnosis, prevention, monitoring, treatment or palliation of diseases, compensation for injuries or handicaps, examination, replacement or change of the anatomy or a physiological process or contraception, provided that the expected principal effect in or on the human body is not elicited through pharmacological, immunological or metabolic means, but which effect can be supported through these means.11

In borderline cases the DMA may decide that the product or group of products shall exclusively be regulated by the Medicines Act. Classification as a medicine is normally given priority over classification as foods, cosmetics etc. Medicines approved by the European Medicines Agency (EMA) will maintain their classification status in Denmark.

ii Non-clinical studies

Conducting non-clinical studies of compounds must be made in compliance with the principles of good laboratory practice (GLP) defining the standards for planning, conduction, monitoring, recording and reporting of in vitro and in vivo studies.12 The Animal Experiments Inspectorate (AEI) grants permission to conduct animal studies on vertebrate animals and foetuses of mammals in accordance with the Animal Experiments Act.13 The Act implements parts of Directive 2010/63/EU regarding conduction of animal studies.14 The AEI approves all animal experiments in Denmark and undertakes inspections of facilities where animal experiments are carried out.

11 Consolidated Act No. 139 of 15 February 2016 on Medical Devices as amended by Act No. 1554 of 18 December 2018.
12 Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.
iii Clinical trials

Conducting clinical trials of medicines in humans is regulated by the Medicines Act\(^\text{15}\) implementing Directive 2001/20/EC\(^\text{16}\) and Regulation (EU) No. 536/2014.\(^\text{17}\) Application for authorisation of clinical trials of medicinal products in humans must be filed to the DMA by the sponsor. The sponsor or its representative must be domiciled in the EU or EEA. Application for authorisation can take place through DKMA.net. Guidelines can be found on DMA's website. Clinical trials of medicines in humans must be conducted in accordance with the principles of good clinical practice (GCP).\(^\text{18, 19}\) Before consenting to participate, trial subjects must receive adequate written and oral information about the clinical trial. Informed consent forms must be signed by the trial subjects and stored by the primary investigator.\(^\text{20}\) The informed consent must also contain information about inspections performed by the DMA and a description of the DMA's unconditional access to all trial and patient data. A publicly funded compensation scheme covers injuries to human subjects occurring in clinical trials (see Section VI).

The definition of the term ‘sponsor’ in Danish law is not the same as in Directive 2001/20/EC defining a sponsor as an individual, company, institution or organisation that takes responsibility for the initiation, management or financing of a clinical trial.\(^\text{21}\) Danish law defines the clinical trial sponsor as the individual, company, institution or organisation that takes the overall responsibility for the initiation, management and, in some cases, financing of the clinical trial.\(^\text{22}\) The clinical trial sponsor must comply with obligations regarding registration of the trial in EudraCT, reporting of trial results to EudraCT and reporting of suspected unexpected serious adverse reactions\(^\text{23}\) that arise during the trial to the DMA.

iv Named-patient and compassionate use procedures

The DMA may in special circumstances and to a limited degree authorise the sale or dispensing of approved medicines or pharmacy compounds that are not licensed for marketing in Denmark.\(^\text{24}\) Such compassionate use permits are only issued for medicines manufactured by pharmaceutical companies and in situations where the unlicensed medicine cannot

\(^{18}\) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
\(^{19}\) Executive Order No. 695 of 12 June 2013 on good clinical practice in clinical human trials.
\(^{20}\) Executive Order No. 498 of 13 May 2018, Sections 6, 7, 8 and 9 on informed consent of participating in clinical trials.
\(^{21}\) Directive 2001/20/EC, Article 2(e).
\(^{22}\) Executive Order No. 695 of 6 December 2013, Section 2(1), No. 6 on good clinical practice.
\(^{23}\) Executive Order No. 295 of 26 April 2004 on clinical test with medicines in humans.
be substituted by a medicine already marketed in Denmark and provided that there are therapeu-
tic reasons to choose a medicine not marketed in Denmark. Doctors, veterinaries and
dentists may apply for a single permission for use of unlicensed medicine in specific patients
or apply for a general permission to hospital departments. The application for compassionate
use permits must be filed to the DMA containing information about the indication for use,
name of the medicine, active ingredients, medical form, strength, producer, distributor and
medical justifications for the application. Medicines prescribed for compassionate use are also
subject to the rules for reporting adverse events to the DMA.  

v Pre-market clearance

Medicines can only be marketed and sold in Denmark upon approval by the EMA or the
DMA. The same applies for natural medicine products and strong vitamins and minerals.
Approved medicines must be included in the medical register. The applicant for and holder
of a Danish marketing authorisation must be established in the EU or EEA or represented in
Denmark by a company established in the EU or EEA. The averted application procedure
may be applied for authorisation of generic medicines. In such case the applicants may omit
some or all of the preclinical and clinical trial data if bioequivalents can be documented with
a reference product and regulatory data exclusivity for the reference product has expired.

To ensure that medical devices meet all requirements for quality, safety and efficiency,
manufacturers must follow a number of procedures including conformity assessments before
marketing the devices.

vi Regulatory incentives

For medicines patents may be granted for 20 years from the date of filing in accordance with
the Danish Patent Act. The holder of a marketing authorisation for a medicine may benefit
from a data protection period of 10 years from the first marketing in the EU or EEA. The data
protection period may be extended to 11 years if new indications are approved later. EU
regulations concerning supplementary protection certificates (SPCs) for medicinal products
allow for a supplementary protection of a maximum of five years without the possibility of

25 Executive Order No. 1823 of 15 December 2015 on reporting of adverse events for medicinal products.
27 www.medicinpriser.dk.
28 European Commission. EudraLex – Volume 2. Pharmaceutical legislation on notice to applicants and
regulatory guidelines for medicinal products for human use.
Community code relating to medicinal products for human use amended by Directive 2004/27/EC,
Sections 10, 10a, 10b and 10c.
Community code relating to medicinal products for human use amended by Directive 2004/27/EC,
Sections 10, 10a, 10b and 10c.
31 Executive Order No. 1263 of 15 December 2008 on medical devices, Executive Order No. 1269
of 12 December 2005 on medical devices for in vitro diagnostic, Executive Order No. 1264 of
15 December 2008 on active, implantable medical devices.
33 Directive 2001/83/EC on the Community code relating to medicinal products for human use amended by
34 Executive Order on Marketing Authorisation No. 1239 of 12 December 2005, Sections 9(2) and 12.
extension. However, if the patentee has tested the suitability of the medicines for children, the supplementary protection for medicines may be extended by an additional six months. If the regulatory authority approves a paediatric indication, a further six months’ extension of the SPC can be allowed. An application for a paediatric extension should also be filed with the Danish Patent and Trademark Office (DKPTO).

vii Post-approval controls

Holders of marketing authorisation for medicines must (1) establish and maintain a pharmacovigilance system; (2) comply with national rules on reporting of suspected adverse reactions; (3) have access to a person qualified within pharmacovigilance domiciled in the EU, and (4) report periodic safety updating to the DMA or the EMA. Side effects must be reported to the DMA or the EMA. Doctors, dentists, midwives, veterinaries and pharmaceutical companies must report all suspected adverse events and exposure reactions in patients or animals they are treating no later than 15 days after the said persons have become aware of the event. It is not mandatory to report adverse events caused by medication errors to the DMA. Apart from generic medicines, during the first two years of marketing all adverse events must be reported. Thereafter reporting only covers serious or unexpected adverse events and exposing reactions. The reporting requirements apply from the time when marketing of the medicine has begun. Pharmacists, consumers, patients, relatives and lawyers may all report adverse events directly to the DMA. The DMA has introduced strict reporting of all adverse events occurring for medicines under special surveillance. A list of these medicines can be found on the DMA website. The DMA may amend, suspend or revoke a marketing authorisation for a medicine. The same applies to medical devices involving a health or safety risk.

viii Manufacturing controls

Manufacturing of medicines and intermediates requires an authorisation from the DMA. Manufacturing of medicines must be made in accordance with good manufacturing practice (GMP) guidelines and European Commission guidelines listed in Volume 4 of the Rules

40 Executive Order No. 1823 of 15 September 2015 on reporting of adverse events from medicine use.
41 id., Section 4.
42 id., Section 4.
43 https://laegemiddelstyrelsen.dk/da/bivirkninger/supplerende-overvaagning/.
governing medicinal products in the European Union.47, 48 Manufacturers must have at least one qualified GMP person permanently and continuously at their disposal. The DMA may amend, suspend or revoke a permission, if the conditions for the permission or the terms set out the by DMA are not met.

ix Advertising and promotion
Advertising of medicines must be adequate and objective and must not mislead or exaggerate the characteristics of the medicinal product.49, 50 In addition, advertising of medical devices must not be suitable to endanger the safety or health of the patient, the user or any third party.51 The advertising information must be in accordance with the authorised summary of product characteristics. Advertising for prescription medicine to the general public is not allowed. Direct advertising to healthcare professionals (HCPs) is, however, permitted.52, 53

x Distributors and wholesalers
The DMA issues authorisations to distributors and wholesalers of medicines.54 Such authorisation requires a separate regulation for the specific type of permission (e.g., transport and import of medicines and intermediates, wholesale of medicines or retail sale of non-pharmacy prescription medicines).55 Information about authorised distributors and wholesalers can be found on the DMA website. Transport companies that only provide transportation of medicines do not need an authorisation. However, pharmaceutical companies must ensure that medicines are transported in compliance with the GDP rules.56 Distributors and wholesalers must approve and review their suppliers regularly to monitor the suppliers’ compliance with the GDP rules.

xi Classification of products
The DMA determines whether medicines are classified as prescription medicines or as over-the-counter medicines (OTC) and divides the prescription-only medicines into groups.57 Since 2018 some OTCs are placed freely in pharmacies, shops and retail stores and are no longer to be placed behind a counter or locked in a cabinet. A list of these OTCs

50 Executive Order No. 1153 of 22 October 2014 on advertising rules for medicines.
51 Executive Order No. 1155 of 22 October 2014 on advertising rules for medical devices.
53 Executive Order No. 1153 of 22 October 2014 on marketing of pharmaceuticals, Section 11.
56 Executive Order No. 1358 of 18 December 2012 on good distribution practice of pharmaceuticals.
can be found on the DMA website. Natural medicines, traditional herbal medicines and homeopathic products are also regulated by the DMA, whereas complimentary medicines and vitamins are regulated by the Danish Veterinary and Food Administration.

Pharmacies are legally obliged to substitute the cheapest medicine within the relevant substitution group when dispensing medicine. If a medicine has a patented indication, it may have an effect on how the DMA establishes the substitution group to which the medicine belongs. The marketing authorisation holder of a medicine with a patented indication must therefore inform the DMA about the patent or SPC and its expiry date. The DMA will then verify the patent or SPC in collaboration with the DKPTO. If the patent or SPC affects the substitution rules and groups, these will be changed accordingly. In practice this means that the pharmacy should dispense the medicine with the patent-protected indication.

**xii Imports and exports**

Import of medicines and intermediates requires an authorisation from the DMA. Guidelines and application forms for authorisation can be found on the DMA website. Companies authorised by the DMA to import medicines are supervised regularly by the DMA. Inspections are performed in accordance with the GMP and/or GDP rules. A list of companies authorised to import medicines and intermediates in Denmark (in Danish) can be found on the DMA website. The DMA regularly submits import authorisations to EMA’s EudraGMDP database as they are issued.

**xiii Controlled substances**

Manufacturers, wholesalers and others who handle medicines classified as narcotics or psychotropic substances (euphoriants) must apply to the DMA for an authorisation. Such authorisations may be granted if the substances are prescribed to drug addicts for medical purposes. Dispensing of the medicines may be made for doctors, pharmacists and institutions involved in treatment of drug addicts. A list of euphoriants subject to control by the Danish authorities is available on the DMA website.

---

59 Executive Order No. 1239 of 27 November 2017 on the regulation of complementary medicines.
60 Executive Order No. 1297 of 28 November 2019 on the prescription and dose dispensing of medicines, Section 62(7-8).
65 Executive Order No. 557 of 31 May 2011 on euphoriants.

© 2020 Law Business Research Ltd
On 1 January 2018, a four-year medicinal cannabis pilot programme was introduced whereby the DMA may grant authorisation to produce cannabis intermediate products and to cultivate cannabis for medicinal use and produce cannabis bulk and cannabis primary products from Danish-grown cannabis.

xiv Enforcement

The DMA inspects the development, manufacturing, distribution, dispensing and monitoring of medicines and medical devices to ensure that obligations and requirements set by legislation are complied with. The representatives of the DMA have access to holders of authorisations and companies registered with the DMA without a court order in order to comply with their inspection tasks and to comply with a request from another EU or EEA country, the European Commission or the EMA. The DMA normally gives a notice of 14 days or more prior to an inspection visit. An inspection can last a few hours or several days depending on the area of complexity and risk.

Violation of the regulatory requirements in the Medicines Act, Sections 7, 39 and 64 regarding marketing, advertising, sale, import and distribution of medicines is sanctioned by fines or prison from four months and up to 18 months. Legal entities are subject to criminal liability. The DMA may also amend, suspend or revoke an authorisation.

III PRICING AND REIMBURSEMENT

i Pricing

There is free price formation on medicines in Denmark. When bringing a pharmacy-only medicine to the market in Denmark, the pharmaceutical company must register the pharmacy cost price and any changes thereof no later than 14 days before the price comes into force. Prices are fixed for 14-day periods. The pharmaceutical companies must provide to the DMA the price list with information about prices for medicines for sale during the subsequent 14-day period. According to the national substitution rules, when dispensing prescribed medicine, pharmacies are obliged to substitute the prescribed medicine to the cheapest generic or parallel-imported medicine. The rules on rebates are very strict. A distributor can only give rebates to private pharmacies that are strictly related to cost-saving activities.

70 id., Section 104(1) and (2).
71 id., Sections 15, 16 and 40.
72 See also Section VIII.
74 Executive Order No. 1399 of 2 December 2015 on prices and delivery of medicines.
75 Executive Order No. 1297 of 28 November 2019 on prescriptions and dose dispensing of medicines, Section 62. See also Section II.ix.
77 Executive Order No. 1153 of 22 October 2014 on advertising of pharmaceuticals, Part 9.
In the secondary healthcare sectors, Amgros, the joint procurement service of the Danish Regions, conducts tendering procedures for purchase and supply of medicines and medical devices.

ii Reimbursement
The DMA determines which medicines are eligible for reimbursement based on advice from the Medicines Reimbursement Committee. Reimbursement is provided from the Danish Regions and can be granted as general reimbursement or as conditional reimbursement for prescription-only medicines. General reimbursement is determined by the DMA upon application from the pharmaceutical company bringing the medicine to the market. In a trial period from 1 January to 31 December 2021, the DMA may upon application determine to grant general reimbursement for a prescription-only medicine on terms of risk sharing. In special cases, the DMA may determine to grant individual reimbursement, which is granted upon application from the doctor or dentist and is given to prescription-only medicines for individual patients. The doctor must document in the application why the patient concerned needs treatment with a particular medicine. For terminal patients the DMA can decide to grant 100 per cent reimbursement of the medicine ordered by the doctor, if the doctor has determined that the prognosis is a very short life expectancy (e.g., a few weeks or months) and that hospital treatment with a view to recovery must be regarded as futile. A doctor can also apply for an increased reimbursement if a patient needs a more expensive generic medicine, even if there are less expensive alternatives on the market, for example if the patient is allergic to additives contained in the less expensive medicine. Increased reimbursement means that the grant is based on the actual price of the medicine instead of the reimbursement price.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES
The DMA is the national administrative body under the Ministry of Health. The DMA administers the legislation on medicines, reimbursement, pharmacies, medical devices and euphoriants and is responsible for the monitoring, control and enforcement of medicines, clinical trials and pharmacy regulations. Decisions made by the DMA can in general be appealed to the Ministry of Health. A negative decision from the DMA or the Ministry of Health can be appealed to the courts if challenged by a party with a legal interest in the case.

78 www.amgros.dk/en.
79 www.regioner.dk/services/in-english.
80 Executive Order No. 1781 of 18 December 2018 on the medicines compensation system.
81 Health Act. Consolidated Act No. 903 of 26 August 2019, Section 143.
82 id., Section 152(2).
83 Executive Order No. 1781 of 18 December 2018.
84 id., Section 10.
85 id., Section 12.
V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The Danish Health Act provides the legal framework for pharmaceutical companies’ relationship with healthcare professionals (HCPs). The interaction between HCPs and the pharmaceutical industry is highly regulated to ensure that any cooperation takes place in an ethically responsible manner. Apart from the national rules in the Health Act, an ethical code issued by the Ethical Committee for the Pharmaceutical Industry (ENLI) applies. Only members of ENLI are covered by its special regulations and subject to its sanctions.

i  HCPs’ affiliation with pharmaceutical companies and medical devices companies

Doctors, dentists undertaking clinical duties and proprietary pharmacists cannot operate or be affiliated to a pharmaceutical or medical company or a specialty store with medical devices unless the HCP has notified the DMA of such relationship or received permission from the DMA to such affiliation. Affiliation means ownership or co-ownership, whether personal or via another legal entity, or ownership of securities or other financial affiliation. The rules apply to pharmaceutical companies that have a marketing authorisation from the DMA in Denmark (Medicines Act, Section 7(1)), or a permission from the DMA to produce, import and distribute medicines in Denmark (Medicines Act, Section 39) and to medical companies established in Denmark manufacturing, importing or distributing medical devices in risk class IIa, IIb or III. The rules also apply to medical devices for in vitro diagnostics or active, implantable medical devices and representatives for such companies, apart from public hospitals and to specialty stores that are established in Denmark and where the distribution of medical devices consists of more than 50 per cent of the range of products or turnover. The obligations do not cover affiliations between public hospitals and HCPs.

ii  Financial benefits for HCPs

As a main rule, pharmaceutical companies, etc. cannot, for advertising purposes or to otherwise promote the sale of medicines, give or offer financial support to HCPs. However, two exceptions apply. It is permitted to pay for services from a HCP or a pharmacy if such payment is proportionate to the service. Payment can only be made in the form of direct payment, not by set-off, payment in kind or other indirect manner. HCPs must apply for permission from or notify their affiliation to a pharmaceutical company, etc. to the DMA when receiving such payment. Moreover, HCPs attending educational and promotional activities with a scientific or professional purpose may receive financial support in the form of payment of the reasonable cost in relation to dining, travelling and accommodation. Pharmaceutical companies’ financial support to HCPs’ activities outside Denmark is subject to notification to the DMA. Information about financial support is published on the DMA’s website for a period of two years. Such information includes unambiguous identification of the HCP (name and authorisation number, if any, profession, pharmaceutical company,

87  www.enli.dk.
88  Executive Order No. 693 of 3 July 2019 on healthcare professionals’ relationship with pharmaceutical companies and medical devices, Sections 8, 9, 10 and 12.
89  Executive Order No. 1153 of 22 October 2014 on advertising for medicines, Section 24.
90  id., Sections 26-28.
Denmark

information about activity and date of termination of the activity). Similar rules apply to financial support with respect to medical devices. The rules regarding financial support in respect of medical devices do not include discounts on medical devices.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

In Denmark, a publicly funded compensation scheme has been established to cover injuries occurring in connection with medical treatments in the public and private healthcare system and injuries that result from adverse events from medicine use or personal injuries occurring during clinical trials. The persons that are covered by the compensation schemes are patients, trial subjects and donors. To obtain compensation the person must have been injured by a treatment made by a HCP or from the use of medicines. The time of injury and causal relationship must be documented. Compensation cannot be awarded to injuries that may be related to the basic condition of the patient. If the personal injury is covered by the compensation scheme, the patient or relatives cannot claim compensation directly from the courts or based on other applicable law. The Patient Compensation Association (PCA) is the competent body to perform assessment of the claim. Decisions by the PCA can be appealed to an independent board. If the independent board upholds the decision, a legal complaint may be filed to the ordinary courts. In cases where compensation has been awarded and patient injury was caused by a defect or flawed, dangerous characteristic of the medicine, the government can file a recourse claim against the producer. Filing for recourse is limited as producers are only legally responsible for injuries caused by a defective medicine, and not developmental injuries or already known adverse effects.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The Danish Competition Act implements general European competition law principles and legislation. There are no specific competition rules for the life sciences sector but the Act comprises block exemptions that are of importance to the sector. Of particular interest are sanctions for entering into cartel agreements, which may include imprisonment of up to 18 months if the infringement is intentional and of an aggravated nature. In 2018, the Danish Competition Council ruled that a pharmaceutical distributor had abused its dominant position by charging unfair prices (a 2,000 per cent price increase over a six-month period) for a particular medicinal product for which the distributor held an exclusive distribution contract. The Competition Appeals Tribunal (CAT) upheld the decision. The distributor

91 Executive Order No. 1155 of 22 October 2010 on advertising for medical devices.
95 id., Section 5(1).

© 2020 Law Business Research Ltd
Denmark

has appealed the CAT’s decision to the Maritime and Commercial High Court. The case has been submitted to the Danish State Prosecutor for Serious Economic and International Crime.

ii Transactional issues

Transactional issues of special relevance to medicines and medical devices in the Danish life sciences sector are not considerably different from those in other European jurisdictions. The issues of particular relevance relate to intellectual property rights and permits and licences and certificates required for operations to remain valid after a transaction. This may include manufacturing authorisations, licences for the wholesale of pharmaceuticals and licences for the handling, import or wholesale of substances such as narcotics and marketing authorisations.

VIII CURRENT DEVELOPMENTS

On 19 March 2019, the Danish Regions and the Danish Association of the Pharmaceutical Industry (LIF), a trade association for the researching pharmaceutical industry, entered into a new agreement regarding prices on medicinal products sold to hospitals for the period from 1 April 2019 to 31 March 2023. The agreement reduces the list prices of hospital-only medicines with a total of 12.5 per cent over the four-year period. In addition, an agreement between the LIF, the Danish Regions and the Ministry of Health on a cap on the prices of prescription medicine was entered into for the period from 1 April 2019 to 31 March 2022. This agreement introduces a price ceiling on the prices of prescription medicine for the named period.

Medicine prices are unrestricted in Denmark with respect to the primary and secondary health sector. Since 2009 price cap agreements have been made between the Ministry of Health, the Danish Regions and the LIF regarding hospital-only medicines and since December 2006 regarding prescription medicine. The new agreements extend the original agreements with subsequent extension agreements. The agreements will apply to hospital-only medicine and prescription medicine marketed by the LIF’s member companies. The members will, if permissible under competition rules, comply with the terms of the price cap agreements.

From October 2020 the Danish Medicines Council (DMC) will apply the quality-adjusted life-year (QALY) method when assessing whether new hospital medicines shall be recommended as standard treatment. The main purpose of the QALY method is to ensure better transparency in the decisions of the DMC. However, the QALY method will not stand alone as the DMC will continue to apply the seven principles for prioritising of hospital medicine as decided by the Danish Parliament. In addition, the severity of a disease can also be included as a parameter in its decision-making. With the introduction of the QALY method, the review time will increase to 16 weeks instead of 12 weeks.

The Danish Regions propose to introduce a new ‘Treatment Council’. The purpose is to assess whether the price on different treatments and technologies measures up to the effect for the patients. The Treatment Council will have 14 members including patient representatives,

97 www.lif.dk.
98 www.medicinraadet.dk/om-os/in-english.
health finance managers and representatives from the hospitals, the Danish Medical Society and the Danish Society of Nurses. The purpose is to identify new technological solutions from business and industry which can be extended to the entire healthcare system. The Danish Regions’ proposal is in consultation until 29 January 2020. After the consultation, the board of the Danish Regions will decide on a final model in March 2020. The plan is that the new Treatment Council can start at the beginning of 2021.
I INTRODUCTION

Medicines for human use are regulated primarily by Directive 2001/83/EC\(^2\) and Regulation (EC) No. 726/2004.\(^3\) The legislation lays down the requirements and procedures for marketing authorisation, as well as harmonised provisions for manufacturing, distribution, pharmacovigilance and advertising of medicines. By virtue of the European Economic Area Agreement, European Economic Area (EEA)\(^4\) Member States (Iceland, Liechtenstein and Norway) have implemented the EU’s pharmaceutical regime and references to the European Union in this chapter can therefore often be read to encompass the entire EEA.

The European Medicines Agency (EMA) is the principal EU-level regulatory body for medicines, and its Committee for Medicinal Products for Human Use (CHMP) is responsible for the scientific evaluation of applications for EU marketing authorisations via the centralised procedure. It does so using the resources and expertise of the EU Member States. However, the European Commission is responsible for the granting of EU marketing authorisations and for defining policy in this area. It has produced detailed procedural guidance on a variety of topics, which is compiled in the Rules Governing Medicinal Products in the European Union.

National competent authorities regulate medicines approved by national procedures, the decentralised procedure and the mutual recognition procedure, and are also largely responsible for enforcement of the medicines legislation.

Directive 2001/83/EC and other related EU directives are not directly effective in the EU Member States but have to be implemented into the national laws. This has resulted in national differences in the interpretation and enforcement of EU medicines legislation.

At the time of writing, medical devices are regulated by a series of EU directives: Active Implantable Medical Devices Directive 90/385/EEC,\(^5\) Medical Devices Directive 93/42/

II THE REGULATORY REGIME

i Classification

Product definitions in the applicable EU legislation provide the starting point for distinguishing between medicines, medical devices and other regulated products. These definitions are supplemented by various borderline principles, specific rules and guidelines. In particular, EU case law has held that, when a product falls under the definition of two product types that are regulated under EU law, it must be classified under the EU rules that provide the higher level of public health protection.\(^{10}\) Article 2(2) of Directive 2001/83/EC formally incorporates this principle into EU law. It provides that:

\[
\text{In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this Directive [i.e., the medicines rules] shall apply.}
\]

EU legislation also lays down certain borderline principles. For example, both Directive 93/42/EC and Regulation (EU) 2017/745 contain specific principles for devices that are intended to administer medicines; devices and medicines that form single integral products, intended exclusively for use in the given combination and that are not reusable; and devices that incorporate, as an integral part, a substance that, if used separately, may be considered to be a medicine and that is liable to act upon the body with action ancillary to that of the device.

The European Commission also publishes various manuals on the scope of the application of EU legislation. For example, it has published a ‘Manual . . . on the scope

---


\(^{10}\) C-112/89, Upjohn Company and Upjohn NV v. Farzoo Inc and J Kortmann.

National competent authorities, acting under the supervision of the national courts, must determine borderline issues case by case, taking into account all the characteristics of the product.

ii  Non-clinical studies

Non-clinical studies to demonstrate the health or environmental safety of new chemical or biological substances must be conducted in compliance with the principles of good laboratory practice (GLP).\(^{11}\) The principles of GLP provide a framework within which laboratory studies, both in vitro and in vivo, are planned, performed, monitored, recorded, reported and archived. Directive 2001/83/EC expressly provides that certain non-clinical (pharmaco-toxicological) studies of medicines must be carried out in conformity with GLP.

All tests on animals conducted in the EEA must be carried out in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes.\(^ {12}\) Directive 2010/63/EU anchors the principle of the ‘three Rs’ (to replace, reduce and refine the use of animals) in EU legislation. It also lays down minimum standards for housing and care, and regulates the use of animals through an evaluation requiring an assessment of pain, suffering, distress and lasting harm.

iii  Clinical trials

Medicines

Clinical trials of medicines for human use are regulated under Directive 2001/20/EC,\(^ {13}\) at least until Clinical Trial Regulation (EU) No. 536/2014\(^ {14}\) becomes applicable, which has been postponed by the EMA due to IT system technical difficulties and is now unlikely to occur before the second half of 2021. Clinical trials of medicinal products in human subjects require notification to, or authorisation by, the relevant Member State’s competent authority. In addition, a clinical trial of a medicinal product requires a favourable opinion by an ethics committee. The sponsor of a clinical trial, or its legal representative, must be based in the EEA.

Clinical trials must be conducted in accordance with internationally recognised principles of good clinical practice (GCP) and must comply with the Declaration of Helsinki.

---

\(^{11}\) Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, as amended.


Medicines used in clinical trials must be manufactured in accordance with standards of good manufacturing practice (GMP) and released by the holder of a manufacturer’s authorisation in the EEA.

A clinical trial may be undertaken only if provision has been made for, among other things, insurance or indemnity to cover the liability of the investigator and sponsor, and the receipt of informed consent from the trial subjects.

Companies must report all suspected serious unexpected adverse reactions to the competent authorities and to ethics committees within 15 days, and seven days in the event of a fatality, and must submit an annual listing of all suspected serious adverse reactions that occurred during that period.

Although the European Commission has previously consulted on specific rules for ‘non-commercial trials’, no such rules have been adopted.

**Medical devices**

As at the time of writing, clinical investigations of medical devices are governed by Directive 93/42/EEC, Directive 90/385/EEC or Directive 98/79/EC, as applicable. The rules on clinical investigations of devices apply to studies of non-CE-marked devices, and to CE-marked devices if they are not CE-marked for the purpose being investigated. The Directives do not recognise the concept of the ‘sponsor’; rather, the manufacturer of the device intended for use in the clinical investigation is responsible for ensuring compliance with the relevant requirements. Compliance with certain standards, such as EN ISO 14155:2011 on clinical investigations of devices, raises a presumption that the manufacturer complies with the applicable provisions under the Directives.

The study must be conducted in accordance with the latest version of the Declaration of Helsinki, which includes requirements for the informed consent of study subjects. Prior to conducting a study in the EEA, the manufacturer, or its authorised representative based in the EEA, must seek ethics committee approval and notify the device regulators in the relevant jurisdictions. All serious adverse events must be reported immediately to the competent authorities.

The Directives do not contain specific requirements for compensation and insurance for injuries to study subjects. There are also no special rules for investigator-initiated studies.

Regulation (EU) 2017/745 contains detailed new clinical trial rules for medical devices, modelled on those applicable to clinical trials of medicines. The new rules relating to the procedure for authorisation and oversight of clinical investigations will only apply once a new expanded EU database of medical devices (‘Eudamed’) becomes fully operational, which is currently not expected before 2022. However, other new rules relating to clinical investigations will apply to any clinical investigation of a medical device commenced in the EU from 26 May 2020. Among other things, these new rules impose obligations on the sponsor of the investigation, and contain specific requirements for compensation and insurance for injuries to study subjects. Regulation (EU) 2017/746 contains similar rules for clinical trials of IVDs, and will apply from 26 May 2022.
iv Named-patient and compassionate use procedures

**Medicines**

Generally speaking, no medicinal product may be placed on the market in the EU without a marketing authorisation. However, this is subject to a number of exemptions, including the ‘named-patient’ exception.\(^\text{15}\) The named-patient exemption covers the provision of unauthorised medicines with assumed benefits in situations where alternative treatment options are either non-existent, unsatisfactory or have been exhausted.

The named-patient exemption applies only where the supply of a medicine is:

\(a\) in response to a bona fide unsolicited order;

\(b\) formulated in accordance with the specification of a doctor and for use by his or her individual patients on his or her direct personal responsibility; and

\(c\) to fulfil a ‘special need’. This exception must be construed narrowly, and in accordance with the overarching principle underlying Directive 2001/83/EC that ‘the protection of public health must take precedence over economic considerations’, and that the precautionary principle should be applied so as to err in favour of protecting public health where there is any doubt about the efficacy or safety of a product.

Article 83 of Regulation (EC) No. 726/2004 also specifies that Member States may make certain medicines available for ‘compassionate use’. The Regulation defines ‘compassionate use’ to cover:

*making a medicinal product . . . available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product.*

To qualify for compassionate use, the medicine must be either subject to a marketing authorisation application or be undergoing clinical trials. Member States must notify the EMA whenever they make use of the compassionate use procedure outlined in the Regulation.

EU Member States interpret the named-patient and compassionate use regimes differently, and application requirements and administrative procedures vary significantly in each jurisdiction.

**Medical devices**

A medical device must comply with the applicable essential requirements and bear a CE mark before it can be placed on the market in the EEA. There is no EU-wide ‘named-patient’ or ‘compassionate use’ exemption for medical devices, although a number of Member States operate similar schemes under national laws for medical devices. However, the EU medical devices Directives permit the supply of ‘custom-made devices’ without a CE marking, provided they meet applicable requirements under the Directives. Essentially the same rules will continue to apply under Regulation (EU) 2017/745. A ‘custom-made device’ is any device specifically made in accordance with a duly qualified medical practitioner’s written prescription which gives, under his or her responsibility, specific design characteristics and

\(^{15}\) Article 5(1) of Directive 2001/83/EC.
is intended for the sole use of a particular patient’. The definition excludes mass-produced devices that need to be adapted to meet the specific requirements of the medical practitioner or any other professional user.

The manufacturer of a custom-made device must draw up a statement containing certain information, including:

- the manufacturer’s name and address;
- a statement that the device is intended for exclusive use by a particular patient, with the name of the patient;
- the name of the medical practitioner or other authorised person who made out the prescription for the product;
- the specific characteristics of the product as indicated by the prescription; and
- a statement that the device conforms to the essential requirements and, where applicable, indicating which essential requirements have not been fully met, with the grounds.

v Pre-market clearance

Medicines

Manufacturers of medicines must obtain a marketing authorisation before they can place their products on the EEA market. For certain products, including, in general terms, biotechnology products, advanced therapy medicinal products, orphan drugs and new active substances for the treatment of AIDS, cancer, neurodegenerative disorder, diabetes, autoimmune diseases, other immune dysfunctions and viral diseases, the marketing authorisation application must be submitted to the EMA for review through the centralised procedure. The CHMP also has the discretion to permit other products to use the centralised procedure if it considers them sufficiently innovative. Using the resources of selected national medicines agencies, the CHMP considers the application and gives an opinion on the approvability of the product. However, the marketing authorisation itself is granted by the European Commission and this is valid throughout the EU and, by extension, the EEA.

For all other products, the competent authorities of the Member States are responsible for granting marketing authorisations for products that are sold in their markets. Applicants who intend to market such products in more than one Member State may seek marketing authorisations under the mutual recognition procedure or the decentralised procedure. If the product has already been authorised in one Member State, the mutual recognition procedure facilitates mutual recognition of the existing authorisation in another Member State. The decentralised procedure, on the other hand, may be used in cases where the product has not received a marketing authorisation in any Member State. Under this procedure, the applicant submits an identical dossier to each relevant Member State and one, known as the reference Member State, takes the lead in reviewing the application.

The applicant for a marketing authorisation under any of these procedures must be established in the EEA. It must submit sufficient data to demonstrate the quality, safety and effectiveness of the product. The format for the marketing authorisation application form and the underlying dossier is consistent for all medicinal products. Dossiers must follow the International Conference on Harmonisation common technical dossier format, in which quality and manufacturing, preclinical and clinical trial sections are accompanied by associated summary reports.

There is scope for applicants to omit some or all of the preclinical and clinical trial data if the product falls within the definition of a generic of a reference product for which regulatory data exclusivity protection has expired. The marketing authorisation underpinning
the reference medicinal product must be based on a complete dossier; a generic application referring to a generic dossier is not possible. Generic applicants may need to submit additional preclinical or clinical data if their product does not fall within the definition of a generic (i.e., where there are differences in active substances, therapeutic indications, strength, pharmaceutical form or route of administration, in relation to the reference medicinal product, or where bioequivalence cannot be demonstrated through standard bioavailability studies). In these cases, bridging data is required to demonstrate that the differences do not affect the product’s relative safety and effectiveness inappropriately.

Preclinical and clinical data can be omitted and replaced with references to scientific literature if the product has been in well-established medicinal use in the EU for at least 10 years. An existing marketing authorisation holder may also give consent for a subsequent applicant to reference the pharmaceutical, preclinical and clinical data on file for the original product.

Specific rules govern biological medicinal products and acknowledge that complex substances, or mixtures of substances, of biological origin are sensitive to changes in source materials and manufacturing processes. The rules therefore focus less on the characterisation of substances themselves from a chemical perspective and more on control of the manufacturing and quality control processes to produce substances or mixtures of comparable quality, safety and effectiveness. This is reflected in special rules for the approval of biological medicinal products that are similar to a reference product. Once the reference product’s data exclusivity period has expired, the applicant may file an application equivalent to a generic application but will generally need to submit a body of data demonstrating comparable quality, safety and efficacy.

There is a simplified registration process for traditional herbal medicinal products. A herbal product is only ‘traditional’ if the applicant can produce bibliographical or expert evidence that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, 15 of which must have been within the EU.

There is also a simplified procedure for homeopathic medicines. Although the safety and quality of such products has to be demonstrated, the products are not permitted to make medicinal claims. The scheme is restricted to homeopathic products for oral and external use and does not allow indications (the descriptions of diseases or conditions for which the medicine is intended to be used).

**Medical devices**

There is no pre-market government review of medical devices in the EU unless the device also contains a medicine or a blood derivative. However, all medical devices placed on the market in the EEA at time of writing must meet the relevant essential requirements set out in Directive 93/42/EEC, Directive 90/385/EEC or Directive 98/79/EC, as applicable, taking account of the intended purpose of the device.

More detailed requirements and technical specifications are set out in voluntary harmonised European standards. Compliance with harmonised standards is not mandatory, provided that the manufacturer demonstrates compliance with the essential requirements. However, compliance with applicable standards raises a presumption of conformity with the essential requirements.

Manufacturers must demonstrate that their devices comply with the relevant essential requirements through a conformity assessment procedure. The method for assessing
conformity varies depending on the type and class of the product, but normally involves a combination of self-assessment by the manufacturer and a third-party assessment by a notified body, an independent and neutral entity appointed by a country to conduct the conformity assessment. As a general rule, clinical evidence is required to demonstrate that the device functions as intended and that it is safe. The clinical evidence may comprise studies on the device itself and, where appropriate, relevant data on equivalent devices from the peer-reviewed literature. Devices that conform to the essential requirements must bear a CE mark and can then be commercially distributed throughout the EEA.

For IVDs, custom-made devices and Class I medical devices, where the manufacturer self-declares conformity with the essential requirements, the manufacturer, or its authorised representative in the EEA, must register with the competent authority in the country in which it is established prior to placing any such product on the market.

The general principles for CE marking will remain the same under Regulation (EU) 2017/745 and Regulation (EU) 2017/746, although there will be additional regulatory authority involvement in the conformity assessment of certain Class III and Class IIb devices, as well as devices incorporating medicinal substances or tissues and cells of human or animal origin. Regulation (EU) 2017/746 will reclassify all IVDs into Classes A, B, C and D and the conformity assessment procedures under the Regulation for all but Class A IVDs will require the involvement of a notified body.

vi Regulatory incentives

Medicines

A supplementary protection certificate, extending the term of a patent with respect to a particular medicinal product, will be granted if, in the EU Member State in which the application is submitted and at the date of the application:

- the product is protected by a basic patent in force;
- a valid marketing authorisation has been granted for the product;
- the product has not already been the subject of a certificate; and
- the marketing authorisation in question is the first marketing authorisation for that product.

The certificate takes effect at the end of the patent term for a period equal to that between the filing date of the basic patent and the date of first marketing authorisation for the product, reduced by five years, provided that the duration of the certificate cannot exceed five years.

Regulatory data exclusivity in Europe is independent of a product’s patent position. New chemical entities approved on the basis of a complete, free-standing data package are entitled to eight years’ regulatory data exclusivity from the date on which the product is first approved in the EEA. During that period, generic applicants cannot file applications referring to the innovator’s safety and efficacy data. At the end of that eight-year period, generic applicants may file and the authorities may review applications. However, the innovator is granted a further two years of ‘market exclusivity’ before any generic product may launch. This period of market exclusivity can be extended by a further year if a new therapeutic indication that provides a significant clinical benefit is approved during the first eight years of data exclusivity. For applications prior to 20 November 2005 for centralised approvals, authorisation holders were entitled to 10 years’ data exclusivity protection. For applications
for national approvals prior to 30 October 2005, authorisation holders are entitled to 10 years’ exclusivity in Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Sweden and the United Kingdom, but six years in every other EEA jurisdiction.

Regulation (EC) No. 141/2000 contains additional data exclusivity provisions for ‘orphan medicinal products’. These are products intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EEA; or that without incentives is unlikely to generate sufficient return to justify the necessary investment. An orphan designation can be granted only if there is no satisfactory method of diagnosis, prevention or treatment of the condition authorised in the EEA, or if the product will be of significant benefit.

If a medicine is approved as a designated orphan medicine, the product will benefit from 10 years’ market exclusivity during which regulators cannot accept applications for similar medicinal products for the same indication, unless they offer a significant clinical benefit (i.e., in terms of safety or efficacy). Similar medicinal products are those with the same or similar active moieties.

Regulation (EC) No. 1901/2006 also provides specific incentives for the development of products with paediatric indications. If a product is approved on the basis of a dossier that includes paediatric clinical trial data generated in accordance with an approved paediatric investigation plan, the applicant will benefit from one of two periods of exclusivity: (1) if the product is an orphan medicine, it will benefit from an additional two years of orphan drug exclusivity (i.e., a total of 12 years’ orphan exclusivity); or (2) if the product is not an orphan medicine and is eligible for patent term extension (referred to as a supplementary protection certificate), the patent term will be extended by six months.

**Medical devices**

The EU medical devices rules do not provide for any form of regulatory exclusivity. These innovations are almost exclusively protected through patent rights and protection of confidential know-how.

vii Post-approval controls

**Medicines**

The marketing authorisation holder for a medicine is ultimately responsible for any product placed on the market under its approval, and must also fulfil several obligations by virtue of its status. While the associated legal responsibility and liability cannot be delegated, the marketing authorisation holder can delegate the performance of related tasks to third parties, provided that this delegation is appropriately documented.

The marketing authorisation holder must establish and maintain a pharmacovigilance system and must have permanently and continuously at its disposal within the EEA a qualified person for pharmacovigilance, who is responsible for oversight of the pharmacovigilance system, documented in a pharmacovigilance system master file. Key requirements include

---


expedited reporting of suspected serious adverse reactions within 15 days, reporting of suspected non-serious adverse reactions within 90 days and submission of periodic safety update reports (PSURs). The marketing authorisation holder must comply with good pharmacovigilance practice guidelines adopted by the EMA.

The marketing authorisation holder must have a ‘scientific service’ responsible for disseminating scientific and medical information on its medicinal products, predominantly to healthcare professionals, but also to regulators and patients.

Since July 2012, all new marketing authorisation applications must include a risk management plan (RMP) describing the risk management system that the marketing authorisation holder will put in place. Previously, an RMP was only required ‘where appropriate’, such as for biological products or products containing a new active substance. The RMP must identify or characterise the safety profile of the product, document measures to prevent or minimise the risks associated with the product, and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation. Such risk-minimisation measures or post-authorisation obligations may include additional safety monitoring, more frequent submission of PSURs or the conduct of additional clinical trials or post-authorisation safety studies.

A new marketing authorisation is valid for five years. Upon renewal, the authorisation will become valid indefinitely, unless the competent authority concludes that safety grounds merit a further five-year fixed term.

Variation applications must be submitted to the competent authorities to make any amendments to marketing authorisations, the summary of product characteristics or package leaflet for the product, or the underlying dossiers. Variations are classified as Type IA, which should be implemented and then notified to the competent authorities, Type IB, which should be notified to the competent authorities in advance and may be implemented if the authorities have not objected within 30 days, and Type II, which require prior approval from the competent authority.

Transfers of marketing authorisation require the prior approval of the competent authority. The procedure and timing varies depending on the marketing authorisation approval procedure and the country, but in all cases an application will need to be submitted to the competent authority, with documentation provided by both the transferor and the transferee. There will usually be an agreed transition period of three to six months before the transfer is completed. Generally speaking, the competent authorities discourage transfer applications while renewal or variation procedures for the marketing authorisation are in train.

The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or lacks therapeutic efficacy, that the risk-benefit balance is not favourable or that its qualitative and quantitative composition is not as declared. Marketing authorisations may also be suspended, revoked or varied if incorrect information was submitted in the marketing authorisation application, the marketing authorisation has not been updated appropriately, or conditions of the marketing authorisation, such as commitments to perform post-authorisation safety studies, have not been satisfied.

© 2020 Law Business Research Ltd
Once a product has been launched in a jurisdiction, there is an obligation on marketing authorisation holders and their distributors to meet demand in that jurisdiction. EU law includes sunset clauses for marketed medicines. These provide that a marketing authorisation shall cease to be valid if the product is not placed on the market within three years of the marketing authorisation being granted, or if a previously marketed product is no longer actually present on the market for a period of three consecutive years. For centrally approved products, the sunset provisions would not be triggered provided the product was marketed in at least one EEA jurisdiction.

Medical devices

Device manufacturers are required to put in place and maintain a systematic procedure for review of post-market experience, including reporting of incidents to competent authorities when required, and to implement any necessary corrective actions.

A device manufacturer (along with its authorised representative) must maintain a copy of the technical documentation underpinning its CE marking and make this available for inspection by national device regulators on request. The dossier should be kept up to date. If the applicable conformity assessment procedure has involved a notified body, any significant changes to the dossier or the manufacturer’s quality system should be submitted to the notified body for approval and may require an update or reissue of any certificates of conformity issued by the notified body.

Notified body certificates of conformity are valid for a fixed duration (which shall not exceed five years). Throughout the term of the certificate, the manufacturer will be subject to periodic surveillance audits to verify continued compliance with the applicable requirements. In particular, there will be a new audit by the notified body before it will renew any certificate.

There is no set process for transferring ownership of notified body certificates of conformity. The transferor and transferee should contact the relevant notified body and agree on the process. If the transferee will be operating the same manufacturing process at the same facility, a new or updated certificate of conformity can be issued in a matter of days. If, however, the transferee will be manufacturing the device at a different facility, the notified body may need to conduct a new conformity assessment prior to issuing a certificate of conformity in the name of the transferee.

Regulation (EU) 2017/745 contains more stringent requirements than the Directives, including the requirement for a formal post-market surveillance plan prepared in accordance with the specifics set out in the Regulation. Manufacturers will also be required to prepare periodic safety update reports (PSURs) for Class IIa devices at least every two years, and at least annually for Class IIb and III devices. Similar requirements will be introduced by the new IVD Regulation (EU) 2017/746.

Manufacturing controls

Manufacturers of both marketed and investigational medicinal products must have a manufacturing authorisation from the competent authority in the EU Member State in which they are established. The manufacturing authorisation will be limited to the premises and the medicinal products specified in the manufacturer’s application. Importers of medicinal products from outside the EEA may also require a manufacturing authorisation.
Medicinal products must be manufactured in accordance with the principles of GMP, set out in Directive 2003/94/EC\(^{19}\) and the European Commission’s guidelines in Volume 4 of the Rules governing medicinal products in the EU.

Manufacturers must have at least one qualified person permanently and continuously at their disposal. The qualified person is ultimately responsible for certifying that each batch of finished product released onto the market has been manufactured in accordance with GMP and the specifications set out in the marketing authorisation or investigational medicinal product dossier. For medicinal products that are imported from outside the EEA (irrespective of where the product was actually manufactured), the qualified person must ensure that each batch of product has undergone full quality control testing in an EEA Member State prior to release onto the market.

The procedure for transfers of manufacturing authorisations is a matter of national law, but the EU rules require manufacturers to notify the competent authority of any changes to the particulars in the manufacturing authorisation application, including in particular any change in the identity of the qualified person.

Active substances intended for use in the manufacture of medicinal products must have been manufactured in accordance with GMP. Importers, manufacturers and distributors of active substances must register with the competent authority in the EU Member State in which they are established and may be subject to an inspection. The registration application must identify the active substances and the premises concerned. The applicant must update the registration annually, and must notify the competent authority immediately of any changes that may have an impact on the quality or safety of the active substances.

**Medical devices**

There are no EU rules requiring approval of manufacturing facilities for medical devices. However, the conformity assessment procedures may involve a notified body assessment of the manufacturer’s quality system. The manufacturer can demonstrate conformity with the requirements for the quality system by complying with the applicable harmonised standards, including ISO 13485:2016 on Standards for Quality Management System on Medical Devices. Any changes to the assessed quality system must be submitted to the notified body for approval.

**Advertising and promotion**

**Medicines**

Medicines advertising is defined broadly to include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products. It includes visits by sales representatives, the supply of samples, provision of gifts and hospitality, and sponsorship of meetings. Certain activities are specifically exempted from the medicines advertising rules, including responses to specific questions about a medicinal product and the dissemination of factual, informative announcements and reference material. These are only exempted if they are non-promotional in nature.

All medicines advertising must be consistent with the product’s approved summary of product characteristics, factual, accurate, balanced and not misleading. Advertising of medicines pre-approval or off-label is prohibited. Advertisements to healthcare professionals must also be presented in a certain format, for example, indicating the brand and generic name of the relevant product with suitable prominence, and must contain certain minimum information about the product. Direct-to-consumer advertising of prescription medicines is prohibited, and there are strict rules governing the content of direct-to-consumer advertising of non-prescription medicines.

No gifts or other benefits may be given to healthcare professionals unless they are inexpensive and relevant to the practice of medicine. Any hospitality provided in conjunction with an event must be limited to the main purpose of the event and given only to healthcare professionals. There are also specific rules on the provision of samples to healthcare professionals.

Medicines advertising enforcement is largely on the basis of self-regulation. The European Federation of Pharmaceutical Industry Associations (EFPIA) has adopted a consolidated code of practice covering interactions with healthcare professionals, patient organisations and the disclosure of transfers of value. Most national pharmaceutical industry associations have adopted their own codes of conduct based on the EFPIA codes.

Medical devices

Unlike the medicines rules, there are no harmonised European level rules governing the advertising and promotion of medical devices, resulting in Member States adopting somewhat divergent approaches to the regulation of medical device advertising. However, the general advertising rules requiring that advertisements are substantiated, factual, balanced and not misleading apply to medical device advertising.

Medical devices and IVDs may be displayed at trade shows and exhibitions before they are CE-marked and placed on the market, provided that they are not used for their intended medical or diagnostic purpose and that a sign makes clear that the devices cannot be marketed or put into service until they have been made to comply with the relevant rules.

Distributors and wholesalers

Any company engaged in wholesale distribution of medicinal products in the EU must have an authorisation to engage in the activity, and the licence must state the premises for which it is valid. Manufacturing authorisations include the right to engage in wholesale distribution. Wholesale distribution is defined as all activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public.

Traditionally, most Member States have taken the view that wholesale distribution only takes place where the products are handled physically; mere paper transactions have not been regarded as wholesaling. In some Member States, however, the authorities interpret the terms ‘procuring’ and ‘supplying’ to cover the act of buying and selling medicines (i.e., the transfer

---

20 The EFPIA Code of Practice.
of legal title), even if the company never physically handles the product. This interpretation is becoming more prevalent, following references in Directive 2011/62/EU to ‘wholesale distributors, whether or not they physically handle the medicinal products’. 21

Wholesalers may only obtain their supplies from authorised manufacturers or wholesalers, and may only supply medicinal products to other wholesalers or to persons entitled to supply medicinal products to the general public. The holder of a wholesale dealer licence is subject to various record-keeping obligations, to demonstrate that product is supplied only to those entitled to receive it and to allow for an effective recall of product if necessary. The licence holder must also have at its continuous disposal the services of an appropriately qualified person, who is responsible for ensuring that a quality management system is implemented and that the company complies with the principles of good distribution practice (GDP).

Directive 2011/62/EU introduced the concept of brokering, defined as all activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.

Brokers must have a permanent address and contact details in the EU, so as to ensure accurate identification, location, communication and supervision of their activities by competent authorities. They must register with the competent authorities in which they have their permanent address. Brokers must comply with the principles of GDP and are subject to the same record-keeping obligations that apply to wholesale distributors.

Medical devices

To date, there have been no EU-harmonised rules that govern the distribution of medical devices, although some Member States regulate the activity. However both Regulation (EU) 2017/745 and Regulation (EU) 2017/746 will introduce greater statutory obligations for distributors. Distributors will be required to verify all devices have been correctly CE marked and labelled, who the manufacturer is and that the manufacturer has a assigned a ‘unique device identifier’ (UDI). Distributors must also ensure that devices under their responsibility are stored and transported in accordance with the manufacturer’s conditions. If a distributor considers or has a reason to believe a device is non-conformant with the regulation, it must immediately inform the manufacturer and any other applicable ‘economic operators’ in the supply chain (e.g., the manufacturer’s authorised representatives and importers, if any). Distributors must maintain a register of all complaints, non-conforming devices, recalls and withdrawals and provide this information to all relevant national component authorities upon request.

Classification of products

Medicines

Competent authorities must classify medicines as prescription-only or non-prescription but are entitled to further subdivide this classification. For example, competent authorities can, if they wish, classify prescription-only medicines as being subject to ‘special medical prescription’ (e.g., controlled substances under the UN Conventions and other substances

with a risk of abuse or dependency) or ‘restricted prescription’ (e.g., products that can only be used in a certain setting or by certain specialists). Some Member States also subdivide the classification of non-prescription medicines to allow for products that can only be supplied under the supervision of a pharmacist, over-the-counter products and products for general retail sale.

Medicinal products must be classified as prescription-only if they:

a. are likely to present a danger either directly or indirectly if utilised without medical supervision;

b. are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health;

c. contain substances or preparations, the activity or adverse reactions of which require further investigation; or

d. are normally prescribed by a doctor to be administered parenterally.

The applicant for a marketing authorisation has to identify in the initial application a proposed classification of the product. However, the classification is ultimately decided by the competent authorities when they grant the marketing authorisation.

The marketing authorisation holder can apply to have the product reclassified in light of new information (such as significant post-marketing experience with the product). If the change of classification has been authorised on the basis of significant preclinical tests or clinical trials, the competent authorities may not refer to the results of those tests for one year when examining reclassification applications by other marketing authorisation holders.

Medical devices

Medical devices are classified as Class I, IIa, IIb or III, but this is for the purposes of determining the appropriate conformity assessment procedure. Other than the differentiation between active implantable medical devices, in vitro diagnostic devices and other medical devices, there are no EU-harmonised rules that govern the classification of medical devices for the purposes of prescription or sale. Manufacturers often choose to classify devices as being for professional use only.

Imports and exports

Medicines

An entity importing medicinal products, including bulk product, from countries outside the EEA must hold a manufacturing authorisation. The holder of a manufacturing authorisation must retain the services of a qualified person, who will be responsible for ensuring that any imported product has undergone appropriate quality control testing prior to batch release onto the EEA market.

EU rules on the import of active pharmaceutical ingredients (APIs) require that APIs imported into the EEA must be manufactured in compliance with standards equivalent to EU GMP. Since July 2013, the competent authority of the exporting country has been required to confirm this compliance in writing. The written confirmation must accompany the imported APIs.

The definition of ‘wholesale distribution’ in Directive 2001/83/EC includes the export of medicinal products. An entity exporting medicinal products out of the EEA must therefore hold a wholesale distribution authorisation or manufacturing authorisation. As part of their import requirements, certain countries require medicinal products to be accompanied by an
export certificate. These certificates confirm that the product or manufacturer to which the certificate relates has met statutory requirements in the country of export. Export certificates can take one of several forms, including a certificate of a pharmaceutical product, or a certificate of manufacturing status. The exact procedure for obtaining these certificates differs according to the laws of the country of export.

Medical devices
There are currently no EU-harmonised rules that govern the import or export of medical devices. When effective, Medical Devices Regulation (EU) 2017/745 and IVD Regulation (EU) 2017/746 will introduce new obligations for entities importing medical devices from countries outside the EU, including verifying any device they place on the market is in conformity with the standards of the applicable regulations. Importers will need to register themselves on ‘Eudamed’ (the EU’s electronic medical devices database), and must include on the devices’ packaging or accompanying documentation their name, any trade name or trade mark, and a registered address. If an importer considers or has a reason to believe a device is non-conformant with the regulation, it must immediately inform the manufacturer and any other applicable economic operators. Importers must also maintain their own register of complaints, non-conforming devices, recalls and withdrawals, to be made available to all relevant national competent authorities upon request.

Controlled substances
The United Nations (UN) Single Convention on Narcotic Drugs (1961) and the UN Convention on Psychotropic Substances (1971) codify internationally applicable control measures to ensure the availability of narcotic drugs and psychotropic substances for medical and scientific purposes. The individual Member States of the EU are all signatories to these UN Conventions. All signatories have a dual obligation to ensure that these substances are available for medical purposes and to protect populations against abuse and dependence.

The UN Conventions require signatories to require all persons manufacturing, trading (including exporting and importing) or distributing controlled substances to obtain a licence from the relevant authority. Each individual export or import of a controlled substance must also be subject to an authorisation. Before the relevant authority can issue an export authorisation for a particular shipment, the exporter must provide the authority with a copy of the import authorisation issued by the relevant authority of the importing country.

Enforcement
Medicines
The EMA is responsible for coordinating inspections to verify compliance with GCP, GMP, GLP and pharmacovigilance requirements for all centrally approved products. The EMA does not have any inspectors itself, but instead relies on inspectors from the national competent authorities to conduct inspections on its behalf. If an inspection identifies any non-compliance, typically corrective actions would be agreed with the marketing authorisation holder or other company inspected and, provided these were implemented, no further action would be taken. If the non-compliance gives rise to safety concerns about a particular product, the EMA could recommend to the European Commission that the authorisation be suspended or revoked.
In serious cases of non-compliance for centrally approved products, the European Commission could impose sanctions under the EU Penalties Regulation. The European Commission can fine the marketing authorisation holder up to 5 per cent of the holder’s EU turnover in the preceding business year. If the infringement continues, the European Commission may impose further daily fines of up to 2.5 per cent of the holder’s average daily EU turnover in the preceding business year, until the infringement ceases. Non-cooperation with the European Commission’s investigation of the infringement attracts an additional fine of 0.5 per cent of the holder’s Community turnover in the preceding business year.

The national competent authorities are responsible for conducting inspections for products that are not centrally approved and in relation to manufacturing and distribution authorisations. The sanctions for non-compliance are determined by national laws.

**Medical devices**

Manufacturers of medical devices are not subject to regular inspections by competent authorities, although notified bodies will conduct surveillance audits as part of the ongoing conformity assessment procedures for many devices. National competent authorities are responsible for enforcing the medical device rules in their jurisdiction and sanctions are determined by national laws. Safeguard measures in the medical devices directives also allow Member States to restrict or prohibit the marketing of medical devices or to withdraw devices from the market where a device, although correctly marketed and used, may compromise the health and safety of patients, users or others.

### III PRICING AND REIMBURSEMENT

#### i Medicines

EU Member States are responsible for establishing and organising of their national social security schemes, including healthcare policies to promote the financial stability of their healthcare insurance systems. Differential pricing and reimbursement of medicinal products in Member States, however, may affect the free movement of these goods in the internal market.

Directive 89/105/EEC lays down a general procedural framework to increase the transparency of national pricing and reimbursement measures to limit the potential impact on these measures on the internal market for medicinal products. This Directive does not harmonise national pricing and reimbursement measures in the EU, nor does it identify substantive criteria on which Member States must base their pricing and reimbursement decisions. This is in line with the limited competence of the EU in the field of management.

---


of healthcare resources and the principle of minimum interference in the organisation by Member States of their domestic social security policies, as confirmed by European case law. For example, in ABPI v. MHRA, the CJEU confirmed that public bodies forming part of a national public health service are not precluded from implementing prescribing incentive schemes that offer financial inducements to doctors to prescribe or switch patients to generic medicines, to achieve cost savings provided that the schemes comply with Directive 89/105/EEC.

Directive 89/105/EEC lays down three key requirements with respect to national pricing and reimbursement decisions: (1) decisions must be made within a specific time frame (90 to 180 days); (2) decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria; and (3) decisions must be open to judicial appeal at national level.

ii Medical devices

There are no EU-harmonised rules governing the pricing and reimbursement of medical devices; this remains the competency of Member States. Directive 89/105/EEC does not apply to medical devices.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

i Medicines

Under EU law, it is possible to challenge directly, and in some instances indirectly, the decisions of the European Commission and EMA concerning medicinal products. Article 263 of the Treaty on the Functioning of the European Union (TFEU) permits direct challenges to the legality of EU acts and allows the EU courts to review the legality of acts of EU institutions, bodies and agencies that are intended to produce legal effects against third parties.

For an EU act or decision to be successfully challenged, an application must satisfy certain basic requirements, including that the relevant act and body must be amenable to review, the applicant must have standing, and the application must be brought within the relevant time limit.

Article 263 TFEU sets out four specific grounds under which the EU courts may review an EU act: lack of competence, infringement of an essential procedural requirement, infringement of the TFEU provision or any rule of law relating to its application, and misuse of power. The EU courts have used these grounds as a framework through which to develop general principles and grounds for review under EU law by drawing on concepts found within national legal systems. These include fundamental rights (e.g., right to be heard, duty to give reasons, consultation and participation), proportionality, legitimate expectations, legal certainty, non-discrimination, transparency and, more recently, the precautionary principle. The same potential grounds of review apply to indirect challenges to EU acts under Article 267 TFEU.


26 The EU courts are known as the Court of Justice of the European Union (CJEU) and comprise three courts: the Court of Justice, the General Court and the Civil Service Tribunal.
Article 267 TFEU allows any court or tribunal of a Member State to make a preliminary reference to the CJEU in cases concerning: ‘the interpretation of the Treaties’ or ‘the validity and interpretation of acts of the institutions, bodies, offices or agencies of the Union’. Thus, if an EU act addressed to a Member State or national competent authority requires specific action, an individual affected by that action may challenge the validity of the decision on which the action is based via the national courts.  

Under Article 267(3) TFEU, a national court or tribunal has an obligation to make a preliminary reference to the CJEU where the court or tribunal considers that a decision on the question of EU law raised is ‘necessary to enable it to give judgment’. The Foto-Frost doctrine also requires that if a national court or tribunal entertains serious doubts as to the validity of an EU act, it must make a preliminary reference, as the CJEU has exclusive jurisdiction to declare EU acts to be unlawful.

Appeals and judicial reviews of decisions by national competent authorities are governed by the rules of the specific EU Member State.

Medical devices

The general administrative principles outlined in Section IV.i apply to challenges of decisions or acts of EU institutions, bodies or agencies that concern medical devices, such as an unfavourable decision by the EMA in relation to a medical device incorporating a medicine or a blood derivative. Appeals and judicial reviews of decisions by national competent authorities are governed by the rules of the specific EU Member State.

V. FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

i. Medicines

Directive 2001/83/EC regulates the promotion of medicinal products and also interactions between pharmaceutical companies and healthcare professionals. Communications or activities of pharmaceutical companies involving prescribers and payers must comply with the EU medicine advertising rules, if they are promotional.

If a communication is a genuine attempt to provide meaningful and relevant information that would assist the payer in making pricing, reimbursement or formulary or other positive listing decisions, then it is unlikely to be deemed promotional, even if the outcome might lead to an increased prescription or use of a particular product. On the other hand, any communication or activity intended simply to raise the profile of a product in the eyes of a payer may be promotional unless it contributes meaningfully to the payer’s consideration of a medicinal product for pricing, reimbursement or formulary-listing purposes.

Companies should take particular care when communicating with non-healthcare professional representatives of payers. If communication with such individuals is promotional, the company may contravene the general EU prohibition on the advertising of prescription-only medicines direct to the public, as some medicine advertising regulators treat non-healthcare professional administrative staff within hospitals or health service providers

29 See Section II.ix.
as consumers. The general principle, therefore, is that information about medicines sent to payers should be non-promotional. Non-promotional information, as with promotional information, must be fair, balanced, capable of substantiation and not misleading.

Directive 2001/83/EC also provides rules restricting the supply of medicine samples, promotional aids, gifts and hospitality to healthcare professionals. There is a general prohibition on inducements to prescribe and companies may only supply inexpensive gifts to healthcare professionals. Companies may provide reasonable hospitality to healthcare professionals provided that it is strictly limited to the main purpose of a promotional or scientific meeting and never extended to persons other than healthcare professionals. Since most healthcare professionals in the EEA are also government employees or contractors, companies must also consider anti-bribery laws.

The provisions of Directive 2001/83/EC are supplemented at EU level by the EFPIA Code on the promotion of prescription-only medicines to, and interactions with, healthcare professionals (the EFPIA HCP Code), which provides additional guidance to companies on problematic compliance areas, including gifts, sponsoring of healthcare professionals and hospitality.30

ii Medical devices

There is no EU harmonised legislation that governs the interaction of medical device companies with prescribers and payers. MedTech Europe, the European medical device trade association, however, has published the Medtech Europe Code of Ethical Business Practices that provides detailed guidance on this issue.

The MedTech Europe Code is intended to assist medical device companies to comply with general anti-bribery and corruption law concepts by setting minimum standards that companies and their representatives should adhere to when interacting with healthcare or other government officials. However, the MedTech Europe Code is not designed to supplant or supersede national laws or other professional or other business codes (including company codes), which may have stricter requirements.

The MedTech Europe Code provides specific guidance on some key compliance areas, including gifts, engaging healthcare professionals as consultants, sponsoring scientific meetings and the level of subsidy, entertainment and hospitality associated with such events. The provisions of the MedTech Europe Code are enforced through a self-regulatory regime operated mainly at national level. Where no dispute resolution mechanism exists under a national applicable code, the MedTech Europe Compliance Panel may rule on the dispute. MedTech Europe members should require that third-party intermediaries, who interact with healthcare professionals in connection with the sale, promotion or any other activity involving their products, comply with standards equivalent to the MedTech Europe Code.

30 EFPIA HCP Code, updated June 2014.
VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

i  Medicines

There is no pan-European scheme to compensate individuals injured by medicinal products. However, EU legislation on clinical trials requires the provision of an indemnity or insurance to cover the liability of the investigator or sponsor for the death or study-related injuries of subjects.31

Directive 85/374/EEC32 harmonises the EU rules on strict liability for defective products and provides that a ‘producer’ is liable for damage ‘caused by a defect in its products’. A product is considered defective when it ‘does not provide the safety which a person is entitled to expect’. In defining the term ‘producer’, Directive 85/374/EEC seeks to ensure that an injured party will always have someone within the EU against whom they can bring a claim. The term includes any manufacturer of finished products, raw materials or parts within the EU; importers of products from outside the EU; and any person who places their name or mark on a product (which would include a product’s marketing authorisation holder). It also includes any intermediate suppliers of products, which could include distributors, retailers, healthcare professionals and their employers. However, intermediate suppliers are only liable under the Directive if they fail to identify any other producer further up the supply chain within a reasonable period.

Separately, Directive 2001/83/EC provides that in the event of a public health emergency (e.g., an influenza pandemic), companies should not have civil or administrative liability in respect of the supply or use of unapproved medicinal products or use of approved medicines outside their authorised indications, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. The effect of this provision is that, in circumstances where a national competent authority recommends or requires the use of a medicinal product pre-approval or off-label in response to an emergency threat, the company has statutory immunity from liability in negligence or contract for the consequences of that use. Strict liability under Directive 85/374/EEC, however, will remain as a cause of action for persons injured by the product.33

ii  Medical devices

There is no EU-level scheme or system to compensate individuals injured by medical devices, but the principles of strict liability under Directive 85/374/EEC apply to devices.

VII  TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

The European Commission (the Commission) has continued to focus on patent settlement agreements. In 2013, the Commission found that Lundbeck’s settlement agreements relating to its citalopram drug restricted competition by object and infringed Article 101

31  Directive 2001/20/EC; see Section II.iii on clinical trials.
33  Article 5(4) of Directive 2001/83/EC.
Shortly thereafter, the Commission found that Servier’s reverse payment patent settlement agreements restricted competition both by object and by effect (the Commission also concluded that Servier’s commercial strategy was an abuse of dominance under Article 102 TFEU). The General Court delivered its judgment in Lundbeck in September 2016 confirming the Commission’s decision and upholding the fines that the Commission imposed on Lundbeck and the generic companies (totalling €146 million). Lundbeck and the generic companies have appealed the General Court’s judgment to the ECJ. Similarly, in Servier, the General Court held that four out of five of Servier’s patent settlement agreements restricted competition by object. However, the General Court ruled that the Commission had failed to prove the relevant market was limited to the drug perindopril, and therefore did not uphold that Servier had abused its dominant position. Both Servier and the Commission have appealed the General Court’s judgment to the ECJ.

Pay-for-delay agreements have also attracted regulatory scrutiny from the national competition authorities (NCAs). The United Kingdom’s Competition and Markets Authority (CMA) issued its first pay-for-delay infringement decision on 12 February 2016, fining GlaxoSmithKline (GSK), Generics UK Limited (GUK), Merck KGaG (GUK’s former parent company), Actavis UK Limited, Xellia Pharmaceuticals ApS and Alpharma LLC a total of £45 million for delaying market entry of generic versions of GSK’s anti-depressant Seroxat (paroxetine) in the United Kingdom. The decision has been appealed to the UK Competition Appeal Tribunal (CAT), which has made a referral to the ECJ.

NCAs have also begun to scrutinise excessive pricing. In October 2016, the Italian Competition Authority fined Aspen over €5 million for excessive pricing of its anti-cancer drugs Alkeran (melphalan), Leukeran (chlorambucil), Purinethol (mercaptopurine) and Tioguanine (thioguanine). Shortly thereafter, in December 2016, the CMA found that Pfizer and Flynn Pharma had abused their dominant positions by charging excessive and unfair prices for phenytoin sodium capsules (drugs used to treat epilepsy) in the United Kingdom. An appeal was brought to the CAT, which ruled against the CMA’s decision. The CMA has received permission to appeal the CAT’s decision to the UK Court of Appeal. Further, in January 2018, the Danish Competition Council ruled that CD Pharma had charged unfair prices for Syntocinon (drug used to induce labour during childbirth). On 29 November 2018, the Danish Competition Appeal Tribunal upheld the Competition Council’s decision. A number of other investigations relating to excessive and unfair prices are under way in the United Kingdom and one in Italy. In a related vein, public health authorities have increasingly litigated, seeking compensation for overspending as a result of alleged illegal behaviour by pharmaceutical companies.

Several other types of behaviour have been investigated and continue to be scrutinised by the NCAs. In 2014, the Italian Competition Authority found that Hoffmann-La Roche

---

36 Case T-472/13 Lundbeck v. Commission [2016].
37 Case T-691/14 Servier v. Commission [2018]. The General Court disagreed with the Commission’s finding that the settlement agreement between Servier and Krka constituted a restriction of competition either by object or effect and annulled the Commission’s decision for that part.
38 ibid.
39 Case CE/9531-11, Paroxetine investigation: anticompetitive agreements and conduct.
40 Case A480, Antitrust’s investigation on the price increase for Aspen’s anticancer drugs.
41 CE/9742-13, Phenytoin sodium capsules: suspected unfair pricing.

© 2020 Law Business Research Ltd
and Novartis had entered into an anticompetitive agreement aiming to discourage and limit off-label use of Hoffmann-La Roche’s oncology medicine Avastin for treatment of age-related macular degeneration (AMD) (i.e., the main cause of age-related blindness in developed countries), and fined Hoffmann-La Roche and Novartis €90.6 million and €92 million, respectively. Following a preliminary reference in the second-instance appeal procedure against the decision, the ECJ held that an agreement to disseminate misleading information to the authorities, medical professionals and general public about the safety of a medicine being used off-label may restrict competition by object. Beyond this, at least one NCA is investigating whether cross-distribution arrangements amount to market sharing. Finally, while the Commission concluded its inquiry into the pharmaceutical sector in 2009, a number of NCAs have since pursued sector inquiries (e.g., the Italian Competition Authority announced on 25 May 2016 the results of its sector inquiry into ‘Markets for vaccines of human use’ and the Danish Competition Council published its analysis on competition between pharmaceutical wholesale suppliers in October 2016).

**ii  Transactional issues**

EU competition law prohibits agreements that have as their object or effect the prevention, restriction or distortion of competition within the EU. The European Commission has issued a series of block exemptions, which grant an automatic exemption to certain categories of agreement, provided that the market shares for the products covered by the agreement are below the specified threshold, and the agreement does not contain any ‘hard-core’ restrictions, such as resale price maintenance or prohibitions on unrelated research and development. Two block exemptions are particularly relevant to in-licensing and collaboration agreements in the pharmaceutical and medical device sectors: the R&D Block Exemption, which provides for a market share threshold of 25 per cent in the case of agreements involving competitors, and the Technology Transfer Block Exemption, which provides for a market share threshold of 20 per cent in the case of agreements involving competitors and 30 per cent for those involving companies that are not competitors.

Since the approval of the competent authorities is required to transfer marketing authorisations and other pharmaceutical licences, including manufacturing authorisations, medicinal product divestments and other transactions structured as asset deals need to take into account the delay between agreeing to transfer the product or business and completion of the regulatory procedures necessary to give effect to the transfer. This delay can be many months or even years, so it is common for parties to enter into transition services agreements, determining how the parties will market, distribute and perform the regulatory tasks associated with the products during this transitional period.

---

42 Case C-179/16 F. Hoffmann-La Roche Ltd and Others v. Autorità Garante della Concorrenza e del Mercato [2018].
VIII CURRENT DEVELOPMENTS

In May 2017, the EU adopted new legislation to revise the regulatory framework for medical devices. Directives 90/385/EEC and 93/42/EEC will be repealed and replaced by Regulation (EU) 2017/745 with effect from 26 May 2020, while Directive 98/79/EC will be repealed and replaced by Regulation (EU) 2017/746 with effect from 26 May 2022. Importantly, unlike directives that must be implemented into national laws, the Regulations will be directly applicable in all EU Member States. The Regulations do not set out a radically new system but (as touched upon throughout this chapter) clearly envisage, among other things, stricter controls of medical devices, including strengthening of the conformity assessment procedures, increased expectations as regards clinical data for devices and pre-market regulatory review of high-risk devices. The Regulations also envisage greater control over notified bodies and their standards, increased transparency, more robust device vigilance requirements and clarification of the rules for clinical investigations. Under transitional provisions, medical devices or IVDs with notified body certificates issued under one of the Directives prior to the effective date of the applicable Regulation may continue to be placed on the market for the remaining validity of the certificate, until 27 May 2024 at the latest. With very limited exceptions, there are no transitional provisions for devices or IVDs whose conformity assessment has not involved a notified body, so unless the devices have been CE marked in accordance with the new requirements of the applicable Regulation, such devices may no longer be placed on the market after the effective date of the applicable Regulation. At the time of writing, only eight notified bodies have been designated under Regulation (EU) 2017/745 and only two notified bodies have been designated under Regulation (EU) 2017/746, meaning in practice it is likely to be difficult to quickly bring any other medical devices to market under the new regulations if notified body input is necessary.

The Clinical Trials Directive 2001/20/EC is also to be repealed and replaced with a Regulation on clinical trials on medicinal products for human use, which was adopted in early 2014. The Clinical Trials Regulation will revise current rules, in particular as regards the authorisation procedures, introduce new principles, such as co-sponsoring, and increase clinical trial transparency.

The Regulation has the same scope as Directive 2001/20/EC but amends some existing definitions (clinical trial, non-interventional clinical trial) and introduces new definitions, such as ‘clinical study’, ‘low-intervention clinical trial’ and ‘auxiliary medicinal product’. The new rules show a risk-based approach to clinical trials and distinguish between low-intervention clinical trials and other clinical trials. The Regulation also introduces a new streamlined single authorisation procedure via an EU portal linked to an EU database managed by the Commission, although an ethics committee review will still be needed in each Member State in which the trial will be conducted. The EU database will provide public access to protocol information and clinical trial results, suggesting greater clinical trial transparency in the European Union. Overall, the new regime should reduce administrative costs for industry, better reflect the variety of clinical trials, and increase clinical-trial transparency. The new Regulation is now not expected to come into effect until the second half of 2021, once the

new EU portal and database are fully operational. There will be a transitional period of three years, during which the rules under the Clinical Trials Directive will continue to apply to existing clinical trials.
I  INTRODUCTION

The Medicines Directive 2001/83/EC has been implemented in Finland, but national requirements that are stricter than the Directive’s minimal requirements also exist.

The Finnish Medicines Agency Fimea (Fimea) is the national competent authority for regulating pharmaceuticals. Fimea grants, inter alia, marketing authorisations (MAs) and wholesale licences for medicinal products (medicines). Reimbursement of medicines in Finland is subject to reimbursement status and reasonable wholesale prices, which are confirmed by the Pharmaceutical Pricing Board, operating under the Ministry of Social Affairs and Health. Until the end of 2019, the National Supervisory Authority for Welfare and Health (Valvira) was the national competent supervision authority for medical devices and supervised their compliance with legislation. Since the beginning of 2020, Fimea has been the competent authority for medical devices and supervises their compliance with legislation.

II  THE REGULATORY REGIME

The legislation of medicines and medical devices in Finland is harmonised with EU legislation. The national applicable legislation for medicines includes the Medicines Act (395/1987) and the Medicines Decree (693/1987). Additionally, the national codification is supplemented by the regulations and guidance issued by Fimea. Pharma Industry Finland (PIF), an organisation of the innovative pharmaceutical industry, has also issued a Code of Ethics (PIF Code) containing very detailed provisions regarding marketing of medicines, which are binding for members of PIF. The PIF Code is based on medicine, competition and consumer legislation and on the marketing guidelines of the equivalent European and international federations, the European Federation of Pharmaceutical Industries and Associations, and the International Federation of Pharmaceutical Manufacturers and Associations.

The Finnish Medical Devices Act (629/2010) and orders issued by the competent authority Fimea, or issued by the former competent authority Valvira, govern medical devices and the marketing of such devices. Regulations EU/2017/745 and EU/2017/746 govern or will govern the medical devices sector after the transitional periods. This chapter reflects the applicable legislation as at the beginning of 2020. Sailab – MedTech Finland, a registered association of health technology suppliers, has issued its own code of ethics, which

---

1 Hanna Paloheimo is a counsel and Hilma-Karoliina Markkanen is a senior associate at Castrén & Snellman Attorneys Ltd.
is based on the MedTech Europe Code of Business and governs, inter alia, the marketing of medical devices. This code entered fully into force after the transitional period ended on 1 January 2019.

Generally, the marketing of medicines and medical devices to consumers is also regulated by the Finnish Consumer Protection Act (38/1978) and government decree on Unfair Practices in Marketing and Customer Relations (601/2008).

i Classification

According to the Medicines Act, a medicinal product means a product or substance intended for internal or external use to cure, alleviate or prevent a disease or its symptoms in human beings or animals. Medicinal products are also considered to include substances or combinations of substances, used internally or externally, that can be used to restore, correct or modify the vital functions of human beings or animals through pharmacological, immunological or metabolic influence, or to determine the state of health or the reason for a disease. In ambiguous cases, the provisions of the Medicines Act are primarily applied if no special grounds for other interpretations exist. Such borderline cases have concerned mainly dietary supplements, cosmetic products and medical devices. The definition of medicinal products is rather broad in Finland and may include products that would not be considered medicinal products in some other EU Member States.

The Medical Device Act defines a medical device as any instrument, apparatus, appliance, software, material or other article intended by the manufacturer to be used for human beings for the purpose of, inter alia, diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap. Medical device also means any product intended for the purpose of investigation, replacement or modification of the anatomy or of a physiological process or control of conception. The Medical Device Act states that when assessing the distinction between the Medicines Act and Medical Device Act, the primary action of the product in question must be considered. The final assessment is concluded by Fimea, which adheres to a large extent to the European Commission’s guidance. Finally, the distinction between a medical device and a cosmetic product is defined by the intended purpose of the product itself.

ii Non-clinical studies

The Medical Research Act (488/1999) and the Medicines Act together regulate pre-clinical safety tests of medicines, which are subject to an approval granted by Fimea. Fimea’s approval may include restrictions or supplementary conditions for laboratories. The tests are also supervised by Fimea.

The Act on the Protection of Animals Used for Scientific or Educational Purposes (497/2013) is applied to the use and breeding of animals for scientific or educational purposes and for the supply of their organs or tissues for scientific or educational purposes. The purpose of the Act is to ensure that animals are kept and used for the above-mentioned purposes only for necessary and important reasons. Additionally, the Animal Welfare Act (247/1996) must be complied with. The Gene Technology Act (377/1995) may also be applicable if gene technology is used. Good laboratory practice must be complied with in
all non-clinical studies intended to be submitted to a national registration authority for the purpose of registering or licensing substances such as chemicals, medicinal products or cosmetic products.

Non-clinical studies are not compulsory before placing a medical device on the market.

### iii Clinical trials

The definition of a clinical trial includes intervention research conducted in human beings to investigate the effects of a medicinal product on human beings and the absorption, distribution, biotransformation or excretion of the product in the human body. Clinical trials are regulated by the Medical Research Act, implementing Directive 2000/20/EC, and by the Medicines Act; further regulations or guidelines may be issued by Fimea and the National Committee on Medical Research Ethics. There are also older guidelines for medical devices by the former supervisory authority Valvira, which are applicable until Regulations EU/2017/745 and EU/2017/746 enter into force. Fimea issued a new regulation regarding clinical trials in 2019.2

All clinical trials must be planned, conducted and reported on, observing the principles of good clinical research practice set forth in Directive 2005/28/EC. Fimea must be notified of every interventional clinical drug trial on medicinal products regardless of whether the product has an MA prior to proceeding. A notification is not required, however, if the trial is non-interventional. In uncertain cases, Fimea decides whether a notification is required.3

A party commissioning a clinical trial of a medicinal product (the sponsor) is obliged to have an insurance policy or other appropriate guarantee to cover the liability of the commissioning party and the researcher. However, the sponsor is not required to have an established place of residence in Finland. Commencement of the research is subject to a favourable opinion of the ethics committee and a licence granted by Fimea, if required. There are no particular insurance requirements for a sponsor of research of medical devices under Finnish local legislation.

### iv Named-patient and compassionate use procedures

For special reasons relating to treatment or public health, Fimea may grant a temporary authorisation (special authorisation) for releasing a medicinal product, according to Section 21(f) of the Medicines Act, implementing the Medicines Directive's Article 5(1).

Special authorisation must be granted if no other means are available to treat an individual patient or animal or group of animals, or if an available treatment would not yield the desired result. Additionally, special authorisation may be granted when a medicinal product with marketing authorisation is not available to treat a group of patients or the population or to prevent an illness, and there are particularly weighty reasons for granting the authorisation. Special authorisation is subject to any statement issued by the European Medicines Agency's Committee for Medicinal Products for Human Use.

---

2 Fimea’s Regulation 8/2019 on Clinical Trials.
3 To be classified as non-interventional, the trial must meet the following criteria: the medical product is prescribed in the usual manner in accordance with the terms of the MA during the trial, the prescription of the medicine is clearly separated from the decision to include a patient in the trial, and assignment of the patient to a particular therapeutic strategy is not decided in advance in the research plan. Additionally, no supplementary diagnostic or monitoring processes are applied to the patients, and methods shall be used for the analysis of collected data.
When special authorisation is granted, the supplier is obliged to ensure that the user of the product receives sufficient instructions on the correct and safe use of the product, and storage and other instructions.

The Medical Devices Act does not include any equivalent provisions regarding named-patient and compassionate use procedures.

v  Pre-market clearance

A medicinal product may be sold to the public or otherwise released for consumption only after it has been granted an MA, either nationally by Fimea or by the European Medicines Agency. An MA is valid for five years from being granted and it may be renewed. After the MA is granted, the MA holder must file a notification with Fimea upon the launch of the product. The MA holder also has an obligation to ensure that medicinal products that have been granted an MA are constantly available to medicinal product wholesalers and pharmacies to meet the needs of patients and other users.

Any medical device placed on the Finnish market must comply with the essential requirements of law; these requirements can also be defined more precisely by the competent authority. Overall, the device must be fit for its intended purpose, achieve the intended functionality and performance when used for its intended purpose, and must not endanger the health or safety of the patient, user or other person. The device must also bear the CE marking that indicates conformity with the set requirements.

If a medical device has the potential to cause severe risk to health, the manufacturer or an authorised agent with a registered office in Finland must file a notification with Fimea before the device is placed on the Finnish market or at most within one week after the sale of the device has begun. Fimea must also be informed of all adverse incidents relating to medical devices as soon as possible. Valvira issued several regulations regarding medical devices concerning, for example, conformity assessment and the CE marking.

vi  Regulatory incentives

Finland grants supplementary protection certificates under Council Regulation 1768/92/EEC and the Patent Act (550/1967, as amended) for the first patent covering a new medicinal substance. The relation between patents and the MA process is clear in Finland, since patents do not have relevance in the MA application process. The Bolar exemption of Directive 2004/27/EC has been implemented in the Finnish Patent Act to cover research activities required for the MA application. Patent exclusivity does not, therefore, cover research activities required for applying for an MA. Finland also grants the data exclusivity protection for medicinal products, and recognises the paediatric investigation plan exemption for paediatric products of Regulations 1901/2006/EC and 1902/2006/EC. If a medicinal product has been accepted for children, the data exclusivity is extended for six months as a main rule. Finland has no specific national legislation concerning orphan medicine products, but Regulation 141/2000/EC is applied, as is the data exclusivity extension of two years under Regulation 1901/2006/EC for orphan medicine products.

---

4 Note that Fimea is the competent authority for the supervision of the medical devices from the beginning of 2020.

5 Conformity Assessment of Medical Devices 1/2011 and CE marking of Medical Devices 2/2011.
vii  Post-approval controls

Finnish national legislation has been updated to conform to the Pharmacovigilance Directive 2010/84/EC, and Fimea has issued instructions and guidelines for the national implementation of the Directive. The MA holder is obliged to monitor the safety of medicinal products and to take appropriate measures if changes are identified in the benefit-risk analysis commenced by the MA holder. The MA holder is also obliged to keep a record of possible adverse effects and side effects. According to the Medicines Act, the MA holder must report all serious adverse reactions originating in Finland to Fimea. Fimea’s task is to supervise all product defect procedures and to ensure that measures taken by the operators are appropriate.

viii  Manufacturing controls

The industrial manufacturing of medicinal products requires a licence granted by Fimea, which may have conditions attached. Medicinal products may only be manufactured industrially by medicinal product manufacturers that have acceptable production facilities and equipment for production. A medicinal product manufacturer may have a medicinal product manufactured or controlled in part or entirely by another medicinal product manufacturer if it is required for technical, economic or production-related reasons, provided that the contract manufacturer has an industrial manufacturing licence granted by Fimea. Fimea may issue regulations concerning the procedures to be observed. Detailed requirements for an application are stated in the Medicines Decree.

A manufacturer must also comply with the EU Good Manufacturing Practice Guidelines. Only those active substances that have been manufactured in accordance with these guidelines may be used in the manufacture of medicinal products. Medicinal product manufacturers must also have an accountable director, who is primarily responsible for ensuring that manufactured products meet the requirements set for them in the Medicines Act. Additionally, at least one person involved in the manufacturing has to meet the qualification requirements set forth in Directives 2001/82/CE, 2001/20/EC and 2001/82/EC.

Unlike the manufacturing of medicinal products, the manufacturing of medical devices is not regulated in such a detailed manner, and thus, no licence or approval for manufacturing is required. Manufactured medical products must, however, meet the essential requirements set forth in the Medical Devices Act, namely, the manufactured product must be safe and suitable for its intended purpose.

ix  Advertising and promotion

The marketing of medicinal products is regulated under the Medicines Act and Medicines Decree and the concept of marketing is interpreted expansively. Generally, advertising of medicinal products must encourage people to use the products appropriately and it must not induce people to use products unnecessarily. The marketing information provided has to be accurate; it may not include any obsolete information or omit any essential details. Fimea is the supervising authority for marketing and advertising.

Additionally, general consumer protection legislation is applied when medicinal products are marketed directly to the general public. However, the marketing of prescription-only medicines must be targeted only at persons entitled to prescribe or dispense the medicine.

---

6 Fimea’s instructions for national implementation of Directive 2010/84/EC and Fimea’s guidelines for MA holders regarding national implementation of Directive 2010/48/EC.
Voluntary control of pharmaceutical marketing and self-regulation has traditionally been one of the key forms of activity in Finland. Pharmaceutical marketing is, therefore, also covered under the PIF Code and it is controlled by the Supervisory Commission for the Marketing of Medicinal Products, which operates under the PIF. The PIF Code is binding only on members of the PIF, but it may provide evidence of established practices and acceptable conduct.

The marketing rules for medical devices are largely the same as general Finnish marketing legislation, orders and principles, such as the Finnish Consumer Protection Act and the Regulation on unfair practices in marketing and customer relations. The marketing of medical devices is therefore generally allowed, but all marketing activities must be objective and give a truthful and reliable description of the product. The Act on Medical Devices contains a specific provision on marketing. Marketing of medical devices may not be inappropriate and it may not give an exaggerated or erroneous impression of the device, its effect or use. The marketing of medical devices includes all possible direct or indirect actions that have the purpose of promoting the product and influencing the product’s sales. Marketing of medical devices is supervised by Fimea and the Consumer Ombudsman.

Sailab – MedTech Finland ry accepted a new Code of Ethics on 14 December 2017, which entered into force on 1 January 2018. The Code is based on the MedTech Europe Code of Business Practice. This Code will be binding on members of Sailab – MedTech Finland ry from 1 January 2019, and sanctions will be applicable to members not complying with the Code.

x Distributors and wholesalers

The wholesale of medicinal products, meaning all activities aimed at receiving and forwarding orders for medicinal products, to acquire and keep medicinal products in order to distribute them and to export medicinal products, is subject to a licence. The licence is granted by Fimea, which may incorporate certain conditions concerning the operations in a licence. In order to be eligible for a licence, the applicant must be situated in Finland and have proper facilities and equipment for the storage of medicinal products and for ensuring the operations and the personnel required for the operations.

The applicant must also have an accountable director, who is responsible for ensuring that the medicinal products sold by the wholesaler meet the requirements set for them in the Medicines Act or in provisions issued pursuant to it. The accountable director is also responsible for ensuring that the wholesaler complies with regulations and guidelines issued on the storage, handling and labelling of medicinal products. The accountable director must have a master of pharmacy degree and he or she cannot act simultaneously as an accountable director in any other licensed medicinal product wholesale company.

Medicinal products may be sold or otherwise supplied by the wholesaler to a medicinal product manufacturer, another medicinal product wholesaler, a pharmacy, subsidiary pharmacy, the Military Pharmacy, a hospital pharmacy or dispensary, or to a veterinary surgeon for purposes of veterinary medication. In addition, medicinal products that have not had sales restricted by law or other provisions may be sold or otherwise supplied to
retailers of these products. Good medicinal product distribution practice based on the EU provisions must be complied with in all medicinal product wholesaling. Fimea has also issued a regulation regarding good distribution practices.\(^7\)

The Medical Device Act does not regulate how the distribution of medical devices takes place. Therefore, medical devices can be distributed by different operators, such as pharmacies or other distributors, and the distribution or wholesale of such products is not subject to any licence.

\xi\ Classification of products

In connection with granting an MA for a medicinal product, Fimea decides whether the medicinal product may be sold or otherwise released for consumption only on the basis of a prescription. Fimea may also alter its decision on the basis of new information received about the medicinal product that affects its supply classification. It is possible to apply for new classification of a product with Fimea.

The classification affects the marketing of medicinal products, since products subject to medical prescription can be marketed solely to individuals authorised to prescribe or dispense medicines. The Medicines Decree defines detailed requirements for such marketing, and the marketing activities may only take place at medical sales representations organised exclusively for such an audience, in expert field publications or via electronic media targeted and directed solely at such an audience.

Medical devices are classified according to Directives 93/42/EEC and 98/79/EC. The Directives determine the procedures to be used in verifying that products comply with all applicable requirements.

\xii\ Imports and exports

The import and export of medicines is permitted only under a valid MA. Additionally, if medicinal products are imported to Finland from outside the EEA, a licence for the industrial manufacture of medicines is required (see Section II.viii on manufacturing controls). A national wholesale licence is mandatory for import and export from inside the EEA.

In general, provisions applicable to the distribution and wholesale of medical devices also apply to the import and export of such products (i.e., imported and exported products must meet the essential requirements and bear the CE mark and then they may be freely imported within the EEA area). The marketing of medical devices in Finland and placing them on the local market is not subject to any sales permit or licence, unlike for medicines, but the manufacturer is responsible for the product’s compliance with all essential requirements. No permit procedures are applied, and the manufacturer indicates compliance with all necessary requirements by a mandatory CE mark.

\xiii\ Controlled substances

In general, the production, manufacture, import to the territory of Finland, export from the territory of Finland, transportation, transit through the territory of Finland, distribution, trade, handling, possession and use of drugs is prohibited under the general prohibition of the Narcotics Act (373/2008).

---

\(^7\) Fimea’s Regulation 1/2019 on Good Distribution Practices.
Substances regarded as drugs are listed in Finnish Decree 543/2008, as amended, and medicinal products mainly affecting the central nervous system or containing narcotics or psychotropic substances are listed in the Medicines Agency’s Decision 3176/4.6.4/2009. Fimea grants authorisations for the manufacture, import into Finland, export from Finland and handling of these substances. The operator will need a handling authorisation for a drug, which may be granted for a certain limited time. According to the Narcotics Act, the operator is also obligated to notify Fimea every year of drugs, substances, amounts, preliminary estimate of demand, etc.

xiv Enforcement

Intentional or negligent violation of provisions of the Medicines Act is punishable by a fine for a medicinal product offence, namely:

a manufacturing, importing, storing, carrying for sale or supplying medicinal products;

b neglecting to make a notification, provide information or keep records concerning medicinal products; or

c failing to comply with a prohibition issued by Fimea.

A medicinal product offence may also be punished under the Finnish Criminal Code (39/1889), in which case the penalty is either a fine or a maximum of one year’s imprisonment.

Fimea has the right to prohibit the import, manufacture, distribution, sale or other release for consumption of a medicinal product if conditions for granting the MA or for registration no longer exist, or if the requirements and obligations concerning manufacture or import of the medicinal product are no longer met. Fimea may also revoke, in part or in full, a licence granted for practising the manufacture or wholesaling of medicinal products, if any of the requirements for granting the licence are no longer met or if an obligation essential to safety or quality has not been met.

III PRICING AND REIMBURSEMENT

The Finnish reimbursement system is a national system that forms a part of the Finnish national health insurance system. The insurance scheme covers all permanent residents of Finland. The reimbursements are made directly to the patient when the medicinal product is sold by the Social Insurance Institution of Finland. There are three types of reimbursement: basic, lower special reimbursement and higher special reimbursement. The special reimbursement categories are set according to the severity of the treated condition and the necessity of the drug treatment, and they are specified by a government regulation. Some medicinal products may also have a restricted eligibility for reimbursement.

According to the Health Insurance Act (1224/2004, as amended), the costs of a medicinal product may be reimbursed only if the valid MA holder has applied for reimbursement and a reasonable wholesale price has been set. The Pharmaceutical Pricing Board, which operates under the Ministry of Social Affairs and Health, confirms the reimbursement status and the reasonable wholesale price. The medicinal product’s therapeutic value is taken into consideration in the decision on basic reimbursement status and the assessment is made by overall consideration. If reimbursement status is not sought and no reasonable wholesale price has been confirmed, the pricing may be implemented without any restrictions. Non-prescription medicines can also be reimbursed, provided that the doctor has prescribed the medicine to the patient and the Board has confirmed a reasonable wholesale price and
the reimbursement for the medicine. The reimbursement status can also be granted on a conditional basis if the pharmaceutical company and the Board so agree. The relevant conditions may include an agreement on further evidence provided by the company or on financial credits payable to the Social Insurance Institution of Finland (KELA).

Under the reference price system that applies in Finland, medicinal products are divided into reference groups by substance. Reference prices are determined based on MA holders’ price notifications, and prices are updated four times a year. This determined reference price is the highest possible price based on which the reimbursement can be calculated. The price notification is the prerequisite for reimbursement of the products in this system. A generic substitution policy is applicable, whereby if a patient prefers the more expensive medicine prescribed by a doctor, the excess costs are paid by the patient. The patient must also be informed about the lowest-priced prescription medicine at the time when the medicine is collected by him or her from the pharmacy.

Since the pricing of medical devices is not regulated in Finland, the pricing is basically free, taking into account, however, general competition law pricing principles. Generally speaking, medical devices are not reimbursed in Finland, except in some very limited cases; for example, when a person has a disability or illness that restricts him or her from undertaking work or study-related tasks. In these limited cases, the costs incurred by the purchase of such assistive devices may be reimbursed.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Decisions made by administrative authorities such as Fimea may be appealed according to the general provisions and principles concerning administrative matters. According to the Administrative Judicial Procedure Act (586/1996), the appeal must be lodged at the administrative court within 30 days of the decision’s date of issue. The Supreme Administrative Court is the appellate court for the decisions of the administrative courts. In some cases, a leave of appeal is required.

An appeal regarding an unsatisfactory decision by the Pharmaceuticals Pricing Board can be lodged with the Supreme Administrative Court within 30 days of receiving the decision. Courts have ruled in favour of pharmaceutical companies in many cases but, unfortunately, the appeal process may be rather slow compared to the usual timelines of pharmaceutical pricing.

As a main rule, an administrative appeal has a suspensive effect on the decision. However, there are several exceptions to this rule. For instance, the MA decisions made by Fimea can be implemented even before becoming final, unless the appeal authority orders otherwise.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Financial relationships between prescribers and payers are governed by the Medicines Act, the Medicines Decree and the Criminal Code. According to the Medicines Act, whoever, either intentionally or through negligence, violates the provisions issued in the Medicines Act on the marketing of medicinal products, or asks for, accepts or receives prohibited inducements, benefits or gifts, will be sentenced to pay a fine for a medicinal product offence or, ultimately, the Criminal Code may be applied. Self-regulatory systems such as the PIF Code also include provisions applicable to PIF members regarding appropriate interaction.
In general, the PIF Code prohibits giving promotional gifts related to prescription-only medicines. The distribution and offer of promotional gifts related to the marketing of self-care medicines must also be reasonable. The promotional gifts must have only minor economic significance for the recipient, and they must have a bearing on their professional operations. The company must also document and publish all the economic benefits targeted at healthcare organisations or professions according to the PIF Code. The provisions of the Sailab – MedTech Finland Code are much like the PIF Code.

According to the Medicines Act, the MA holder or other party engaging in marketing must also keep available for public review an up-to-date list of all direct and indirect financial and comparable support that they have given to associations in the fields of medicine and healthcare, and to patient organisations.

VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

A statutory obligation to compensate for pharmaceutical-related injuries can be based on the Finnish Product Liability Act (694/1990), the Patients Insurance Act (585/1986) and the Damages Act (412/1974). No special legislation on damages caused by medicines or medical devices exists. According to the Product Liability Act, a prerequisite for compensation is that the injury or damage was sustained or incurred because the product was not as safe as could have been expected at the time when the product was put on the market. The injured party shall prove the injury or damage, the defect in the product as well as the causal relationship between the defect and the injury or damage. The legislation is based on Directive 85/374/EEC on liability for defective products. General principles of tort law may also be applicable to pharmaceutical-related injuries – mainly liability owing to negligence.

Finnish Pharmaceutical Injury Insurance is a voluntary and additional insurance policy system founded by members of the pharmaceutical industry and pharmaceutical importers to cover damages caused by pharmaceutical products under the Medicines Act. According to general insurance terms and conditions, pharmaceutical injury refers to any bodily illness or injury or a psychic disease likely to have resulted from a pharmaceutical product taken by the injured party. However, pharmaceutical injuries do not include illnesses or injuries resulting from a pharmaceutical product failing to produce the intended effect or occurring in connection with measures that should not have been taken in view of the intended or recognised effect of the pharmaceutical product concerned. Additionally, pharmaceutical injuries do not include illnesses or injuries resulting from an error in the prescription, and further, compensation is not paid for known side effects of the medication if these were in proportion to the illness being treated in the case of a necessary risk taken in the treatment of a serious illness. Minor damages are not compensated.

The Patient Insurance Act requires that hospitals and clinics acting in Finland have a mandatory patient insurance that covers bodily injuries that have been caused to patients because of healthcare treatment.
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law
General European competition law principles and legislation are applicable in Finland. There are no recent and relevant enforcement actions or case law regarding the life sciences sector. Patent settlements are conducted in accordance with general EU policies. Patent litigation in the pharmaceutical industry has been active in Finland, and EU-level guidelines and decisions are closely monitored by the local industry.

The Finnish pharmacy system has been a long-term topic of conversation in Finland. The system is not open to free competition because, under the Medicines Act, the operation of a pharmacy business requires a pharmacy licence issued by Fimea. The granting of a licence is subject to a means test based on the size of the population in the area where the pharmacy is located; there are also other aspects that have been seen as competition-restricting by some participants in the discussion. On the other hand, the system is seen to grant sufficient pharmacy services also in the scarcely populated parts of Finland. The Finnish Competition Authority (FCA) drafted a report in 2012 regarding the functionality and competition aspects of the system where it recommended, inter alia, abolishing the means test for pharmacy licences, but no measures have been taken to follow the recommendation. A later report by a working group for the Ministry of Social Affairs and Health has stated that the current pharmacy licence system should be retained.

ii Transactional issues
No major transactions have been conducted recently in the pharma sector in Finland. From a legal point of view, competition law must be taken into account regarding possible merger and acquisition activities by major players in the market, and a decision by the FCA may be required. The tax law and practical aspects are also important when planning mergers and acquisitions.

VIII CURRENT DEVELOPMENTS
An extensive organisational change in healthcare services is still under way, and a topic raising political debate in Finland. There are plans for the responsibility for organising social welfare and healthcare services to be moved from municipalities to social welfare and healthcare regions. This would have a significant effect on the life sciences sector. The renewal of the entire system has, however, proved politically difficult, and at the beginning of 2020 the process is still at an early stage.

The pharmacy system has been a topic of conversation, and there have been a couple of suggested changes that would increase competition between pharmacies by facilitating the granting of new pharmacy licences and allowing price competition between pharmacies for over-the-counter medicines by regulating only the maximum price of such medicines. According to the suggestion, pharmacies would remain relatively small business units subject to a pharmacy licence from Fimea, and owned by private persons fulfilling the criteria set forth by Medicines Act, who are personally responsible for maintaining the pharmacy. The changes in the pharmacy system, too, have proved politically difficult to carry out.

The wholesale of medicines is conducted via a single-channel system, in which the distribution of medicines from manufacturer to pharmacies is generally run by wholesale traders based on exclusive agreements between the manufacturers and the wholesale traders.
In practice, two major wholesale trade players exist in Finland, and they both have a market share of nearly 50 per cent. Naturally, this arrangement is, from time to time, under examination by the FCA, but so far, it has not been found necessary to intervene in the single-channel system.

Sailab – MedTech Finland ry accepted a new Code of Ethics on 14 December 2017, which entered into force on 1 January 2018. The Code is based on the MedTech Europe Code of Business Practice. It became binding on the members of Sailab – MedTech Finland ry from 1 January 2019, and sanctions are applicable to members not complying with the Code. A similar system for the pharmaceutical sector has been in existence and active use for a long time through Pharma Industry Finland.
I    INTRODUCTION

France has a rather high-quality, strongly regulated, healthcare system that offers universal coverage for citizens, regardless of age or economic situation. It consists of an integrated network of healthcare professionals and pharmaceutical professions, hospitals or health and social care facilities (which can be either private or public) as well as a multidisciplinary ecosystem of other actors, including industry, financing and innovation support players or associations of patients.

It is administered by public policy at a national and regional level:

a the state directly finances and organises the delivery of health and social services;
b regional health agencies (ARS) manage and animate the healthcare system at a regional level, including health security, observation, prevention and promotion or the anticipation and management of sanitary crisis. They also have broad inspection-verification powers in three areas: health safety, how facilities and services are run, and medical procedures and practices; and
c some agencies are also involved in the regulation, including medical-economic aspects, of the health system in their respective fields of competence, such as the High Authority for Health (HAS), the National Agency for the Security of Health Products (ANSM), the Biomedicine Agency and the Digital Health Agency.

In 2018, health expenses in France represented €203.5 billion (i.e., 1.5 per cent more than in 2017), with an average expense value of €3,037 per inhabitant. Therefore, the pressure put by regulatory authorities on costs is high.

French healthcare regulation is broadly in line with the EU framework with some specificities, for example the notion of ‘exploitant’ or a price reimbursement regime, that are detailed further below.
II THE REGULATORY REGIME

Medicines and medical devices are highly regulated in France throughout their life cycle (including R&D, manufacturing, distribution, pharmacovigilance, and advertising activities): while products’ security and the safety of patients is under the scrutiny of the ANSM, products’ performances are observed by the Ministry of Health and Social Security.

Although historically under a lesser control than medicines, which are subject to a prior marketing authorisation, medical devices now tend to be more tightly controlled with the EU Medical Device Regulations 2017/745 and 2017/746 of 5 April 2017 becoming compulsory in May 2020 and May 2022 respectively.

Medicines’ and medical devices’ legal regimes, though separate, are showing a number of similarities, such as in the advertising or price reimbursement domains.

Eligibility of medical products’ reimbursement by the French social security system is assessed by the HAS while the Economic Committee for Health Care Products (CEPS) is in charge of negotiating reimbursement prices with rights holders, with the final decision made by the Ministry of Health. Owing to budgetary constraints and with the impact of new innovative products arriving on the market, French authorities tend to the reduction of reimbursement eligibility cases and prices.

The development of digital health and artificial intelligence is also becoming significant. For instance, on 12 April 2019, a first digital app, Moovcare, has been pre-admitted by the HAS on the social security reimbursement list while the HAS recently issued new evaluation guidelines dedicated to publishers of AI-based products, which shall become final during the first half of 2020. In anticipation of those guidelines, on 7 February 2020 the HAS released its first opinion on a medical device operating a learning AI tool, admitting its moderate but effective improving effect on rendered medical service (i.e., in French an 'ASA III' level, the same as the one recognised by the Moovcare app) and pre-eligibility to social security coverage as well.

i Classification

The definitions of medicines and medical devices are common to all Member States of the EU. French law is aligned on those principles.

In the same way, French law implements the EU principle under which a combination medicine/medical device product may either be regulated as a medicinal product or a medical device based on its primary mode of action. If the medicine and medical device do not form a single integral product, but rather are packaged together, then the two components will be regulated separately as a medicinal product and a medical device respectively.

The European Commission guidance on the borderline between medical devices and medicines (MEDDEV Guidance), will be followed by French authorities: a medical device’s function is typically achieved by physical means; medical devices may be assisted in their function by pharmacological, immunological or metabolic means, but if these means are not ‘ancillary’ with respect to the principal intended action of a product, the product no longer

4 About the Diabeloop Type I Diabetes automatic management tool: https://www.has-sante.fr/jcms/p_3150658/fr/dblg1-system.
5 MEDDEV 2. 1/3 rev 3, Guidance on ‘Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative’.
fulfils the definition of a medical device and thereby will be classified as a medicine. Where a product is classified as a medical device and contains, as an integral part, a medicinal product, the notified body assessing the device must consult with the European Medicines Agency or the relevant national competent authority.

Where a product may satisfy the definition of a medicinal product and that of other product categories, the medicines regime takes precedence over less restrictive regimes, such as those for medical devices.

In France, there is a wide variety of products in the vicinity of health products that are not medicines or medical devices and which are the subject of specific legal regimes that are either purely national or derived from EU law, such as cosmetic or veterinary medicinal products, contraceptives, tattoo products, etc. A case-by-case analysis is made.

ii Non-clinical studies

Before being tested on humans, medicines and medical devices may be tested in vitro or on animals. These studies are called ‘pre-clinical’ studies in France.

Data collected from pre-clinical trials is used to predict health products’ effects on humans, and to support further market access procedural steps.

Experimentation on animals shall only be carried out by entities having received an authorisation to handle animals from the Ministry of Agriculture. These animals shall be housed in conditions approved by the Directorate of Veterinary Services (DSV).

Pre-clinical trials on animals shall be carried out as part of a quality assurance programme certifying that their conditions are optimal in terms of reliability and reproducibility. The commonly accepted quality policy is based on the ‘good laboratory practice’ standard.

Article 18 of EU Regulation 1223/2009 provides that animal testing is prohibited for all finished cosmetic products placed on the European market. France is aligned with this regulation.

iii Clinical trials

Clinical trials are particularly regulated. France is the fourth-largest EU country in terms of the recruitment number of patients, with an average 13 per cent decrease per year. A 133-day term is necessary to obtain the necessary prior authorisation and contract with the clinical site, on average.6

EU Directive 2001/20/EC on clinical trials of medicinal products has been transposed into the French Public Health Code.

Decree No. 2016-1537 of 16 November 2016 implements Act No. 2012-300 of 5 March 2012 on research involving the human person (known as the Jardé Act, one of the major texts on clinical trials in France). It specifies the procedures for carrying out research involving humans (definitions applicable to the various categories of research falling within its scope, functioning of ethics committees, procedures for requesting an opinion from the ethics committees, as well as the rules applicable to vigilance). Decree No. 2016-1538 also imposes a unique convention template to be used by sponsors when contracting with clinical sites, under certain conditions.

In France, clinical trials on humans that are not justified by their usual care require a prior authorisation of the ANSM, after having obtained a favourable opinion of the competent ethics committee. Clinical trials are also subject to compliance with ethical standards, must take place under specific material and technical conditions and are undertaken under the supervision of a medical practitioner with the necessary expertise. In the event of an incident, the sponsor is held to an obligation of compensation.

iv  Named-patient and compassionate use procedures

In France, under exceptional circumstances, certain medicinal products may be used and prescribed without a marketing authorisation. These uses are subject to an authorisation through the ‘temporary use authorisation’ regime (ATU), which is issued by the ANSM.

There are two types of ATUs: cohort ATUs (request by pharmaceutical companies for a group of patients – the interested company is expected to have already filed or must file a marketing authorisation (MA) application), and individual ATUs (request by a physician for an individually named patient).

Medicines benefiting from an ATU are 100 per cent covered by the public health insurance system. They are provided to the healthcare facility by the pharmaceutical company holding the rights on the product. This provision is either free of charge or subject to payment of an amount freely determined by the company.

Under Article L. 5121-12-1 of the Public Health Code, it is also possible, on an exceptional basis, to distribute a medicinal product for an unapproved use on the basis of a ‘temporary recommendation for use’ (RTU). The ANSM may authorise an RTU for a period of three years for a medicinal product that has already been approved for different use, provided that the benefit-risk ratio of this use is considered to be favourable, and that a PUT (a therapeutic use and information collection protocol), is being elaborated and executed between the ANSM and the relevant pharmaceutical company.

v  Pre-market clearance

Two MA procedures coexist: a national procedure and a European procedure (for medicines).

In France, the legislation provides for the requirements and procedures for obtaining an MA, as well as harmonised provisions for manufacturing, distribution, pharmacovigilance, and advertising of medicines, in line with EU law rules.

Similarly, French rules on market access of medical devices are in line with EU laws and the coming Medical Device Regulation (EU 2017/745) (MDR), including that they may only be placed on the market, put into service, or used if they have received a ‘certificate of conformity’ certifying the device complies with the essential requirements, which is confirmed by the affixing of the CE mark to the device. Companies manufacturing or marketing medical devices must register with the ANSM.

An MA for a medicine may only be granted to an applicant established in the European Union. Beginning with the MDR, medical devices’ manufacturers must be established in the EEA or appoint a representative established in the EEA.

To allow faster access to innovative treatments for patients or faster development of existing products, the ANSM may implement a fast-track process for examining applications for authorisation of clinical trials on medicinal products, while respecting patient safety.

Since 18 February 2019, trials on complex design medicines and advanced therapy medicines have been additionally eligible for the fast track.
After having validly completed their market access procedures, medical product manufacturers must implement pharmaco- or materiovigilance procedures in order to monitor, evaluate, prevent and manage the risk of adverse reactions resulting from the use of medicines and medical devices.

Subject to some exceptions, herbal medicinal products, like all other medicinal products, are supplied by pharmacies, or on the websites of registered pharmacies. Medicinal plants can be used for the manufacture of medicines, but can also be supplied in bulk or in the form of pharmaceutical preparations by pharmacies.

The effectiveness and regime of homeopathic products are currently questioned, leading the French government to decide recently that they should no longer be reimbursed by social security as of 2021. For now, a specific registration procedure is provided by the Public Health Code to distribute homeopathic products.

**vi  Regulatory incentives**

Pharmaceutical patents are granted, like all other patents, for a period of 20 years from filing, and are subject to the payment of annual fees. However, the MA is generally not issued for several years. To compensate for this period during which the patent cannot be exploited, a special title has been created: the Supplementary Protection Certificate (CPP), which extends the rights of the owner of a patent on a pharmaceutical product.

EU Regulation 1901/2006 of 12 December 2006 provides the possibility of obtaining a six-month extension from the CPP expiry data, for medicines that have been researched for a pediatric use.

Other national incentives or practices exist in particular at the pricing and reimbursement stage, for instance in princeps/generics positioning or for biosimilars on other innovative products.

**vii  Post-approval controls**

The promotion, marketing, pharmacovigilance, batch tracking, withdrawal, storage and wholesale of medicinal products can only be performed in France by companies having an ‘exploitant pharmaceutical establishment’ title duly authorised by the ANSM (note that the exploitant may differ from the MA holder). Such exploitation shall be supervised by a responsible pharmacist (the equivalent of a qualified person). The MDR aligns medical devices with this rule, obliging medical devices manufacturers to appoint a qualified person.

Once marketed, the medicine remains under surveillance.

Thus, the benefit-risk ratio of the product is continuously evaluated to measure known or newly identified adverse effects. In the case of a health risk, a medicinal product may be subject to a health policy decision in the form of a restriction or change of indications. The medicine may also be withdrawn from the market.

The French Public Health Code expressly authorises the transfer of an MA from a given holder to another, for free or against a payment. Yet, transferring an MA still requires the prior approval of the ANSM. Such a transfer between seller and purchaser may be carried out by an agreement. The purpose of this agreement will not be the transfer of the MA in itself, but the transfer of the right to apply for an MA as well as of the file and information necessary to obtain it, such as the related regulatory documentation.
Manufacturing controls
Manufacturers and operators of medicinal products (branded and generic specialities) must be authorised as pharmaceutical establishments by the ANSM, meet the appropriate manufacturing and inspection requirements, and comply with applicable rules of good practice (manufacturing, distribution, etc.).

A pharmaceutical manufacturing site shall be supervised by a responsible pharmacist, whose statutory position is governed by the Public Health Code and who shares potential civil and criminal liability with the company’s manager.

Transfers of the ‘pharmaceutical exploitant’ status shall be submitted to the ANSM for prior approval.

Again, the new MDR will bring the obligation of a qualified person in the medical device field, regarding manufacturing controls.

Advertising and promotion
In principle, advertising of a drug to the public is only allowed on the condition that it is not subject to medical prescription, none of its different presentations is reimbursable by compulsory health insurance schemes and the MA or registration does not prohibit or restrict advertising to the public because of a possible risk to public health.

Such advertising to the public, as well as advertising to healthcare professionals, is subject to the prior authorisation of the ANSM.

For the advertising of medicines and medical devices, the use of certain media is regulated or prohibited, while some statements are mandatory and others are prohibited. In addition, the broadcast of some of these advertisements is subject to an authorisation of the ANSM.

For instance, ‘medical software’ is not among the media commonly accepted by the ANSM for advertising medicines and medical devices. The ANSM also seems to accept advertising taking the form of ‘pop-ups’, under specific conditions.

Advertising may only cover medicines that have obtained MAs or parallel import authorisations. In addition, advertising for medicines undergoing a reassessment of their benefit-risk ratio is prohibited.

Advertising must also comply with the essential requirements concerning the safety and health of patients and must not include a list of information expressly prohibited by the Public Health Code.

Based on the ANSM’s guidelines, advertising for a medical device must present it objectively, including in its performance or compliance with essential security requirements, and promote its proper use.

In the same sense, an advertisement cannot mention a position taken by an administrative authority or an advisory body with regard to a medical device in a manner likely to alter its meaning or objectivity.

Advertising must not be misleading or present a risk to health.

Distributors and wholesalers
The distribution of medicines is carried out by distribution establishments that have obtained an authorisation from the ANSM. In these establishments, all activities are carried out in accordance with the wholesale distribution good practices.
The wholesale distribution good practices specify the fundamental principles that must be respected in the wholesale distribution of pharmaceutical products, particularly in terms of general organisation, including quality management, staff, premises, and equipment (including computerised systems).

The application of the regulations relating to the wholesale distribution of medicines (including good practices) is periodically controlled during inspections carried out by the ANSM or the regional health agencies, under the aegis of the ANSM.

The French model of a pharmacy is based on three main principles. The establishment of pharmacies on the territory depends on demographic thresholds, in order to enable the need of medicines to be optimally met. The ownership of pharmacies is exclusively reserved for pharmacists in order to ensure professional independence. Finally, the sales of medicines and other products over the counter is reserved exclusively for pharmacists, practising in pharmacies and registered with the Order of Pharmacists.

Online selling of medicines by pharmacies has to be authorised by the ANSM, and only concerns off-the-shelf medicines.

Classification of products

Medicines are listed in multiple categories. Each list is regulated by specific provisions covering distribution, dispensation or promotion for instance.

Among the latter fall two categories: ‘advice’ medicines, which are prescribed by pharmacists to patients who seek advice from the pharmacist when a symptom occurs; and ‘general public’, which are medicines that are allowed to be promoted in the media (after having obtained an authorisation granted by the ANSM).

Some medicines are more strictly regulated, and classified as ‘poisonous substances’. They present various types of risks (toxic, teratogenic, carcinogenic, mutagenic, etc.). Their manufacture, sale, possession and use require special authorisations. Only healthcare professionals are allowed to prescribe these substances, subject to time limit on use. Narcotic substances that could lead to addiction also are specifically regulated.

Non-listed medicines are available off-the-shelf.

Imports and exports

Any entity importing medicines, including bulk product, from countries outside the EEA must first obtain an import authorisation from the ANSM. However, if the medicine has obtained an MA (or an ATU) this will fulfil the import authorisation requirement. Where the product has an MA or an ATU, imports into the EEA may only be performed by an entity holding a manufacturer’s import licence (authorisation) issued by the ANSM, which requires, among other things, the holder of the licence to appoint a responsible pharmacist.

Any entity importing medical devices from countries outside the EEA may only do so if the device has a certificate of conformity. Any entity importing medical devices must declare this activity with the ANSM and once the MDR comes into force, will need to be established in the EEA or appoint a representative established in the EEA.

Exports to non-EU countries of medicines that are not subject to MA in France are subject to a declaration to the ANSM. The export of medicines without an MA in France to an EU Member State is not subject to a prior export declaration.

For reasons of public health, the export of medicines without MA or of medicines likely to trigger risks not proportionate to the expected benefits may be prohibited by the ANSM.
Medical devices may not be exported if they give rise to a sanitary decision of the ANSM prohibiting the same. Free trade certificates can be issued by the Paris Île-de-France International Chamber of Commerce in order to facilitate exports outside the EU (this also applies to medicines).

**xi** Controlled substances

In France, any operation relating to narcotics and psychotropic substances is expressly prohibited, unless an authorisation has been granted by the General Director of the ANSM. Those substances are closely observed and their use, transportation and flows are entered into a special register.

The ANSM endorsed the proposals of an expert group on a practical framework for the purpose of allowing access to cannabis for medical use, for an experiment in France in July 2019. On this basis, the Social Security Funding Act for 2020 launched a two-year experimental phase during which the practical conditions for experimentation and distribution of products, products to be used, training of health professionals, and conditions for patient care and follow-up will be studied with possible funding by social security.

Some medicines present a risk of addiction for patients. In addition to the usual monitoring of adverse reactions (pharmacovigilance), a specific monitoring has been created in cases of abuse, dependence and misuse, called ‘addictovigilance’.

‘Addictovigilance’ is based on a network of regional centres responsible for collecting and evaluating these cases: the Centres for Assessment and Information on Drug Dependence (CEIP), led by the ANSM.

**xiv** Enforcement

The ANSM frequently conducts inspections on the manufacturing of medicinal products, clinical trials, and the implementation of pharmacovigilance by MA holders.

The General Director of the ANSM may pronounce injunctions and financial penalties against operators if they do not comply with the laws and regulations applicable to medicines.

Three types of enforcement procedures may be underlined:

- the ANSM may issue an injunction, following a contradictory procedure, to an operator to regularise the situation within a specified period;
- in the event of a risk to public health due to the placing on the market or use of a health product, the ANSM may take health policy measures such as a suspension of the MA, of the manufacture, of the distribution, or a restriction of use, etc.; and
- the ANSM may impose financial penalties on the operator. These financial penalties depend on the gross turnover of the operator, and the nature of the breaches noted by the ANSM.

The European Medicines Agency may also control and impose specific measures to operators in cases of violations of international regulations.

Medical devices, which used to be under less scrutiny on the field including because no central registration was available, will become more tightly controlled by the authorities, including the ANSM, thanks to the enforcement of the new MDR.

Other agencies or directorates may participate in this enforcement, for instance on fraud or competition law aspects.
III PRICING AND REIMBURSEMENT

In France, prices and reimbursement issues are determined by two separate public bodies: the HAS, assessing the reimbursable status and level of reimbursement of the drug (based on its Rendered Medical Service (SMR) and the Improvement of the Rendered Medical Service (ASMR); and the CEPS for the determination of the price. Once the HAS Transparency Commission has issued its opinion on a proposed SMR and ASMR for the product, the CEPS (an inter-ministerial organisation placed under the joint authority of the Ministry of Health and Social Security and the Ministry of Economy) proposes and negotiates a reimbursement price with the holder of the rights on the product, giving rise to a specific agreement between the two.

The Ministry of Health and Social Security ultimately is the one setting the reimbursement rate and price of the product by a decree.

Only prices of reimbursed drug products are regulated by the law.

The rules governing prices of reimbursed drug products are contained in the French Social Security Code (SSC) and supplemented by an agreement called the Accord Cadre (Framework Agreement), between the CEPS and an organisation representing pharmaceutical manufacturers (the ‘Leem’), as well as HAS and CEPS doctrine.

Additionally, French law provides a specific mechanism for funding drug products under an ATU, for which the pharmaceutical manufacturer may independently determine the sales price of the drug to hospitals. The manufacturer must inform the CEPS of this price, which is then published. Once the CEPS determines the price (as noted above) and the price is published, the pharmaceutical manufacturer must pay back to French social security the difference between the sales billed to the hospitals and those same sales calculated with the CEPS-determined price.

Further considerations apply for the prices of drugs purchased by hospitals. Because sales of drugs to hospitals are generally made through a public tender, the price proposed by the pharmaceutical manufacturer to the hospital is generally lower than the sales price agreed upon with the CEPS (as prices within public tenders are generally low due to competition).

This same mechanism applies for medical devices.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The ANSM is a public establishment; it is therefore subject to administrative law.

There are two types of administrative appeals: *ex gratia* and hierarchical appeals. An *ex gratia* appeal is lodged with the person who issued the administrative act. Hierarchical appeals are addressed to the administrative authority that is superior to the one having issued the administrative act (decision) in question.

The hierarchical appeal may follow an *ex gratia* appeal, or it may be brought without the latter. In the same way, both appeals may be lodged simultaneously.

If the petitioner’s request is not granted, an appeal may be lodged to the administrative court (contentious appeal). Appeal of a decision of the administrative court has to be brought before the French Council of State, the Administrative Supreme Court. The court controls the legality of the decisions of the ANSM, the HAS and of its specialised commissions.
V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

Owing to the increasing volume of care consumption, the social security fund has been largely indebted and healthcare professionals are under pressure regarding the quantity of medical care acts or medicines they prescribe if reimbursed by social security (for instance, sick leave).

For the same purposes of reducing social security debt (but not only), financial relationships between companies and healthcare professionals are under high scrutiny and susceptible to a variety of criminal offences in France.

For instance, the Public Health Code prohibits any form of advantages – direct or indirect – (e.g., cash and in-kind benefits) granted to a number of identified health-related actors including healthcare professionals, or a public entity (or a public servant), by a pharmaceutical company or a medical device manufacturer manufacturing or marketing products that are reimbursed by the French social security system or certain sanitary or cosmetic products, or a care services supplier.

Violating those anti-gift rules can be sanctioned by a one-year prison sentence and a €75,000 fine.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

French law provides special liability and compensation systems for injuries caused by medicines and medical devices.

For clinical trials, the Public Health Code provides that the sponsor of the trial must assume the compensation of patients in the case of harmful consequences, unless he or she can prove that the damage does not result from his or her fault. Research involving human beings requires prior subscription of an insurance policy guaranteeing the sponsor's civil liability.

In addition, the Public Health Code provides for two liability regimes: a fault-based liability regime and a no-fault liability regime.

The National Office for the Indemnisation of Medical Accidents (Oniam) has the mission of organising the amicable, rapid and free compensation scheme for victims of certain faulty medical accidents (in the event of insurance failure) and not at fault, without going through legal proceedings. It may compensate the patient if he or she is the victim of abnormal consequences of his or her state of health directly related to the medical act including: a medical accident or damage attributable to a biomedical research activity; an iatrogenic condition (or side effect linked to medical treatment), or a nosocomial infection (i.e., an infection contracted in a healthcare establishment).

Pharmaceutical product and medical devices manufacturers shall be responsible for defective products they distribute. Patients may obtain compensation directly from the company.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The European Union and France face major competition issues in the healthcare sector and the French Competition Authority has not hesitated to sanction pharmaceutical companies. In 2017 for instance, the Authority imposed on Janssen-Cilag a €25 million fine for impeding
and then limiting the development of a competing medicine. In 2013, a €40.6 million fine was imposed on Sanofi-Aventis for denigrating a competitor medicine to health professionals in order to limit its entry into the French market.

Medicine prices and their reimbursement by the social security system is also one of the major issues of competition law. To ensure that medicines prices are not excessive, the French Competition Authority tends to regulate the market by, for instance, encouraging parallel importations through a European MA.

On 21 November 2017, the French Competition Authority announced the launch of a major sector inquiry into the functioning of competition in the pharmaceutical and medical biology sector.

ii Transactional issues

The healthcare sector is active in the French M&A market. 2018 has been a particularly dynamic year in terms of M&A deals with mega deals in the pharma sector and the multiplication of operations in the medical technology (medtech) and biotechnology sectors that contributed to the structuring of the market.7

Medtech is in a good position, in particular e-health companies. Investment funds are showing their appetite for a variety of players, for instance in the AI-based medical imaging, diabetes, orthopaedics and sterilisation markets.

VIII CURRENT DEVELOPMENTS

The French healthcare and life sciences market is dynamic and relatively performing with a high life expectancy and good access to care services.8 Innovative technologies, including in the digital sphere, are on their way to trigger in-depth transformation of the sector and sustain the development of French investments and progresses on the international scene. However, budget constraints push the French government to reduce funding by the social security system, putting high pressure on products’ pricing. Also, capital venture or private equity investments amounts are lower on average compared to financing available in other regions such as the US, leading a number of national entrepreneurs to develop and market their products outside the French territory. A new momentum has come to counter this phenomenon with a new digital health framework policy having been launched in 2019, with the creation of a new digital health space for every citizen and the creation of a national Health Data Hub to sustain research and innovation and the sharing of data, enhancing the use of digital tools and practices, including artificial intelligence, at all levels of the healthcare life cycle, while the new bioethics bill may soon introduce a new human warranty concept in French law for the use of AI in the medical practice in line with EU guidelines.

7 https://www.pwc.fr/fr/publications/fusions-acquisitions/m-and-a-explorer-industries-de-sante.html.
I INTRODUCTION

India, the largest democracy in the world, has rightly been termed the ‘pharmacy of the world’. The country’s objective data speak for themselves. There are more than 4,655 pharmaceutical manufacturing plants, including the world’s third-largest in terms of volume and 13th in terms of value, and it accounts for 20 per cent in terms of volume and 1.4 per cent in terms of value of the global pharmaceutical industry. In 2016–2017, the domestic pharmaceutical market stood at US$16.4 billion and pharmaceutical exports at US$16.8 billion, which is expected to grow to US$55 billion by 2020. According to data released by the Department of Industrial Policy and Promotion (DIPP), this sector attracted cumulative foreign direct investment (FDI) inflows worth US$15.57 billion between April 2000 and September 2017. In view of the growing market and demand, the government has, from time to time, had to upgrade its regulatory framework. The Guidelines on Similar Biologics for regulating the approval process for biosimilars were introduced in 2012 by the Ministry of Health and Family Welfare, and a draft Drugs and Cosmetics (Amendment) Bill 2015 was released so as to amend the Drugs and Cosmetics Act 1940. The objective of the said bill is to introduce provisions for clinical trials and regulation of medical devices.

II THE REGULATORY REGIME

i Classification

India has a federal form of government and the regulatory framework is divided between national and state authorities. The Drugs and Cosmetics Act 1940 (DCA) and the Drugs and Cosmetic Rules 1945 (DCR) regulate the manufacture, sale, import, export and clinical research of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare regulates pharmaceutical products through the Drug Controller General of India (DCGI). The DCGI registers all imported drugs, new drugs and drugs in selected categories. It also has responsibility for clinical trials and quality standards. The state licensing authorities (SLAs), which are currently 35 in number, register all other products, accredit manufacturing plants and conduct the bulk of quality monitoring and inspections.

In addition to the DCA and the DCR, the other pieces of legislation that regulate the approval mechanism of drugs, cosmetics and food include the Pharmacy Act 1948, the Drugs

---

1 Pravin Anand is a managing partner and Archana Shanker is a senior partner at Anand and Anand. The information in this chapter was accurate as at March 2015.
and Magic Remedies (Objectionable Advertisement) Act 1954 (the DMR Act), the Narcotic Drugs and Psychotropic Substances Act 1985, and the Drugs (Prices Control) Order 1995 (under the Essential Commodities Act). Food-related substances other than those referred to above are covered by the Food Safety and Standards Act 2006.

With the increasing market for biologics expected to touch US$250 billion by 2020, the CDSCO issued in 2012 the Guidelines on Similar Biologics, which laid down the regulatory pathway for a biologic claiming to be similar to an already authorised reference biologic.

The DCA and DCR apply to the following categories: (1) ‘cosmetics’, which means any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness or altering the appearance, and includes any article intended for use as a component of a cosmetic; (2) ‘drugs’, which means all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on the human body for the purpose of repelling insects, such as mosquitoes; (3) such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of vermin or insects that cause disease in human beings or animals; and (4) ‘devices’ intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals.

ii Non-clinical studies

Pre-clinical trials on animal models are regulated by the protocols outlined in Schedule Y of the DCA. Prior to conducting animal studies, statutory approvals from an institutional biosafety committee and an institutional animal ethics committee must be submitted. The studies should ideally be conducted pursuant to good laboratory practices (GLPs). Standard operating procedures should be followed for all tasks related to these studies. Further, a Committee for the Purpose of Control and Supervision of Experiments on Animals has been constituted under the Prevention of Cruelty to Animals Act 1960 to ensure that animals are not subjected to pain or suffering before, during or after the performance of experiments. An amendment to the Breeding of and Experiments on Animals (Control and Supervision) Rule 1998 was made in 2001 and 2006 to regulate animal experimentation. The government prohibited animal testing for cosmetics2 and made further amendments to prohibit the import of cosmetics tested on animals.3

iii Clinical trials

In India, clinical trials are regulated through various mechanisms, including the Drugs and Cosmetics Act 1940 and Rules 1945, Schedule Y regulations for conducting clinical research issued by the CDSCO, and guidelines for interpreting the regulations, such as the Indian Council of Medical Research guidelines and the Indian Good Clinical Practice (GCP) Guidelines. While not legally binding, these guidelines for conducting clinical trials have been accepted by the industry in India.

---

2 Notification No. GSR 346(E) of May 2014.
3 Notification No. GSR 718(E) of October 2014.
The prerequisites for conducting clinical trials in India are permission from the DCGI, ethics committee approval and mandatory registration of the trials. The Clinical Trials Registry – India was set up by the National Institute of Medical Statistics to compulsorily register clinical trials. The ethics committee is required to review and accord its approval to the clinical trial (CT) protocol. The ethics committee will not approve any clinical trial protocol without it being registered with the licensing authority. In addition to having a clinical protocol registered with the licensing authority, the trial site will also have to be registered. It is mandatory for clinical trials to be conducted in compliance with the approved protocol requirements of Schedule Y of the GCP guidelines.

A three-tier process was put in place in 2014 for reviewing and evaluating CT applications: first by the Subject Expert Committees (SECs) (formerly New Drug Advisory Committees (NDACs)) or the Investigational New Drugs (IND) committee, next by the Technical Committee, and thereafter the Apex Committee will review the recommendations of the SEC or IND committee.

A Supreme Court order in 2013 stayed approximately 157 clinical trials in India and directed that no trials for new drugs should be permitted unless the consent of the subject is recorded through an audiovisual medium. The Supreme Court also emphasised the need for a balanced approach and laid down three principles for approving trials, namely assessment of risk versus benefit to patients, the need for innovation with regard to existing therapeutic options, and the unmet medical needs in the country.

Through a series of amendments to the DCR, the government introduced provisions relating to free medical management and financial compensation for clinical trial subjects, specifying the prerequisites for obtaining licensing authority permission to conduct clinical trials with human subjects, creating a system for the pre-screening of ethics committee registration applications, creating procedures for analysing the reports of serious adverse events occurring during clinical trials, and procedures for payment of compensation in cases of trial-related injury or death.

On 15 December 2014, the government inserted a new rule, Rule 122 DAB, providing a compensation formula to determine clinical compensation in cases concerning a serious adverse event of death during a clinical trial. Pursuant to the provisions of the amendment, an independent expert committee has to be constituted to examine the report of a serious adverse event of death and give its recommendation to the licensing authority within the prescribed period. The DCGI shall decide the quantum of compensation to be paid by the sponsor or representative, as the case may be.4

iv Named-patient and compassionate use procedures
There is no provision under the DCA and DCR that provides for compassionate use of medicines and medical devices. However, Rule 34(a) of the DCR permits the importation of small quantities of new drugs for the purpose of treatment of patients suffering from life-threatening diseases or diseases causing serious permanent disability, or such diseases requiring therapies of unmet medical needs. Rule 36 further provides for imports of small quantities of drugs for personal use. Further, Rule 122A of the DCR authorises the licensing authorities to waive local clinical trials in the public interest and grant permission for the importation of new drugs based on clinical trials done in other countries. There has also

4 Gazette notification GSR 889(E) dated 12 December 2014.
been an increase in the off-label use of drugs by medical practitioners. Currently, there is no guideline that regulates off-label use. However, if any company is advertising or selling a drug for an indication that has not been approved, they can be liable for an action under the DMR Act.

v Pre-market clearance
For commercial distribution and sale of any medicine and drug, approval from the licensing authorities is necessary. Under Rule 122E of the DCR 1945, a new drug includes (1) a drug, be it chemical or biotechnological, that has not been used in the country to any significant extent and that – except during local clinical trials – has not been recognised in the country as effective and safe for the proposed claims; (2) a drug already approved by the licensing authority for certain claims but that is now proposed to be marketed with modified or new claims, namely indications, dosage, form (including sustained release dosage form) and route of administration; or (3) a fixed-dose combination (FDC) of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, namely indications, dosage, form and route of administration.

The Central Licensing Authority (CLA) is responsible for approving new drugs. A new drug continues to be considered as a new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier. Once a drug ceases to be a new drug, manufacturing approvals can be obtained from the state regulatory authorities. The form prescribed for seeking approval of a new drug is Form 44. For the importation of a new drug, permissions have to be obtained from the licensing authority on Form 44 accompanied by a fee of 50,000 rupees. The rules further provide for a reduced official fee in the event that the same applicant applies for approval of the same drug in a modified dosage form or a new claim alone. Besides having to submit forms and paying the prescribed fee while seeking an import licence, the importer has to submit data, including those released from local clinical trials carried out in accordance with the guidelines prescribed by the Act. After the licensing authority is satisfied, permission is granted to import the raw material or finished formulation on Forms 45 and 45A.

In view of the definition of a ‘drug’ including certain medical devices and drugs, a similar approval procedure prescribed for chemical or biotechnological drugs will also apply to medical devices. In India, approval of medical devices has been quite unregulated. The CDSCO has introduced guidelines applicable to medical devices and has appointed the Central Licensing Approval Authority to oversee the approval of such medical devices. In practice, regulated medical devices that are imported can be legally sold in India after submission of the technical dossier to the Central Licensing Approval Authority. The bill of 2015 is an attempt by central government to regulate the medical device approval process. This follows the incorporation, in August 2014, of the amendment of the DCR provisions regarding the manner of labelling, and the qualification of competent persons to manufacture and test medical devices.5

---

5 The Drugs and Cosmetics Rules 1945 were amended vide GSR 690(E) dated 25 September 2014.
Schedule Y of the DCR prescribes the approval process of generic drugs and the biosimilar guidelines for the approval of similar biologics. Appendix 1A of Schedule Y provides an outline of the nature of data that has to be submitted to the licensing authority to import and manufacture a new drug already approved in the country and includes submission of bioavailability (BA) or bioequivalence (BE) and comparative studies in accordance with the BA and BE guidelines.

vi  Regulatory incentives

In India, there are no regulatory incentives and therefore patent term extensions, patent linkage, data protection or data exclusivity for the originator’s products are not provided. By conducting BE studies, the second applicant can obtain regulatory approval of the innovators product. In the *Bayer v. CIPLA* case, the Supreme Court of India clearly held that India neither provides nor recognises patent linkage. However, the Delhi High Court in *Bristol Myers Squibb v. Hetero Drugs* made the following observation with regard to patent linkage: ‘It is expected that the Drug Controller General of India while performing statutory functions will not allow any party to infringe any laws and if the drug for which approval has been sought by the defendants is in breach of the patent of the plaintiffs, the approval ought not to be granted to the defendant.’

There is no procedure in India for expedited approval. However, in the public interest, the DCGI can expedite the approval process for important products. Recently, in the public interest, the DCGI agreed to a fast-track approval for a licence for Sovaldi, a drug for the treatment of hepatitis. Further, India does not have any legislation akin to the US Orphan Drug Act.

vii  Post-approval controls

Schedule Y of the DCR 1945 prescribes post-approval controls (PSUR), which require marketing authorisation holders to submit a report every six months for the first two years after drug approval is granted. For the subsequent two years, the PSUR report must be submitted annually. Post-market surveillance includes procedures for the distribution of records, complaint handling, adverse incident reporting, product recall and taking of corrective measures. Schedule Y also requires the applicant to inform the licensing authority if the marketing of the new drug is delayed after having obtained marketing approval. In the event that the applicant and manufacturer fail to launch the product in the market within a period of six months from obtaining a licence from the CDSCO, the licence would be treated as cancelled.6 Also in 2010, the CDSCO launched the Pharmacovigilance Programme of India (PvPI) with a view to safeguarding the safety of the Indian population by monitoring drug safety and reducing the risks associated with the use of medicines. PvPI was initiated with the All India Institute of Medical Science as the National Coordinating Centre for monitoring adverse drug reactions (ADRs); 22 ADR monitoring centres were also set up – the number of these was increased to 90 in 2012–2013.

---

viii Manufacturing controls
In the case of imported drugs, the licensing authority, the DCGI, approves the manufacturing site, following inspection, and grants a Registration Certificate. The SLA is authorised to grant manufacturing licences following inspection of the premises. The manufacturer is required to maintain the quality standard as specified in the ICH Q6A guidelines and follow the good manufacturing practice (GMP) prescribed by Schedule M to the DCR. The second schedule to the DCA also provides the standards that have to be complied with by drugs manufactured and marketed in India.

ix Advertising and promotion
The DMR Act, inter alia, regulates the advertising of drugs for treatment of diseases specified in the Schedule. Section 2(a) of the DMR Act states that advertisements include any notice, circular, label, wrapper and other documents and any announcement made orally or by any means of producing a transmitting light, sound or smoke. However, the Act has certain provisions wherein the advertising of drugs can be carried out subject to certain conditions laid down by Section 14, which includes any signboard or notice displayed by a registered medical practitioner on his or her premises, indicating that treatment of any disease, disorder or condition specified in Section 3 of the Schedule and the rules are undertaken in those premises. Schedule J of the DCR also regulates the advertising and marketing of drugs to some extent.

x Distributors and wholesalers
The state licensing authorities provide wholesale and retail licences for distribution and sale of products.

xi Classification of products
The classification of drug products under DCR has been based on their intended use. Broadly, there are two categories of products: prescription-only drugs and non-prescription drugs. Schedules H, H1 and X deal with prescription drugs, whereas Schedule G drugs are considered non-prescription drugs. Additionally, Schedules C and C1 cover drugs derived from biological origin and other related special products, Schedule X covers some narcotic drugs and Schedule F is for vaccines, serums, and the like. New drugs can also be categorised on the basis of their approval status.

xii Imports and exports
Obtaining approvals for the importation of drugs into India consists of three main phases: (1) new drug approval (not necessarily for new drugs only); (2) an import drug registration certificate; and (3) an import licence.

Insofar as the export of drugs are concerned, the Pharmaceuticals Export Promotion Council of India is an authorised agency set up under the provisions of the Foreign Trade Policy by the Ministry of Commerce and Industry in 2004. The Ministry of Foreign Trade has provided some guidelines for the export of special chemical organism materials and equipment and technology items. The CDSCO has published a guidance document on the government submission form for the issuance of no-objection certificates (NOCs) for the
export of unapproved or approved new products or banned drugs. To obtain a NOC the applicant has to provide a valid export order and identify the premises where the drug is manufactured.

xiii  Controlled substances
The DCA includes several provisions for regulating the manufacture, sale and import of controlled substances listed in Schedule X. Essentially, Schedule X drugs cannot be sold without prescription. They have to be stored under lock and key in a cupboard or drawer reserved solely for the storage of these substances, and comply with special packaging and labelling requirements. Further, controlled substances have to be labelled with the symbol ‘Rx’ in red with a special warning. Besides the DCA and DCR, India also enacted the Narcotic Drugs and Psychotropic Substances Act (the NDPS Act) in 1985 to achieve a dual objective of limited use of narcotic drugs and psychotropic substances for medical and scientific purposes as well as preventing abuse of the same. The NDPS Act was framed to comply with three international conventions to which India is a signatory, namely the Single Convention on Narcotic Drugs 1961, the Convention on Psychotropic Substances 1971 and the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988, as well as Article 47 of the Constitution of India.

xiv  Enforcement
Section 27 of the DCA sets out the penalties for the manufacturer for the sale of drugs in contravention of the provisions of the Act. The DCA provides for punishment under the Indian Penal Code in the event that a drug is deemed to be adulterated or spurious and likely to cause death or such harm as amounts to grievous hurt; such offences are punishable with imprisonment and fine. In addition to imprisonment and a fine, the DCA under Section 31 provides for confiscation of goods. Prosecution under the DCA and DCR can be instituted only by an inspector or any gazette officer of the central government or a state government authorised in writing on behalf of the central government or the state government by general or special order, or by a person aggrieved or by a recognised consumer association. Special designated courts have been put in place for the trial of offences under the DCA.

III  PRICING AND REIMBURSEMENT
The health insurance system in India includes voluntary private health insurance and government health insurance schemes, such as the Central Government Health Scheme (CGHS), Rashtriya Swasthya Bima Yojana, the National Rural Health Mission and the Employees’ State Insurance (ESI) Scheme. The health insurance system in India covers approximately 3 per cent to 5 per cent of the population. The national health system covers the cost of medicines for patients registered under the CGHS or ESI schemes. Private insurance companies reimburse expenses incurred for the treatment of diseases and conditions that are listed in their portfolios and for which a patient is hospitalised for at least 24 hours. However, private insurance companies in India generally do not reimburse the cost of medicines that are used for treating chronic diseases, such as blood pressure and diabetes, that require regular medication for prolonged periods of time.

In 1997, the government set up the National Pharmaceutical Pricing Authority (NPPA) as an independent body of experts to deal, inter alia, with issues relating to price fixing and revision, updating the list of drugs included or excluded from price control, and so on. The
pricing of pharmaceutical products is regulated and falls under the Drug Prices Control Order (DPCO) 1995. In 1970, all drugs were controlled, but this control has gradually been reduced (to 347 drugs in 1978, to 163 drugs in 1987 and finally to 73 drugs in 1994). On 15 May 2013, the Department of Pharmaceuticals issued a DPCO that altered the price regulations and substantially increased the number of medicines covered by the price cap umbrella to 348 medicines. The new DPCO includes provisions for regulating the price of new drugs, including patented medicines.

On 29 May 2014, the NPPA issued guidelines for monitoring the inter-brand price difference of non-scheduled formulations and scheduled formulations in the public interest in several therapeutic areas, such as tuberculosis, malaria, diabetes, cardiovascular diseases, HIV/AIDS and asthma. As a consequence, in July 2014, the NPPA brought 108 non-scheduled drugs under price control, including patented drugs. The Indian Pharmaceutical Alliance challenged the NPPA guidelines, which were later withdrawn by the government. Having said this, with a view to promoting indigenous research and development, the National Pharmaceutical Policy 2002 provided a few exemptions in the pricing of new drugs developed through indigenous research and development, drugs produced by an indigenous process and new-drug delivery systems developed through indigenous research and development. These drugs are eligible for exemption from price control for a period of 15 years from the date of the commencement of their commercial production in the country or until the expiry of the patent in India.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

As stated in Section II.x, civil and criminal actions can be initiated for a violation of the provisions of the DCA and DCR and penalties include imprisonment and fines under the Indian Penal Code. Additionally, medicinal product liability can arise under the Consumer Protection Act. Class actions are permitted under the Consumer Protection Act. Consumer associations or consumers having a common interest can make a complaint. Insofar as administrative actions are concerned, by and large they are related to suspension, cancellation or refusal to grant marketing or manufacturing approvals or licences. Any person who is aggrieved by the order passed by the licensing authority may, within 30 days of the receipt of the order, appeal to the central government or state government and the central or state government may, after such enquiry as it considers necessary and after giving the appellant an opportunity for making a representation in the matter, make such orders in relation thereto as it thinks fit.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

There is no specific legislation dealing with interactions with payers, but there are various provisions dealing with the proper conduct of their procurement processes relating to bribery and kickbacks. In general, no health practitioner may manufacture, sell, advertise or promote any medicine or medical device to the public or keep a pharmacy and, equally, may not advocate the preferential use or prescription of any medicine or medical device that would not be clinically appropriate. The Organisation of Pharmaceutical Producers of India (OPPI) Code of Pharmaceutical Practices 2012 clearly provides that member companies shall not provide to a medical practitioner any cash or monetary grant for individual purposes in an individual capacity under any pretext, or provide any gift to a medical practitioner.
The Uniform Code of Pharmaceutical Marketing Practices (UCPMP) is a comprehensive code on marketing practices for pharmaceutical companies. UCPMP states that no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to persons qualified to prescribe or supply by a pharmaceutical company; gifts for the personal benefit of healthcare professionals (such as tickets to entertainment events) are also not to be offered or provided. The OPPI has urged the Department of Petroleum to make the UCPMP a statutory code.

The Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations 2002, as amended in 2009, also bring in regulation for medical practitioners and state the following:

a. A physician must not give, solicit, or receive, or offer to give, solicit or receive any gift, gratuity, commission or bonus in consideration of or in return for the referring, recommending or procuring of any patient for medical, surgical or other treatment.

b. A physician must not, directly or indirectly, participate in or be a party to an act of division, transference, assignment, subordination, rebating, splitting or refunding of any fee for medical, surgical or other treatment.

c. A medical practitioner must not receive any gift from any pharmaceutical or allied healthcare industry and their sales people or representatives.

Recently, the Medical Council of India issued a re-notification requiring medical practitioners to prescribe drugs with generic names. The term ‘generic name’ is not to be confused with off-patent drugs, and means to prescribe the drug by its chemical salt.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The Ethical Guidelines for Biomedical Research on Human Participants, prepared by the Indian Council of Medical Research in 2006, has been accepted as the standard by institutional ethics committees for regulating research on human beings. The sponsor, whether a pharmaceutical company, a government or an institution, should agree, before the research begins, in the a priori agreement to provide compensation for any physical or psychological injury to which participants are entitled, or agree to provide insurance coverage for an unforeseen injury whenever possible. Further special compensation mechanisms and formulas have been introduced by Ministry of Health notifications to pin down the liabilities of sponsors or contract research organisations in cases of clinical trial-related injury or death. Further, the manufacturer or investigator is liable to provide free medical management for as long as is required. The CDSCO has also issued a formula to be used as guidance in determining the amount of compensation that a clinical trial sponsor must pay in the event of clinical trial-related injury.

---

7 Rule 6.4 of the code of Ethics Regulation.
8 Notification No. GSR 53(E) dated 30 January 2013, introduced Rule 122DAB in DCR.
9 Notification No. GSR 889(E) dated 12 December 2014, further amended Rule 122DAB.
VII TRANSACTIONAL AND COMPETITION ISSUES

The past few years have seen several collaborative agreements between pharmaceutical companies: the Sun Pharma-Merck’s marketing and distribution agreement for Januvia and Janumet; Bayer Zydus Pharma, the joint venture agreement between Bayer and Zydus Cadila; Matrix Laboratory’s acquisition by Mylan Inc; and last but not least the Sun-Ranbaxy agreement are all examples of the recent trends. The large number of transactions between pharmaceutical companies and their impact on excessive pricing, availability of drugs and abuse of dominant position led the Competition Commission of India (CCI) to intervene in some such transactions. To regulate the transactions between two or more companies, the CCI has increasingly used Sections 3, 4 and 5 of the Competition Act 2002. The first case to be scrutinised by the CCI was the merger of Sun Pharma and Ranbaxy. The CCI granted approval of that merger.

Section 140 of the Indian Patents Act also provides a list of conditions that are considered as being ‘restrictive or prohibitive’ in any contract for or in relation to the sale or lease of patented articles made by the patented process.

VIII CURRENT DEVELOPMENTS

The CDSCO took several initiatives in the year 2014, which included the introduction of e-governance at CDSCO and the Drugs and Cosmetics (Amendment) Bill 2013 for clinical trials and medical devices based on the recommendations of the Prof Ranjit Roy Chaudhury Expert Committee. The CDSCO also issued 14 orders in July 2014 to ensure that data generated in clinical trials is authentic, while the rights of human subjects participating in the trial are well protected. The DCGI now requires submission of data for safety and efficacy for fixed-dose combinations (FDCs) to the CLA after the DCGI learned of SLA granting licences for FDCs without due approvals.

To further strengthen the regulatory process, the government rolled out reforms for 2015. This began with the Drugs and Cosmetics (Amendment) Bill 2015, including the revision of GMP for drugs as well as medical devices. Radical steps need to be taken to ensure that the applicant for approval provides complete patent details for the application on Form 44, and an intimation to this effect should be given to the innovator, particularly when the DCGI proposes relying on those studies to grant approvals. Notification should also be given to the owner of the original data, in the event that the DCGI relies on the innovator’s data to grant approvals to subsequent approvals irrespective of whether a patent exists or not. Furthermore, to further streamline the functioning of SLAs, a centralised mechanism should be introduced whereby the state authorities, before granting manufacturing approvals, notify the CLA; this is also notified to the public through the official website.

Finally, for the first time, the intellectual property policy of India has been documented and codified into a focused document with a view to creating an innovation ecosystem to improve the innovation index in India (which has been extremely low).
I  INTRODUCTION

Although the Italian legislative framework on life sciences fully implements EU legislation on research and development, manufacturing, marketing, promotion and distribution of medicines and medical devices, the Italian legislature has adopted a more restrictive approach, compared to other EU Member States, in relation to advertising and promotion, interactions with healthcare professionals (HCPs) and healthcare organisations (HCOs), distribution and marketing of medicinal products.

Another peculiarity of the Italian system is the time-consuming and complex reimbursement procedure, which is driven by the need to balance patients’ right to access innovative products, at the expense of the national health service (NHS), and cut public expenditure in the healthcare sector.

The main authorities in the Italian life sciences sector are:

a. the Ministry of Health (MoH), which generally governs the Italian healthcare system and has a more specific role in relation to medical devices; and

b. the Italian Medicine Agency (AIFA), a public entity under the supervision of the MoH, which is responsible, among others, for the manufacturing, distribution, import, promotion, advertising, pricing and reimbursement of medicines in the territory.

II  THE REGULATORY REGIME

In the medicines and medical devices sector, the Italian legislative framework mainly consists of:

a. Legislative Decree No. 219/2006 (the Pharma Code), which implemented Directive 2001/83/EC;

b. Legislative Decree No. 46/1997, implementing Directive 93/42/EEC; and


Regulation EU 745/2017 (the Medical Device Regulation), repealing Directive 2001/83/EC, and Regulation EU 746/2017 (the IVD Regulation), repealing Directive 90/385/EEC,
are expected to be effective as of 26 May 2020. The above regulations establish a modernised and more robust EU legislative framework to ensure better protection of public health and patient safety.

i Classification
There is no specific Italian provision addressing the distinction between medicines, medical devices and other regulated products (e.g., food supplements, cosmetics, chemicals and general consumer products). That said, the Pharma Code provides that, in cases of doubt, where a product may fall within the definition of a ‘medicinal product’ and within the definition of another regulated product, the provisions of the Pharma Code concerning medicines shall apply.

Moreover, Italy applies the guideline documents issued by the European Commission to support manufacturers in the classification of medical devices such as the Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices, the MEDDEV Guidelines and the documents issued by the Medical Device Coordination Group aimed at ensuring the uniform application of the relevant provisions of the Medical Device Regulation and the IVD Regulation within the EU.

In addition, the MoH occasionally issues guidelines to address specific products and clarify their classification criteria.

ii Non-clinical studies
Non-clinical studies should be carried out in accordance with the provisions of EU good laboratory practice laid down in Directives 2004/9/EC and 2004/10/EC.

All tests on animals shall comply with Legislative Decree No. 26/2014 on protection of animals used for experimental and other scientific purposes. According to said provisions of law, the committee for the protection of the welfare of animals, an internal body of the institution where the research is conducted, shall apply for MoH authorisations.

iii Clinical trials
Different pieces of legislation govern non-profit and for-profit clinical trials.

As to non-profit clinical trials, Legislative Decree No. 52/2019 has introduced new rules according to which data and results obtained from non-profit trials, financed by the Italian NHS, can be assigned to third parties if either the sponsor or the assignee refunds and reimburses any direct or indirect associated costs. The consideration paid in exchange for the ownership of the data and results shall also cover the costs of the clinical trial, including the reimbursement of any tax facilitation that the sponsor may have benefited from as a consequence of the trial’s non-profit initial qualification. The above legislation repeals the prohibition on assigning data and results of non-profit clinical trials financed by the NHS to third parties, which was a peculiarity of the Italian system.

For-profit clinical trials are mainly governed by Legislative Decree No. 211/2003 and Legislative Decree No. 200/2007, which, among others, set forth specific rules on permits to carry out the trial, good clinical practice, informed consent, responsibilities of the sponsor, the investigators and the other entities involved in the clinical trials (e.g., contract research organisations). Less stringent rules govern observational studies, according to the AIFA Resolution dated 20 March 2008.
A clinical trial shall meet, among others, the following main requirements:

\( a \) the site where the trial is conducted shall comply with quality standards set forth by AIFA Determination No. 809/2015;

\( b \) the sponsor shall request from the AIFA an authorisation to carry out the trial. The authorisation is implicitly granted if the AIFA does not raise any objection within 60 days of the sponsor’s application; and

\( c \) the relevant ethics committee shall issue its favourable opinion on the trial, assessing various scientific and economic aspects, such as the validity of the study protocol, the economic arrangements with the clinical trial site and the insurance policy, which shall cover potential damages arising from the trial according to Ministerial Decree of 14 July 2009.

EU Regulation 536/2014 on clinical trials on medicinal products will repeal Directive 2001/20/EC as soon as the EU web portal on clinical trials is activated. Among others, the Regulation provides for (1) a streamlined procedure for the submission of the applications and harmonised authorisation dossier; (2) a flexible and swift assessment procedure without establishing a new central bureaucracy; (3) a clear mechanism to appoint a ‘reporting Member State’; and (4) a clear timeline for the issuance of the authorisation with the concept of implicit approval.

**Medical devices**

The above general principles on clinical trials on medicines also apply to medical devices, for which specific rules are set forth by Legislative Decree No. 46/1997 and by the MoH Guidelines of 15 April 2005.

Under Italian law, pre-market clinical investigations must be authorised by the MoH. The authorisation is implicitly granted if the MoH does not raise objections within 60 days. No authorisation is required for post-market investigations, for which a simple notification to the MoH is required.

**iv Named-patient and compassionate use procedures**

**Compassionate use**

According to Ministerial Decree dated 7 September 2017, compassionate use of medicine is available for (1) patients suffering from rare or life-threatening diseases, if no other valid therapeutic alternative is available; (2) patients who have already been treated with clinical benefit in a similar clinical trial; or (3) patients who cannot be included in a clinical trial.

The responsible physician can file a request for compassionate use provided that: (1) a Phase III clinical trial on the investigational medicine is undergoing (in exceptional cases it is allowed to provide medicines for which a Phase II or Phase I trial has been completed); (2) the requested medicine is already authorised for indications other than those required by the patient (‘off-label use’); and (3) the medicine, although duly licensed, is not yet available in Italy.

Compassionate use programmes shall be notified to the AIFA and expire as soon as the medicine is placed on the market. The Italian Council of State, with its Opinion No. 2356/2016, stated that, even though the relevant medicine has already been placed on the market, patients can benefit from free-of-charge compassionate use until the reimbursement agreement has been approved.
**Import of medicines authorised in a foreign country and shortage of medicines**

According to the Ministerial Decree dated 11 February 1997, the import of unlicensed medicines is permitted in two cases: (1) if said medicine is duly licensed in a country outside of Italy; and (2) if a traveller import medicines licensed outside of Italy for his or her personal use in a quantity not exceeding his or her needs for 30 days. An ad hoc authorisation from the MoH is required.

Moreover, in the case of a shortage of medicine at a national level, the MoH can authorise the import of the same medicine available outside of Italy.

**Innovative investigational medicines**

According to Law No. 648/1996 innovative investigational medicines or off-label use of licensed medicines can be provided to patients at the NHS's expense, if the AIFA grants its authorisation.

**Medical devices**

In cases of exceptional need and urgency, in the interest of a single patient, the MoH can authorise the compassionate use of medical devices bearing no mark because the conformity assessment has not been conducted or completed. Compassionate use requires MoH authorisation and the approval of the relevant ethics committee.

**v Pre-market clearance**

Only medicines granted with a marketing authorisation (MA) from the AIFA or European Medicines Agency and medical devices bearing the CE mark (except for custom-made devices) can be placed on the market.

Furthermore, all medical devices, in order to be marketed in Italy, should be notified to the MoH and registered in an institutional register of medical devices.

**vi Regulatory incentives**

**Supplementary protection certificate**

National legislation prevents the NHS from reimbursing a generic medicine, where patent or supplementary protection is in place. This provision has been strongly criticised as representing a form, even if sui generis, of patent linkage, which is prohibited under EU law. In 2015, Assogenerici (the Italian Association of the Generic Medicines) filed a position paper with the Italian Senate requesting the repeal of the above provision on patent linkage.

**Orphan medicines and innovative medicine**

An AIFA National Fund is available for orphan medicines. The AIFA allocates to the fund 50 per cent of the contribution that pharmaceutical companies pay on an annual basis, which amounts to 5 per cent of the annual expenses for promotional activities of pharmaceutical companies. The sites where patients are treated with orphan drugs shall submit applications for access to the AIFA fund.

Moreover, the AIFA has issued a list of innovative medicines that can benefit from a specific national fund introduced by the Budget Law of 2017.
vii Post-approval controls

According to pharmacovigilance obligations provided by the Pharma Code, the marketing authorisation holder (MAH) must ensure a system to collect and maintain a record of suspected adverse events and equally ensure a safety reporting system to the AIFA. Specifically, the MAH shall set up a risk management system for each medicine, appoint a qualified person who shall be responsible for pharmacovigilance activities and notify his or her name to the AIFA.

The pharmacovigilance activities may lead to the suspension or revocation of product approvals by the AIFA, which ensure compliance with the provisions of law inspecting the MAH premises, records and documents in relation to the pharmacovigilance activities covered.

Moreover, according to the Pharma Code the MAH shall appoint a responsible person for distribution and a scientific service, which must be independent from the marketing department.

Medical devices

According to Section 9 of Legislative Decree No. 46/1997, the manufacturer (or its authorised representative) shall inform the MoH immediately of any incident, as well as of the corrective actions taken to reduce the risks of death or serious deterioration of the patients’ health that may occur with the use of a medical device.

viii Manufacturing controls

A manufacturing site shall obtain an authorisation from the AIFA. To issue the authorisation, the AIFA must inspect the site and ensure that the applicant has qualified staff and adequate technical-industrial resources. The authorisation is normally granted within 90 days.

In the case of medicines and investigational medicines imported from third countries, the importer shall ensure that they comply with standards at least equivalent to those in force in the EU. Moreover, the importer shall ensure that medicines are manufactured by duly authorised manufacturers.

ix Advertising and promotion

Introduction and regulatory framework

The advertising and promotion of medicines and medical devices is governed by national legislation, as well as by regional legislation (i.e., laws and regulations issued by the various Italian regions) and industry codes.

In detail, the following pieces of legislation apply to the advertising of medicines and medical devices in Italy:

- the Pharma Code, implementing Directive 2001/83/EC, as amended, on the Community code relating to medicinal products for human use;
- Legislative Decree No. 46/1997 implementing Directive 93/42/EEC on medical devices; and
- Decree of the Ministry of Health dated 23 February 2006 on medical devices advertising.

Specific instructions on advertising of medicines and medical devices through different communication channels, including the internet, SMS/MMS and social networks, are established by various guidelines issued by the MoH.
At a regional level, the promotion of medicines and medical devices to healthcare professionals is regulated by the ‘Guidelines for regional regulations regarding scientific information relevant on medicines’ dated 26 April 2006, as well as by the guidelines issued by each Italian region.

Lastly, additional rules on advertising of both medicines and medical devices are also set out in the codes of conduct adopted by national and international industry associations, such as the Farmindustria and the EFPIA Codes for medicines, and the Confindustria Dispositivi Medici and the MedTech Europe Codes for medical devices. Said codes only apply to pharma and medical devices companies that are members of such industry associations.

**Advertising to the general public**

Advertising to the general public of prescription medicines or medicines containing psychotropic or narcotic substances is forbidden. The prohibition on advertising to the general public also applies to medicines that are reimbursed, even partially, by the NHS. The distribution of medicines to the public for promotional purposes is also prohibited.

In publications, radio or television broadcasting, or any non-promotional messages to the general public, it is prohibited to mention the name of a medicinal product in a context where this results in the promotion of the consumption of the product.

Similarly, it is forbidden to advertise to the general public custom-made medical devices and medical devices that must be ordered by, chosen by or ultimately used with the assistance of, an HCP.

The advertising of medicines and medical devices that do not fall within one of the above-mentioned categories is subject to prior authorisation by the MoH. This authorisation is implicitly granted if the MoH does not raise any objection within 45 days from the date of the filing of the relevant application.

**Promotion to HCPs**

Broadly speaking, the promotion of medicines and medical devices to HCPs is governed by concerns for accuracy in information, adequacy in education and training of medical sales representatives, and the avoidance of undue influence over HCPs’ decision-making processes (including purchasing decisions by public entities). To this end, there are a number of restrictions on how information can be presented to HCPs with respect to seminars, panel discussions, promotional events and the like.

Any advertising of medicines to persons qualified to prescribe or supply such products shall always include the summary of the product characteristics authorised at the time the advertising is disseminated, specify the supply classification of the same product and the sale price and the conditions for its reimbursement by the NHS, if any.

The documentation on the medicinal product must be filed with the AIFA and can be supplied to the HCP after the expiry of a term of 10 days from the filing.

**Distributors and wholesalers**

Italian legislation does not provide for any specific regulation governing the distribution of medical devices. Consequently, the sections below only refer to the distribution of medicines.
**Wholesale distributors**

Wholesale distributors purchase medicines directly from MAHs with the purpose of selling them to pharmacies and healthcare structures that are entitled to purchase medicines. These distributors must be authorised by the region or autonomous province in whose territory the relevant warehouse is located. A wholesale distributor holding warehouses in the territories of different regions or autonomous provinces must obtain an authorisation from each competent authority.

In carrying out their activities wholesale distributors must comply with the good distribution practices issued by the MoH (i.e., a set of rules governing the proper storage and transportation of medicines, traceability and registration obligations and public service obligations, consisting in the duty to ensure availability of a wide range of medicines and to promptly supply pharmacies located in a given area).

**Depositaries**

Unlike wholesale distributors, which own the title to medicines, depositaries merely store and distribute medicines to wholesalers and healthcare structures on behalf of MAHs pursuant to specific agreements entered into with the latter. Depositaries are subject to the same authorisation requirements applicable to wholesale distributors; however, they are not responsible for complying with public service obligations.

**Classification of products**

The classification of medicines is as follows:

- **Class A**: medicines for essential and chronic diseases that are entirely reimbursed by the NHS;
- **Class H**: medicines provided in hospitals, fully reimbursed by the NHS;
- **Class C**: all other medicinal products that are not reimbursed by the NHS; and
- **Class Cnn**: medicines not yet assessed for NHS reimbursement purposes.

With regard to their supply regime, medicines are classified as prescription-only, OTC and medicines that patients can purchase without prescription (SOP).

**Medical devices**

Medical devices are divided into Classes I, IIa, IIb, III, depending on their characteristics and on the potential risk on patients deriving from their use. Annex IX of Legislative Decree No. 46/1997 set forth rules to assess the classification of a device, which is based on the intended use indicated by the manufacturer.

Special classification rules apply to some categories of devices. In this respect, operating field systems and kits represent a particular type of medical device consisting of a series of devices, even if manufactured by different companies and of different classes, which may also include products not classifiable as medical devices, assembled together. An accessory is considered a medical device for all purposes and must be classified separately from the device with which it is used.
xii Imports and exports

Importing and placing on Italian market medicines from extra-EU countries requires a manufacturing authorisation from the AIFA. Moreover, the MoH Decree dated 11 February 1997 governs the import of medicines authorised abroad (see Section II.iv).

Import of medical devices requires health clearance by the Customs authorities.

xiii Controlled substances

The manufacturing, use for investigational and scientific purposes, marketing and distribution of narcotics and psychotropic substances is subject to specific authorisations by the Central Narcotics Office of the MoH, pursuant to Legislative Decree No. 309/1990. As indicated in Section II.viii, medicines containing narcotics and psychotropic substances cannot be advertised to the general public.

xiv Enforcement

The MoH, supported by the Anti-Adulteration Unit of the Carabinieri (NAS) and the AIFA, are the authorities in charge of adopting the necessary measures to ensure compliance, safety and patients’ health. Depending on the kind of violation, enforcement activity may lead to restraining measures (e.g., an order to stop the illicit conduct), pecuniary sanctions or criminal sanctions. In the latter case, the competent body is the relevant criminal court.

III PRICING AND REIMBURSEMENT

Under Law No. 326/2003, the AIFA is the body in charge of negotiating the cost of medicines reimbursed by the NHS and, more generally, monitoring prices of medicinal products.

As to pricing, medicines not reimbursed by the NHS are governed by Law Decree No. 87/2005, under which the MAH can freely determine the price. The AIFA must ensure that: (1) price increases only occur every two years (odd years); and (2) price increases do not exceed the inflation level.

With respect to reimbursement, under Law No. 326/2003, prices reimbursed by the NHS are determined through a bargaining procedure between the AIFA and the concerned MAH in accordance with the modalities and criteria provided for by Resolution No. 3 of 1 February 2001 of the Inter-ministerial Committee for the Economic Planning.

The criteria for the evaluation of a medicine for reimbursement purposes are mainly the following: cost-benefit ratio, increased clinical benefit, considering cost-effectiveness, existence of alternative medicines or treatments, impact on the health system’s budget, evaluation of the market sector related to the product, and the average price of medicines belonging to the same therapeutic area in other EU Member States.

In successful negotiations, the parties enter into an agreement setting the relevant price and the conditions for the reimbursement. The agreement may also provide for an expenditure ceiling applicable to the concerned medicinal product.

The price determined through the agreement is valid for a period of 24 months. Upon expiry, the agreement is automatically renewed for a further 24 months unless the parties agree to amend it within 90 days of the expiry date. The list of medicines reimbursed by the NHS is published on the Official Journal of the Italian Republic and is updated every six months.

On 1 August 2019, the State-Regions Conference expressed its positive opinion on a draft Decree establishing new criteria and procedures for price negotiation of medicines.
reimbursed by the NHS. The draft Decree provides for relevant changes to the existing system giving particular emphasis to the ‘added therapeutic value’ that the medicinal product must ensure with respect to the main treatments to which it is compared, thus replacing the current reference to the ‘advantageous cost-effectiveness’ ratio. The draft Decree also requires pharmaceutical companies to support their requests with information and self-certifications attesting their production capacity and ability to manage unexpected events as well as information concerning the patent status of the relevant medicinal product. To enter into force, the draft Decree must obtain the positive opinion of the Council of State, be reviewed by the Court of Auditors and, subsequently, be published in the Official Journal of the Italian Republic.

i Medical devices
There are no specific provisions of law governing the pricing and reimbursement procedure for medical devices. The NHS normally purchases medical devices through public procurement procedures.

ii Measures to control public expenditure on medicines and medical devices
A core factor affecting the pricing of medicines reimbursed by the NHS is the need to contain pharmaceutical expenditure. Over the past few years, the Italian legislature has introduced various measures to reduce public expenditure, among which are the following:

a Budgets allocated to pharmaceutical companies. The AIFA assigns each MAH of medicines reimbursed by the NHS a yearly budget, which represents the maximum amount that the NHS will reimburse to the MAH. If this amount is exceeded, the MAH shall pay back the difference to the AIFA.

b Budgets assigned to single MAs. In addition to the company’s budget, the AIFA may assign a specific annual budget to single MAs relating to medicines reimbursed by the NHS. If the budget is exceeded, the MAH shall pay back the difference to the AIFA.

c Payback system for medicines and medical devices. The payback system for medicines provides that in the case of overrun of the national expenditure ceiling for medicines, pharma companies selling medicines reimbursed by the NHS are required to bear the relevant costs and payback to the NHS an amount of money proportional to the sales made to the various regions or autonomous provinces in which the expenditure ceiling has been exceeded. Although the payback system has been harshly criticised by pharma companies and challenged in various courts’ proceedings, the legislature has extended it also to medical devices, pursuant to Law No. 125/2015. However, the payback system is still not effective for medical devices, until a decree of the MoH is issued to determine the specific modalities for calculation and payment of the relevant amounts.

d Managed entry agreements. The aim of managed entry agreements is to enable MAHs and payors to share the financial risk of the reimbursement of certain new medicines due to uncertainty surrounding the introduction of new technologies. Managed entry agreements can be outcome based, such as payment by results and risk sharing, or financial based, such as cost sharing agreements and capping.

e Direct distribution. Direct distribution is a form of (direct) supply of medicines to patients. Health authorities carry out this distribution by purchasing medicines from manufacturers and directly distributing them through their own structures to
patients for home consumption. By excluding costs associated with the distribution by pharmacies, this instrument allows health authorities to achieve average savings of 50 per cent.

Tender proceedings. Further reductions may be granted through tender proceedings under which medicines are supplied to public hospitals according to the criteria of the lowest price.

The regulatory framework on this matter is rapidly evolving and is experiencing constant adjustments and developments.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The MoH and AIFA’s decisions can be challenged before the relevant administrative court (in the first instance the Lower Administrative Court – TAR, while in the second instance the Council of State) within 60 days of their notification or actual knowledge. Alternatively, administrative decisions can be challenged before the President of the Italian Republic within 120 days.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The provisions of the Italian anti-corruption law apply to interactions with HCPs. Moreover, Section 123 of the Pharma Code provides that, in the context of promotional activities addressed to HCPs, it is forbidden to grant, offer or promise rewards, pecuniary advantages or benefits in kind, unless they are of negligible value and instrumental to the medical practice.

Specific rules apply to companies that are members of industry associations, whose code of ethics requires them to disclose on their website or on specific platforms various information on transfers of values to HCPs and HCOs.

Under the Farmindustria Code, all its members shall disclose transfers of value to HCOs and HCPs, related to (1) donations; (2) participation in conferences and congresses; and (3) consultancy and professional activities.

Under the Code of Ethics issued by Confindustria Dispositivi Medici, medical device companies must disclose all transfers of value directly or indirectly provided to HCPs and HCOs and third parties, related to (1) training, educational and promotional activities; (2) professional advice and services; (3) donations; (4) research and development activities; and (5) scholarships.

Under both the Farmindustria and Confindustria Dispositivi Medici Code of Ethics, data is normally collected on an individual basis, unless the HCP does not give his or her consent to the processing of personal data. In the latter case, data will be published on an aggregate basis.

The Italian Parliament is currently discussing a legislative proposal (Senate Act No. 1201 that is under consideration by the Hygiene and Health Commission) to strengthen the disclosure obligations of companies of the healthcare industry (see Section VIII).
VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The compensation system in the life sciences sector makes no exception from the ordinary rules of the Italian Civil Code on tort liability (Sections 2043 and 2050) and the Italian Consumer Code, regulating damage caused by defective products. Specific provisions of law apply to compensation due to persons injured by mandatory or recommended vaccinations under Law No. 299/2005.

Moreover, the law requires mandatory insurance for HCOs and HCPs as well as for sponsors of clinical trials.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The report of the European Commission on competition enforcement in the pharma sector, published on 28 January 2019, states that in the period 2009–2017 the Italian Competition Authority (ICA) was the most active authority within the EU, having issued pecuniary sanctions to pharma companies totalling €198.5 million.

The most recent landmark decisions of the ICA in the pharma sector focus on abusive conducts and anticompetitive agreements.

In 2014, in the Lucentis Avastin case, the Italian ICA sanctioned Hoffmann-La Roche and Novartis with a pecuniary fine amounting to €90.6 million and €92 million respectively, as they entered into an anticompetitive agreement aimed at discouraging and limit off-label use of Hoffmann-La Roche’s oncology medicine – Avastin for treatment of age-related macular degeneration. According to the ICA, the arrangement was intended to disseminate information raising concerns about the safety of Avastin used in ophthalmology to shift demand towards the more expensive Lucentis. The decision of the ICA was confirmed by the Council of State with its decision No. 4990 dated 15 July 2019.

In the Aspen case in September 2016, the ICA imposed a €5.2 million fine on Aspen for abusing its dominant position by setting unfair prices for important off-patent medicines used to treat cancer. The ICA found that Aspen abused its dominant position in Italy by threatening to initiate supply termination, imposing price increases of between 300 and 1,500 per cent and by applying particularly aggressive tactics towards the AIFA in negotiating these prices. The ICA decision was upheld by the Administrative Regional Court of Rome. An appeal against this judgment is pending before the Italian State Council.

ii Transactional issues

In mergers, acquisitions and corporate transactions concerning life science companies, various specific industry-related issues should be taken into consideration. Among others, from a transactional standpoint specific attention should be paid to transfers of MAs of medicines and CE marks, assignment of contracts with public entities as a result of the transaction, transfer of pending clinical trials and accomplishment of payback obligations. The above issues require interactions with public entities, which in some cases must issue a specific authorisation.
VIII CURRENT DEVELOPMENTS

The most recent changes in legislation relate to the clinical trial sector, where Legislative Decree 52/2019 has implemented Delegation Law No. 3/2018 (see Section II.iii).

Parliament is currently discussing a legislative proposal to strengthen the disclosure obligations of companies in the healthcare industry. In particular, this proposal provides for the disclosure on a public telematic register called ‘Transparent Health’ of agreements and transfers of money, goods, services or other utilities made by a manufacturing company in favour of HCPs and HCOs.

Finally, a decree establishing new criteria and procedures for price negotiation of medicines reimbursed by the NHS is expected to be published in 2020 (see Section III).
I INTRODUCTION

The life sciences sector is strictly controlled in Japan in terms of regulation and intellectual property.

Drugs, medical devices, cosmetics and other medical or medicine-related products, including computer programs, are primarily regulated by the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, etc. (the PMD Act). Supplemental information regarding pharmaceutical regulations is provided in cabinet orders and ministerial orders relating to the PMD Act, as well as in other related administrative orders, notifications and guidelines.

In order to manufacture, import and/or market medical products, the following conditions are required in terms of licences and approvals: marketing business licences; manufacturing business licences (or manufacturing business registration, in the case of medical devices); accreditation as a foreign manufacturer, for products manufactured outside Japan; and marketing authorisation, required for each medical product.

The Ministry of Health, Labour and Welfare (MHLW) is the principal regulatory authority for medical products. With respect to substantive examination, the Pharmaceuticals and Medical Devices Agency (PMDA), a Japanese regulatory body or a substantive equivalent to the Food and Drug Administration (FDA) in the United States, will perform the regulatory check procedures instead of the main ministry. Additionally, local governments (i.e., prefectural governments, such as the Tokyo metropolitan government) are primarily responsible for overseeing pharmaceutical companies, on behalf of the MHLW, with regard to conventional medical products.

Foods including health-promoting or functional foods are less strictly regulated and are mainly regulated by the Food Sanitation Act, with specialised regulations under the Health Promotion Act and the Food Labelling Act, and thus regulated by a different ministry: the Ministry of Agriculture, Forestry and Fisheries (MAFF), with the assistance of the Consumer Affairs Agency (CAA) in the field of health-promoting or functional foods.

Protection of intellectual property rights is effected mainly through the Patent Act, the Utility Model Act, the Design Act and the Trademark Act (administered by the Commissioner of the Japan Patent Office). The Patent Act grants a 20-year term of protection against the manufacture, use, sale, import or export of a patented invention without the patentee’s permission. The Trademark Act provides a registration framework for brand names,
three-dimensional marks, logos and, in certain cases, sounds and other types of non-classical marks. Pharmaceutical products, including regenerative medical products, are subject to patent term extension, which is also effected by the Patent Act, under certain circumstances; the patent term may be extended by five years at most, in addition to the normal 20-year term. There is also the Orange Book, which lists information about drug approval; however, this is not US-style patent linkage under Japanese practice but substantially speaking, the Japanese practice has an effect of patent linkage practised in the US. Additionally, the Unfair Competition Prohibition Act provides some intellectual property protection such as trade secrets, unfair usage of a well-known sign, misleading representation regarding the place of origin, imitation of the configuration of a third party’s product, etc.

Additionally, amendments to the PMD Act promulgated in December 2019 (the 2019-Amendment), which were scheduled upon the introduction of the 2014-Amendment, have introduced some advanced drug R&D systems in view of the era of the internet and more strict control systems of pharmaceutical products, which are considered to be some of the biggest changes in the past five years in the pharmaceutical system in Japan.

II THE REGULATORY REGIME

i Classification

Types of products

Medical products

Medical products subject to the PMD Act are categorised into the following five product categories:

a drug or medicines;

b quasi-drugs or quasi-medicines;

c cosmetics;

d medical devices; and

e regenerative medical products.

Food products

Foods are categorised into the following categories according to relevant acts (note that foods with health claims are currently classified into three categories):

a foods in general; and

3 Approved Drug Products with Therapeutic Equivalence Evaluations (the list commonly known as the Orange Book) identifies drug products approved by the US Food and Drug Administration on the basis of safety and effectiveness.


5 www.mhlw.go.jp/content/11121000/000463479.pdf.

6 Article 2 of the PMD Act.

7 ‘Medicines’ and ‘quasi-medicines’ are often translated as ‘drugs’ and ‘quasi-drugs’, respectively, and these have the same meaning.

8 Iyakubugaihin.

9 Introduced in the 2014 Amendment to the PMD Act; products that enable skin, cartilage, etc., to be produced through the cultivation of cells (usually the patient’s own cells).
b foods with health claims:
• foods for specified health uses;\(^{10}\)
• foods with nutrient function claims;\(^{11}\) and
• foods with function claims.\(^{12}\)

Foods in general are regulated by the Food Sanitation Act under the supervision of the MAFF, whereas ‘foods for specified health use’ and ‘foods with nutrient function claims’ are regulated by the Health Promotion Act,\(^{13}\) and ‘foods with function claims’ are regulated by the Food Labelling Act, under the supervision of the CAA.

There are also approximately 1,000 ingredients on the Food and Drug Classification List that may be distributed as drugs if their effects and efficacy are labelled, and distributed as foods if their effects and efficacy are not labelled.\(^{14}\)

**Particulars**

**Drugs, quasi-drugs and regenerative medical products**

Drugs are defined as the products that are listed in the Japanese pharmacopoeia (current version is Supplement II, 17th Edition, issued on 28 June 2019), in addition to certain other materials that are specifically used for the diagnosis, treatment or prevention of disease (excluding medical devices, cosmetics and regenerative medical products). Under the definition of the PMD Act, drugs include those for veterinary use. Distinguishing between drugs, quasi-drugs, regenerative medical products, cosmetics, medical devices and foods is sometimes a practical issue that depends not only on the ingredients of the product but also the labelling, advertising and promotion methods utilised for the relevant product, including statements of the product’s virtues and its historical background.

‘Quasi-drug’ is defined as an item for the purpose of: (1) preventing nausea and other discomfort; (2) preventing heat rash, soreness, etc.; (3) encouraging hair growth or removing hair; or (4) exterminating and preventing mice, flies, mosquitoes, fleas, etc. Quasi-drugs include, but are not limited to: deodorants, depilatories, hair growth treatments, hair dyes, perm and straightening products, as well as medicated cosmetics, such as whitening products, anti-ageing products, and oily skin or acne treatment products. Care must be taken for products used for aesthetic purposes, which are often classified as quasi-drugs under Japanese practice.

Regenerative medical products are categorised separately (a requirement introduced in the 2014 Amendment to the PMD Act (the 2014 Amendment)), and the expeditious

---

\(^{10}\) Tokutei Hoken'yô Shokuhin or Tokuho.

\(^{11}\) Eiyô Kinô Shokuhin.

\(^{12}\) Kinôsei Hyôji Shokuhin.

\(^{13}\) These categories were supervised by the MHLW until 2009, and are currently supervised by the CAA.

and conditional authorisation of these products is the aim to meet the high expectations for innovative medicines in this category. Regenerative medical products are defined as processed cells that are intended to be used for:

a the reconstruction, repair or formation of structures or functions of the human body, or the treatment or prevention of human diseases; or

b gene therapy. 15

Drugs are further classified into ethical drugs and over-the-counter (OTC) drugs. Most ethical drugs require a prescription. In vitro diagnostics are usually classified as drugs rather than medical devices according to Japanese practice.

**Medical devices**

Medical devices are devices for treatment, prevention or diagnosis, which are listed in the Cabinet Order of the PMD Act. Medical devices are divided into Classes I, II, III and IV, in order of strictness of control. Class I devices are ordinary medical devices, substantially corresponding to Class I devices under the international task force. Class II devices are controlled medical devices, substantially corresponding to Class II devices under the international task force. Classes III and IV are strictly controlled medical devices, which are basically equivalent to Class III and IV devices under international classification by the Global Harmonisation Task Force. These classes depend on the magnitude of the risk to human health and life posed by the subject device. The type of business licence that is required for manufacturing, marketing or distributing a medical device depends on which of the four classes the subject device falls under. Software or computer programs used for data processing for MRI, CT, X-ray, PET-CT and other medical device hardware are also categorised as medical devices, according to the 2014 Amendment. Besides Classes I to IV, there are additional classifications, which require special maintenance: controlled medical devices requiring special maintenance16 and installation control medical devices. 17

Additionally, the ‘AI’ medical device category shall be introduced as part of the 2019-Amendment. AI medical devices are generally required to update information necessary for appropriate medical evaluation (‘medical bid data’); however, if approval were to be required from the authorities each time additional information is provided, there would be no timely provision of such medical devices. Therefore, Japan introduced a new category in which if the medical device manufacturers provide necessary and sufficient information and a schedule to the authorities, manufacturers will not be required to receive market authorisation once the AI medical device authorisation is obtained. The new category shall be introduced by December 2020.

**Cosmetics**

Cosmetics are defined as substances that have a mild action on the human body, and that are intended to be used on the human body by rubbing, sprinkling or another method, with the aim of cleaning, beautifying and increasing the attractiveness, altering the appearance or keeping the skin or hair in good condition (excluding drugs and quasi-drugs). Cosmetics

---

15 Defined in Article 2(9) of the PMD Act.
16 *Tokutei hoshu kanri iryo kiki*.
17 *Secchi kanri iryo kiki*. 

© 2020 Law Business Research Ltd
generally correspond to their counterparts in other jurisdictions; however, there are a number of discrepancies among various countries and categories. As such, certain products require practitioners’ advice before being introduced into the Japanese market. In particular, products that have medical functions are often classified as quasi-drugs.

ii Non-clinical studies

A non-clinical (or preclinical) study of a drug to be authorised shall be included in the application form for obtaining market authorisation, and as such must be in compliance with the Ministerial Order for Good Laboratory Practice (the GLP Order). Requirements stipulated in the GLP Order particularly include requirements for trial facilities, equipment and trial plans, as well as rules for animal care and breeding in relation to experimentation on animals. Non-clinical studies can refer to the guidelines published by the PMDA.

iii Clinical trials

Clinical trials are mainly regulated by the PMD Act and the Ministerial Order for Good Clinical Practice (the GCP Order). Clinical trials are regulated by the governmental organisations (i.e., the MHLW and the PMDA). Drugs for clinical trials are strictly controlled under the Notice from the MHLW. The Centre for Clinical Trials, Japan Medical Association, also provides guidelines for GCP, etc. Clinical trials specifically for marketing approval are called _chiken_ under the Japanese practice, and are different from other types of clinical trial. Some clinical trials other than _chiken_, classified as ‘specified clinical research’, are controlled under the Act on Clinical Research, which was enacted on 7 April 2017, and came into effect on 1 April 2018. Specific rules regarding regenerative medicine products were amended on 1 April 2019.

Prior registration with the authority

Prior registration documents must be prepared and submitted to the authority before performing a clinical trial for market authorisation. A sponsor should prepare a protocol, which shall be reviewed by the institutional review board (IRB) of a hospital. The IRB must include at least one member who is independent and has no conflict of interest with the product at issue. The reviewed protocol shall be registered and reviewed by the MHLW. There is some difference in terms of the order of procedure between conventional clinical trial and investigator-initiated studies. To assist preparation of the prior registration documents, before the formal registration process with the MHLC, applicants can informally consult with the PMDA by presenting a draft protocol. The sponsor can only request pertinent investigators for the clinical trials after the 30-day period for the PMDA’s review has passed.

---

18 See also Article 14(3) of the PMD Act.
20 See also Articles 2 and 80 bis of the PMD Act; Article 268 of the Rule for implementing the PMD Act.
21 Pharmaceutical practice director notification, Pharmaceutical Affairs Bureau No. 480 dated 31 March 1997, regarding the standard for manufacture control and quality control of drugs for clinical trials, and the standard for good manufacturing practice regarding facilities for the manufacture of drugs for clinical trials (GMP for drugs for clinical trials).
22 www.jmacct.med.or.jp/plan/guideline.html.
Compensation and insurance for injuries

If any adverse effects are observed in a clinical trial, the sponsor shall ensure that the trial subject is compensated for any damage and losses suffered by the subject. It is therefore mandatory that sponsors engaging in clinical trials always obtain insurance cover before a trial commences, since there is a potential risk associated with this type of liability. In addition, if applicable, remedies for damages under the general civil procedures are also available.

Informed consent/assent

Informed consents, or alternatively informed assents in specific cases, must be obtained from a trial subject before participating in a clinical trial, in a written format. Upon obtaining informed consents, a written explanation must be presented to all trial subjects describing the details of the clinical trial. Hospitals and doctors in charge of the trials must present explanation that includes the expected benefits and adverse effects of the trial drug, and, importantly, the trial subject’s right to terminate participating in the trial. Regarding infant patients and those who are not capable of consenting, informed assent may be obtained from the patients in addition to the guardian’s informed consent. There is currently no legal binding to this type of consent.

Safety reporting

Any records of clinical trial results must be maintained at the hospitals at which the clinical trial is being performed. Any party relating to the clinical trials must inform the MHLW of all serious adverse effects from the drug subject to clinical trials.

Investigator-initiated studies

In Japan, investigator-initiated studies (IIS) have been accepted since 2004, as a result of the amendment to the Pharmaceutical Affairs Act in 2003 (now the PMD Act). The GCP requirements are mostly applicable with some modification, and therefore the requirements for IIS are different from those applicable to marketer-initiated studies. IIS are typically used for drugs that are now commercially interested but medically important, such as those for rare diseases (i.e., orphan drugs) or those with extremely advanced medical technologies such as regenerative medicines. In the past, IIS have been conducted for those drugs that have already been authorised in another country but have not been subject to a clinical study in Japan for cost reasons.

iv Named-patient and compassionate use procedures

General prohibition against marketing without authorisation

In principle, drugs, quasi-drugs, regenerative medical products and medical devices cannot be distributed without a marketing authorisation. However, there is an exception to this rule that allows for compassionate use, as explained below.

24 Pharmaceutical practice director notification, Pharmaceutical Affairs Bureau No. 0828014, 28 August 2002. See also, Notification from Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau of the MHLW, 6 July 2016; and Notification from the director of the Pharmaceutical Safety and Environmental Health Bureau No. 1130-1, 30 November 2015.
Special procedure for importing drugs or medical devices\textsuperscript{25}

With respect to a drug or medical device that has only received a foreign (i.e., outside Japan) marketing authorisation, special conditions and procedures are provided. The requirements for obtaining approval under such special conditions are:

\begin{itemize}
  \item[a] marketing authorisation has been obtained in another country that has a marketing authorisation system equivalent to that in Japan;
  \item[b] immediate use of the drug or medical device is necessary to prevent a disease that can cause death or serious harm to the health of citizens in Japan from rising to the level of a pandemic; and
  \item[c] the drug or medical device is specifically designated through an administrative order.
\end{itemize}

Any disease, disorder or death that is supposedly related to the drug, regenerative medical product or medical device subject to these special conditions and procedures must be reported to the MHLW.

There was one case in which this special procedure was applied, which involved the importation of an influenza vaccine produced by non-Japanese manufacturers.

Under the 2019-Amendment, a system for confirming the import of unapproved pharmaceuticals in Japan shall be formally legalised. In parallel, the confirmation step shall be subject to investigations by drug enforcement officers. These amendments shall be in force by December 2021.

\section*{v Pre-market clearance}

To market drugs, regenerative medical products or medical devices, an entity must have a marketing business licence, which makes it an initial marketing entity. Such a marketing authorisation must be obtained for the respective drugs, regenerative medical products or medical devices it intends to market.\textsuperscript{26} Some products, such as regenerative medical products, may be approved for marketing authorisation in an accelerated manner under special conditions. However, such conditional marketing authorisation requires additional clinical data and must be resubmitted for a ‘conventional’ marketing authorisation.

\section*{Application}

An applicant must file an application for marketing authorisation with the MHLW. Alternatively, for some limited drugs and medical devices other than Class IV medical devices, applications may have to be filed with the relevant local government (prefectural government) or a registered non-governmental certifying agency. Generally speaking, an application for a medical product generally must be filed with the PMDA in the first place, although the application must be addressed to the MHLW or a prefectural government in writing.

\textsuperscript{25} Yakkan Shômei.

\textsuperscript{26} Articles 14, 14 bis, 14 octies, 74, 80 and 81 of the PMD Act; Articles 27, 74 and 80(2) of the PMD Act Enforcement Ordinance; Articles 40(1), 43 and 50 of the PMD Act Implementing Rule; and Pharmaceutical practice director notification, Pharmaceutical Affairs Bureau No. 331015, 31 March 2005.
Authorisation conditions
In reviewing an application, key consideration is given to the following:  

a. quality;  
b. efficacy/effectiveness;  
c. safety;  
d. the applicant’s marketing business licence;  
e. the proposed manufacturer’s manufacturing business licence or accreditation as a foreign manufacturer in which good manufacturing practice (GMP) is also checked.

As per the 2019-Amendment, minor changes in manufacturing processes of approval drugs which are deemed not to affect efficacy and safety shall no longer be required to be subject an additional review process: a simple submission notifying the change in the manufacturing process shall be sufficient. This amendment shall be in force by December 2021.

Other conditions
To market drugs, a party must obtain both the appropriate authorisation to market the drug and a marketing business licence. It is possible for wholesalers or retailers to distribute the drug that has been approved. Sometimes, such wholesalers or retailers are important, particularly for foreign enterprises that have little experience in Japanese marketing. In such cases, the wholesalers and retailers taking part in the distribution must also obtain business licences in their respective relevant categories.

Applicants located outside Japan
Japan has no ‘foreign marketing authorisations’ per se. If a foreign manufacturer is interested in exporting a medical product to Japan, the manufacturer must, in principle, obtain marketing authorisation for a foreign-manufactured medical product or let its distributor or licensee in Japan obtain a marketing authorisation. In such a case, the foreign manufacturer must file an application through an agent located in Japan that has a marketing business licence to obtain an appropriate marketing authorisation.

Fee
The application fees for marketing authorisation vary, depending on the type of medical product. The fee for a marketing authorisation for a novel drug ranges from approximately ¥2 million to ¥30 million (note that travel expenses for investigation in a foreign country should also be paid). GMP, GLP and GCP examination fees are also incurred, which together range from ¥3 million to ¥7 million (note that travel expenses for investigation in

27 With respect to the standard, GLP standard, GCP standard and other assurance standards stipulated in Article 43(i), (ii), (iii) of the PMD Act Implementing Regulation.  
28 Article 12 of the PMD Act, and both good manufacturing practice (GMP) and good quality practice (GQP) standards must be satisfied; the licence must be renewed every five years. The GMP standard is defined in Ministerial Ordinance for Standard for the manufacture and quality control of drugs and quasi-drugs (the GMP Order), and the GQP standard is defined in Ministerial Ordinance for Standard for the quality control of drugs, quasi-drugs, cosmetics or regenerative medical products and the like (the GQP Order).  
29 Article 13, 13 ter of the PMD Act.  
30 See www.pmda.go.jp/files/000214630.pdf, which has been updated as of 25 November 2014.
a foreign country have to be borne by the applicant if the applicant is a foreign entity). For applications for marketing business licences and manufacturer's licences, additional fees shall be incurred, ranging from ¥50,000 to ¥150,000. Thus, in total, the maximum fee may go up to approximately ¥50 million.

**Review time, special procedures and conditioned procedures**

The Japanese government announced that it aims to shorten the standard period for reviewing an application for a novel drug approval to 12 months, commencing from the date of the official acceptance of the filed application, and over the past couple of years this has been achieved for 80 per cent of the newly approved drugs. For prioritised examination, the period for the review is set down to nine months, and 70 per cent of the newly approved drugs so far have achieved this goal. It is of course that the actual period of review time depends on factors such as the type of medical product.

With respect to generic drugs, an abridged procedure is provided. The examination of an application for generic drugs mainly focuses on: (1) the equality of the original drug and the generic drug, including bioequivalence, chemical equivalence of active pharmaceutical ingredients (APIs) and stability; (2) the adequacy of the data attached to the application; and (3) the proposed manufacturing facility's compliance with GMP.

To obtain an authorisation through the abridged procedure for generic drugs, all the following conditions (among others) must be met:

- The re-examination period for the original drug must have expired;
- Bioequivalence – in which the quality, effectiveness and safety of the generic drug are to be equal to those of the original drug;
- API equivalence – in which the generic drug is capable of being a substitute for the original drug;
- Stability; and
- The patent for the original drug must have expired. In this regard, there is no equivalent to US-style patent linkage in Japan.

With respect to a 'use' patent, carve-out approvals are possible under current Japanese practice.

With respect to an orphan drug that is being used to cure a rare but serious disease, there is a special rule. Specifically, the review thereof can be expedited and prioritised over applications for novel drugs if the orphan drug is found to contribute to an apparent improvement in the quality of medical care for the subject disease.\(^{31}\) The conditions for a drug to be qualified as an orphan drug include the number of patients that have the particular disease and whether the particular drug is expected to have significant value if approved. The critical number of patients is currently designated as 50,000 by the Notification from the Director of the Department of Pharmaceuticals and Food No. 0401-11 of 1 April 2015.

As per the 2019-Amendment, new special procedures shall come in force for innovator drugs, and there shall be ‘five’ categories for the review system after the revision, which shall come in force by December 2020: (1) standard; (2) prioritised; (3) orphan drugs; (4) conditional early approval; and (5) SAKIGAKE pioneering drugs. Some drugs such as oncology drugs, orphan drugs and regenerative medical products may be qualified as such special categories.

---

\(^{31}\) Article 14(7) of the PMD Act.
For the standard category, the scheduled examination period shall be 12 months from the request to the approval. For the prioritised, orphan drugs and conditional early approval categories, the examination period shall be shortened to nine months. For pioneering drugs, the period shall be shortened to six months. The prioritised category requires severity of the targeted disease and remarkable significance of efficacy and/or safety.

Orphan drugs shall receive additional subsidies or grants from the government and are also subject to a special tax discount.

The conditional and time-limited approval system was introduced by means of the 2014-Amendment, and now shall be legally recognised as a category by the 2019-Amendment. Under this category, Phase III may be ‘skipped’. Specifically, after the safety is confirmed and the results predict ‘likely’ efficacy, the product may be given conditional, time-limited marketing authorisation to enable timely provision of the products to patients. Applicants can, of course, take a ‘normal’ authorisation path. In the conditional and time-limited authorisation path, the initial approval is time-limited and post-marketing safety measures must be taken, including priori-informed consent of risk to patients and obtaining ‘normal’ authorisation by collecting confirmation data of efficacy and safety within a maximum of seven years.

SAKIGAKE pioneering drugs, which are the main topic of the 2019-Amendment, shall receive special assistance from the government during the clinical trial stage such as prioritised consultation and being subject to preliminary evaluation. To be qualified as this category, it shall be necessary that the drug at issue shall be the first in the world that is to be approved in Japan with expectation of high efficacy and severity of the targeted disease. Note that the SAKIGAKE system had already been practised provisionally, and the 2019-Amendment shall formally legalise this system.

Additionally, a new category called ‘specific use drug’\(^{32}\) shall be introduced as part of the 2019-Amendment. The specific use drug mainly covers paediatric use, and once a drug is qualified as a special use drug, the drug shall be categorised as at least prioritised and may receive some financial and administrative assistance from the government under certain conditions similar to the orphan drugs category.

**No US-style patent linkage**

A request form for a market authorisation shall include the relevant patent information. The PMDA is said to stop or suspend a market authorisation if it recognises a patent in issue. However, there is no abbreviated new drug application (ANDA) system, such as in the United States, and thus there is no US-style patent linkage in Japanese practice. Practically speaking, the Japanese practice has an effect of patent linkage practised in the United States. Specifically, the innovator drug company may request suspension of drug approval for which the innovator company believes that the third-party company requested for marketing authorisation. The PMDA shall make an inquiry to the third party regarding the concerns relating to the potential infringement, and the third party must respond to the inquiry. If the response is not reasonable enough, the PMDA shall substantially stay the authorisation process. This is all administrative process, but the parties can file an infringement suit to the

---

32 *Tokutei Yôto Iyakuhin.*
relevant court. Patent cases are heard before the special instance courts, which are the Tokyo and Osaka District Courts. The court of second instance is consolidated to the Intellectual Property High Court of Japan (IPHC-J) located in Tokyo.

vi Regulatory incentives

Patent protection

Medical products, and the technologies related thereto, can be protected by substance patents (also known as compound patents), medical-use patents, formulation patents and manufacture method patents.33 Patent protection lasts for 20 years from the filing date of the application. Payment of an annual fee is required to maintain the patent registration. Methods of medical acts per se, such as methods of treatment, diagnosis and surgery, are not patentable subject matter under Japanese patent practice. Note that second medical use and dosage regimen inventions are patentable under Japanese patent practice. However, this requires a special claim format and it is therefore strongly recommended that a local patent attorney with special knowledge and experience is consulted. Recently, the Supreme Court of Japan issued an epoch-making decision on 27 August 201934 regarding patentability (inventive step or obviousness) for drug-related invention, which is favourable to the patentee. As such, patent protection for pharmaceutical products is expected to be more favourable to innovator manufacturers.

Extending term of patent protection

For medical products, the term of a patent can be extended at the request of the patent owner under certain conditions.35 It is important to note that it is only the patentee who can file a patent term extension application, which may be different from the one who has received a market authorisation. Further, it is also important that the patentee can only file such a patent term extension (PTE) application only after a market authorisation pertinent to the patent is obtained, and more importantly, within three months from the authorisation date. The term of the extension, which may not exceed five years, is generally equivalent to the period during which the patent owner, including its licensees, was prevented from implementing the patented product while waiting for the medical product registration required under the PMD Act. PTE applications may be filed for drugs and regenerative medical products but PTE applications are not allowable for medical devices. It is also important to note that it is not possible to file a PTE application on or after the six months from the patent expiry date. Instead, in such a case, the patentee must file prior notice before the six-months due date comes.

According to recent developments before the Supreme Court of Japan, practically speaking, the scope of the claims for a patent to be extended by a patent term extension request is currently substantially limited to the scope of the market authorisation in issue.36

35 Articles 67(2) and 67 bis of the Japanese Patent Act, Articles 14, 14 quater and 77 bis of the PMD Act; see also Notification from the Director of Division of Economy, Health Policy Bureau No. 0605001, 5 June 2009.
36 Genentech v. the Commissioner of the Japan Patent Office, Supreme Court of Japan, 17 November 2015 (Heisei 26 (gyo-hi) 356).
More recently, the Grand Panel of the Intellectual Property High Court of Japan held that the fact a later approved drug is generic does not necessarily mean that the generic drug infringes a patent covering the original innovator drug, if another ingredient other than an API is different in terms of the scope of the claims.37

**Protection under the PMD Act**

Japan has no explicit data exclusivity or data protection system in an independent format. However, the re-examination period plays a substantially similar role to that of data exclusivity. Specifically speaking, when a novel drug is approved, the new drug is subject to a re-examination. The re-examination period is generally eight years after the initial authorisation for a regular novel drug. As a matter of practice, an applicant for a generic product cannot apply for a marketing authorisation under the PMD Act until the re-examination period for the original (innovator) drug expires (see generic drug requirements above), since such an applicant cannot rely upon the original drug’s clinical data. As such, in substance, this re-examination system has an effect that is equivalent to that of data exclusivity. To encourage new orphan drug development, the re-examination period for an orphan drug is extended to a maximum of 10 years. For novel usage for drugs already approved for different uses, the re-examination period is shortened since some of the regulatory data are considered for the same APIs. For example, regarding novel efficacy, for novel dosage and application and other applications that are different from the original innovator’s drug, a re-examination period of four years is currently granted, and regarding new combination and novel administration, a six-year re-examination period is granted. For novel formulation or similar that is deemed to be identical to the original innovator’s drug, only the remaining period of the original innovator’s drug is granted.

vii Post-approval controls

**Post-marketing commitments and pharmacovigilance obligations (Phase IV)**

After the launch of a drug onto the market, the marketer holding authorisation must conduct post-marketing surveillance regarding quality control, safety and observing adverse effects, etc.38 If a marketer becomes aware of any issue relating to the effectiveness or safety of the marketed drug during the post-marketing surveillance, the marketer must:

- conduct a drug recall campaign;
- report the discovery to the PMDA;
- issue public notices if the issue is important; and

---


38 Quality control, etc.: Articles 17, 42, 43, 56 and 57 of the PMD Act; Ministerial Ordinance relating to the Standard of manufacture and quality control of drugs and quasi-drugs; and Ministerial Ordinance relating to the Standard of quality control of drugs, quasi-drugs, cosmetics and medical devices. Post-marketing safety measures: Articles 12 bis, 68 bis to 68 quindecies, and 79 of the PMD Act; Article 228 vices of the PMD Act Implementing Rule; Ministry Ordinance relating to the Standard of post-marketing safety management of drugs, quasi-drugs, cosmetics, medical devices and regenerative medical products (GVP Ministerial Ordinance); Notification from Department of Environmental Health and Food Safety No. 1031-1, 31 October 2014.

Adverse Effects and Malfunctions Report: Articles 68 decies(2) and 68 terdecies(3) of the PMD Act; and Articles 16(3)(i) and 23(1)(i) of the Personal Information Protection Act.


d take other appropriate measures to prevent further damage or loss to patients.

Period of authorisation and renewals

There is another type of checking system under current law and practice, which is called re-evaluation. As the evaluation process is developed gradually according to the time, the prior approval may not be appropriate after certain period of time. Specifically, although approval for a novel drug is generally subject to re-examination eight years after its initial authorisation, there may be cases where, subject to the type of medical product, the approval period may be shortened. In this regard, the MHLW occasionally conducts re-evaluations of drugs. In the late 1990s, a general re-evaluation was conducted and a number of cerebral ameliorator drugs were cancelled from authorisation.

Amendment to, transfer of and cancellation of marketing authorisations

Any amendment to a product subject to marketing authorisation (except for minor amendments) generally requires approval from the MHLW, while a minor amendment can be made by notifying the MHLW. The transfer of marketing authorisations to another marketer is generally permissible, as long as the new marketer holds an adequate marketing business licence, and after prior notice of the transfer has been submitted to the MHLW. Any amendment to the medical packaging insert accompanying a medicinal product must be reported to the MHLW, and the amended insert must also be uploaded to the marketer’s website. This regulation has been introduced only recently.

Additionally, criminal and administrative sanctions may be imposed. With respect to criminal sanctions, a pecuniary offence or imprisonment involving hard labour, or both, may be imposed. Regarding administrative sanctions, the authorities may issue a product recall administrative order, or an order cancelling a marketing authorisation or marketing business licence in response to a violation of a marketing authorisation.

Pharmaceutical Administrative Evaluation and Monitoring Committee

The 2019-Amendment shall establish a third-party committee within the MHLW. The committee shall evaluate and monitor the implementation status of measures related to ensuring the safety of pharmaceutical products and preventing the occurrence of harm in terms of sanitary and healthcare administration.

viii Manufacturing controls

Application

There are two types of business licence related to the manufacture of medical products:

a a marketing business licence, which is required for the initial marketing of a manufactured or imported medical product in Japan; and

b a manufacturing business licence, which is required to manufacture a medical product. (If a manufacturer of an imported product is located outside Japan, accreditation as a foreign manufacturer is also required).

39 Articles 74 bis and 80(2) of the PMD Act.
40 Chapter 14 of the PMD Act.
41 A manufacturer of a medical device is subject to a prior registration requirement, and is not required to obtain a manufacturing business licence.
The type of licence can affect the nature of the business being carried out. For example, a business entity that has obtained a manufacturing business licence but not a marketing business licence cannot distribute medical products (manufactured or imported by the company) to others (e.g., a wholesaler). A transferee of a medical product manufacturing facility, such as an entity that acquires and takes over a drug manufacturing business, is also required to apply for its own manufacturing business licence to succeed in such a manufacturing business. This is because it is not permitted to transfer a manufacturing business licence.

**Conditions**

The conditions required for obtaining a manufacturing business licence include certain facility, staffing and other standards, as set out under a ministerial order of the MHLW. Medical devices have specific conditions. The manufacturer must comply with the GMP regulations stipulated in the relevant MHLW order.

In addition, an applicant for a marketing business licence must satisfy:

- standards for maintaining quality assurances, as provided under the GQP regulations stipulated in the Ministerial Ordinance relating to standards for quality assurance of drugs, quasi-drugs, cosmetics and medical devices;
- standards for post-marketing safety management, as provided under the good vigilance practice regulations stipulated in the Ministerial Ordinance relating to standards of post-marketing vigilance practice of drugs, quasi-drugs, cosmetics, medical devices and regenerative medical products;
- standards for the good post-marketing surveillance practice regulations, which are stipulated in the Ministerial Ordinance relating to standards of post-marketing study practice of drugs, quasi-drugs, cosmetics, medical devices and regenerative medical products; and
- standards provided under the Ministerial Ordinance relating to GMP (for drugs), the Ministerial Ordinance relating to quality management systems (for medical devices and in vitro diagnostics) and the Ministerial Ordinance relating to good cell and tissue practice (for regenerative medical products).

With respect to medical devices, manufacturers have to obtain a certificate of ISO standard (i.e., ISO13485). In vitro diagnostic products, which fall within the category of drugs, may require conditions similar to those for medical devices.

---

42 Regarding Drugs: Articles 5(iii), 12 and 12 bis of the PMD Act; Article 3 of the Cabinet Order for implementing the PMD Act; Article 8 of the PMD Act Implementing Rule; Ministerial Ordinance relating to the Standard for quality control of drugs, quasi-drugs, cosmetics and regenerative medical products and the like; and Ministerial Ordinance relating to the Standard for post-marketing safety control of drugs, quasi-drugs, cosmetics and regenerative medical products and the like.

43 Regarding medical devices: Articles 5(iii), 23 bis and 145 of the PMD Act; Article 36 of the Cabinet Order for implementing the PMD Act; Article 8 of the PMD Act Implementing Rule; Ministerial Ordinance relating to the Standard for systems performing affairs regarding manufacture or quality control of medical devices or drugs for in vitro diagnosis; and Ministerial Ordinance relating to the Standard for post-marketing safety control of drugs, quasi-drugs, medical devices, cosmetics and regenerative medical products.
Restrictions on foreign applicants
A foreign manufacturer of medical products cannot distribute their products directly in Japan, but must arrange distribution through a licensed marketing business operating entity. In principle, accreditation requirements for a foreign manufacturer are basically the same as those to acquire a Japanese manufacturing business licence. An application for accreditation as a foreign manufacturer can be filed with a marketing business operating entity in Japan.

ix Safety information, traceability, advertising and promotion

Labels
Labels or package inserts are required and as per the amendment to the PMD Act in 2014, the contents thereof must be submitted to the authorities before receiving marketing approval. Further, as per the 2019-Amendment, electronic provision of labels or package inserts shall be formally introduced. Currently, drug providers are required to provide labels or package inserts on paper. Even today, drug providers are required to inform patients of the most up-to-date information. As the 2019-Amendment in this regard shall be in force by December 2021, drug providers are required to take care during this transition period.

Coding for traceability
Under the 2019-Amendment, in order to promote traceability of pharmaceutical products, display of codes such as barcodes or QR codes or the like shall be mandatory on packaging of pharmaceutical products. This provision shall come into force by December 2022.

Restrictions
False, excessive or misleading advertisements are prohibited by the PMD Act in relation to the name, manufacturing method, effectiveness, etc., of medical products, regardless of explicit or implicit communication. In this regard, the MHLW has issued Guidelines for the Adequate Advertisement of Drugs, with official commentary, which provide detailed explanations, including examples of adverts that the MHLW considers to be false, excessive or misleading. Advertising ethical drugs to the general public is generally prohibited. The Manufacturers Association has also issued standards, called promotion codes for drugs for prescription.

Internet advertising
These advertisement-related regulations apply equally to advertising over the internet. Websites and other channels such as the social networking sites of advertisers that contain hyperlinks to other websites are considered together as a single advertisement in determining whether a violation of the advertisement-related regulations exists (even where each website on its own may not explicitly violate these regulations).

44 Tenshu bunsho.
45 Articles 66 to 68, 72 quinquies, 85, 86 and 90 of the PMD Act; Article 64 of the Cabinet Order for implementing the PMD Act; Article 228 decies of the PMD Act Implementing Rule; Promotion Codes for drugs for prescription, JPMA Code of Practice (www.jpma.or.jp/english/policies_guidelines/pdf/code_practice.pdf); and Fair Competition Code relating to the restriction of provision of premiums in the sales of drugs for prescription.
Legal compliance system

Under the 2019-Amendment, drug manufacturers and providers are required to establish a system for legal compliance within their organisation. They are required to establish guidance such that employees shall be aware of legal compliance. Further, drug manufacturers and providers are required to appoint a general production and sales manager who has the necessary skills and experience to comply with laws and regulations and a production manager. Moreover, manufacturers and providers must follow opinions of the general manager and the person in charge of production control and take measures to comply with laws and regulations, if and when necessary. This provision shall be in force by December 2021.

If local government (prefectural government) deem the legal compliance system insufficient, the governor of such a prefecture can now issue an improvement order.

Introduction of administrative penalty system

As per the 2019-Amendment, an administrative penalty or surcharge system shall be introduced for false and exaggerated advertisements similar to that which is in force in the Act against Unjustifiable Premiums and Misleading Representations (AUPMR).46 Those who have earned economic gains through products that have been in violation of false or exaggerated advertisements relating to the names, manufacturing methods, effects, effects or performances of drugs, medical devices, etc. shall be subject to an administrative penalty or surcharge payment of 4.5 per cent of the sales amount relating to the false and exaggerated advertisements. The 4.5 per cent figure is relatively higher in view of the fact that 3 per cent shall be applied to the other products that is subject to the AUPMR. A quasi leniency system shall also be introduced in which those who are in doubt of misconduct voluntarily declare their facts in suspect to the Minister, and shall qualify for a 50 per cent reduction of the penalty or surcharges. However, there is no full exemption from the penalty or surcharges.

Distributors and wholesalers

Wholesaler and retailer business licences

An entity that intends to market drugs, regenerative medical products and medical devices must hold both a marketing authorisation and a marketing business licence.47 There are differences between business licences for wholesalers and those for retailers; in other words, there are two types of licence and one party can apply for both types.48 As such, wholesalers and retailers of drugs, regenerative medical products or medical devices are subject to separate business licence requirements.

---

46 Keihyô hō.
47 For wholesalers: Articles 25, 34 and 35 of the PMD Act; Regulations for Buildings and Facilities for Pharmacies and the like; Articles 138 and 158 bis of the PMD Act Implementing Rule; Regulations for Buildings and Facilities for Pharmacies and the like. For retailers: (store-based distribution) Articles 4, 5 and 26 of the PMD Act; Articles 1(2)(iv) and 1(5) of the PMD Act Implementing Rule; Article 19 of the Pharmacists Act; Ministerial Ordinance for systems performing affairs of pharmacy and items relating to store-based distribution and placement and sales. For placement and sales: Articles 30, 31, 33 and 37 of the PMD Act; and Notification of MHLW No. 26, 6 February 2009.
48 Additionally, the leasing of strictly controlled medical devices requires a leasing business licence.
Marketing through the internet or mail order

Over-the-counter (OTC) drugs can be generally marketed through the internet and by mail order. However, there are some exceptions and certain potent drugs and OTC drugs that were previously classified as ethical drugs (most of which require a prescription, as described below) cannot be sold on the internet or requested by mail order, and require face-to-face communication with a pharmacist before being sold. Under the current practice, such internet or mail order retailers are required to have at least one ‘real-world’ store where they can receive orders from consumers via the internet or mail.

Classification of products

Prescription drug and OTC drug

In addition to the classifications of drugs, quasi-drugs, cosmetics, medical devices and regenerative medical products, drugs are further classified as either ethical drugs (most of which require a prescription) or OTC drugs. In other words, of the drugs authorised in the market, the MHLW designates certain drugs that may not be distributed or sold without a prescription (ethical drugs). The MHLW designates prescription drugs on a case-by-case basis when granting the relevant marketing authorisation in consideration of its prescription drug designation standard. A marketer is required to obtain a marketing business licence to market a prescription drug.

OTC drugs are further classified as either pharmacist’s intervention required medicines (PIRMs) or general OTC drugs. PIRMs were introduced in the 2013 Amendment to the PMD Act, wherein PIRMs cannot be sold without a pharmacist’s intervention and purchasers are strictly limited and controlled to those patients in need of such drugs. PIRMs include ‘switch OTC drugs’ and ‘direct OTC drugs’. General OTC drugs are categorised as first, second or third class, mainly according to the associated risk factors. First-class OTC drugs must be sold by a pharmacist, whereas second-class and third-class OTC drugs may be sold by a pharmacist or a registered sales clerk. First-class and second-class OTC drugs must only be sold with the appropriate information about the drugs.

Prescription drug designation standard

Prescription drug are designated by the MHLW, which includes the following types:

a. drugs that cannot be used effectively or safely without proper selection based on a doctor’s diagnosis;
b. drugs that require periodic medical checks to avoid serious adverse effects; and
c. drugs that can be used for other improper purposes (e.g., recreational addictive use).

Prescription drugs include (1) radioactive drugs; (2) narcotics; (3) psychotropics; (4) analeptics; (5) analeptics raw materials; (6) specific biological products; (7) injectables

---

49 Articles 3, 4(5), 14, 14 quater, 36 septic, 44, 46, 47, 49, 74, 74 quater, 79 and 80 of the PMD Act; Articles 1(3), 7, 62 and 159 bis of the PMD Act Implementing Regulation; first-class and second-class drugs as designated by the Minister of the MHLW based on the provision set forth under Article 36 ter (1) (i), (ii) of the PMD Act; Notification from the director of the Department of Pharmaceuticals and Food No. 0331015, 31 March 2005; and Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 0210001, 10 February 2005.

50 Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 0210001, 10 February 2005.
(excluding (1) to (6) aforementioned); (8) specific substances designated by the MHLW (currently 974 substances) and the derivatives and hydrates thereof, and salts thereof (excluding (1) to (7)); and (9) oxytocin, serum gonadotropin and placental gonadotropin.51

xii Imports and exports

Licences and authorisation for imports

To import and sell a drug, regenerative medical product or medical device in Japan, it is generally required to have the following business licences and authorisation:

a. accreditation as a foreign manufacturer by an offshore manufacturing factory for the products being imported;

b. a manufacturing business licence held by a domestic factory (if part of the manufacturing process, such as packaging of the imported products, is conducted in Japan before marketing);

c. a marketing business licence held by a marketer, for marketing the imported products;

d. a marketing authorisation held by a marketer, for marketing the imported products; and

e. an import report from a marketer, for customs clearance.

Licences and authorisation for exports

The following business licences and authorisations must be obtained to export a drug, regenerative medical product or medical device from Japan:

a. a manufacturing business licence held by a domestic factory for manufacturing products for export; and

b. an export report from a domestic factory for product export.

Even if the products are solely for export and distribution outside Japan, factory manufacturing products for export located in Japan must be subject to a GMP compliance review by the MHLW.

Exportation of medical products from Japan to other countries can be categorised as follows:52

a. when exporting products on the Japanese market that are already approved and licensed or authorised under the PDM Act for domestic markets, without any changes (no further licences are required for such exports);

b. when exporting products on the Japanese market that are already approved and licensed or authorised under the PDM Act for domestic markets with changes (including changing package designs and attaching further labels with translations, etc), it would be regarded as having produced medical products for export. Therefore, in such a case, it would be necessary to obtain authorisation as mentioned above; and

c. when exporting products without having obtained authorisation under the PMD Act, it would be necessary to obtain a manufacturing business licence and an export report.

51 Notification from the MHLW No. 24.
52 Article 80 of the PMD Act, Articles 71 and 74 of the PMD Act Implementing Ordinance, and Article 265 of the PMD Act Implementing Regulation.
Additionally, when exporting products manufactured in Japan, the country which is importing the products may require a GMP conformance certificate.

**xiii Controlled substances**

Certain substances are designated as controlled substances in Japan; for example, narcotics and psychotropic drugs are heavily controlled by the Narcotics and Psychotropic Control Act. This act regulates the import, export, manufacture, sale and purchase, possession, use and disposition of narcotics and psychotropic drugs. Doctors, importers, exporters, manufacturers, wholesalers, retailers, hospitals and research institutions are required to obtain special permission to handle narcotics or psychotropic drugs. The MHLW often provides notifications, which are available from its website.53 Other acts for the control of substances are the Stimulants Control Act, which mainly focuses on (meth)amphetamine, the Cannabis Control Act, the Opium Act, and the Ministry Ordinance for manufacture and handling of radioactive drugs.

Furthermore, certain drugs falling within the scope of substances are controlled by the Poisonous and Deleterious Substances Control Act. This act defines poisonous substances, deleterious substances and special poisonous substances, all of which are high on the list. These substances can be searched for using the database search tool provided by the National Institute of Health Sciences.54

With respect to exceptions on prohibition of narcotics or the like, there is already an exception for narcotics for cancer patients under the relevant acts. In addition thereto, as per the 2019-Amendment, Stimulants such as (meth)amphetamine shall be added to the exception for patients with Parkinson's disease.

**xiv Special remarks on traditional medicines**

There are some issues regarding ‘Western herbs', for which there is no clear definition under Japanese pharmaceutical practice. In terms of ‘food', Western herbs are subject to laws and regulations relating to food control, such as the Food Sanitation Act and the like. In terms of agricultural products, they are subject to the Act on Standardisation and Proper Quality Labelling of Agricultural and Forestry Products (JAS Act). Regarding labelling, they are subject to the Act against Unjustifiable Premiums and Misleading Representations. If Western herbs are intended to be used with health claims, they are subject to laws and regulations relating to foods with health claims. Even if a Western herb of interest is already approved in a country outside Japan, that herb must be subject to general procedures for obtaining marketing approval. However, when submitting an application for marketing approval, some of the required documents can be omitted by relying on documents relating to clinical trials conducted outside Japan. Specifically, clinical trial results submitted to a non-Japanese examination authority as exhibits for obtaining marketing authorisation, such as comparative clinical trials using a substantially equivalent formulation to show effects or efficacy, dosages, regimens, or an academic article submitted and published by an internationally recognised

---

53 www.mhlw.go.jp/bunya/iyakuhin/yakubuturanyou/kanren-tuchi/
medical journal including such results, it is only necessary to submit safety results using Japanese subjects. Some Western herbs previously marketed in Europe have already been approved in Japan.

With respect to Japanese traditional medicine (Kampo), the MHLW has legislated a specific list naming products that satisfy approval criteria as a general OTC drug stipulated by the Japanese government, which require the least documentation of all the OTC categories. As of September 2016, 15 categories are specifically defined, such as analgesics, etc., and types of active pharmaceutical ingredients, formulation types, dosages, administration routes and regimens, effects and efficacies, and packages units. As of April 2017, some Kampo drugs are handled by local administration offices. With respect to Kampo drugs other than the general OTC drugs, it is not possible to rely on ‘historical’ knowledge and it is therefore necessary to conduct new clinical trials, as either Patient Registry Item Specifications and Metadata for Rare Disease (PRIMS) or ethical Kampo drugs.

**Enforcement**

**Monitoring compliance**

The MHLW is recognised to be the main regulator, but in practical terms, it is the PMDA and local prefectural governments that are delegated to conduct a substantial amount of its authority. The regulator can monitor a licensed business operating entity’s business operations, to ensure compliance with the rules and regulations provided under the PMD Act. The regulator can monitor and oversee medical products that are subject to marketing authorisation. Novel drugs are subject to re-examination after a certain period. In addition, an applicant that receives authorisation must have its medical product re-evaluated upon receipt of an MHLW order.

**Imposing penalties**

The regulator can take actions against licensed business operating entities, which include:

- inspecting offices and factories;
- ordering the disposal, recall or other appropriate treatment necessary to protect public health;
- requiring that access be granted to the inspector designated by the regulator, who is responsible for the subject investigation;
- temporarily suspending pharmaceutical business operations;
- ordering the replacement of certain key personnel relevant to the pharmaceutical business;
- cancelling a business licence or accreditation it had previously granted; and

---

55 Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 322001, 22 March 2007.
56 Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 0830-1, 30 August 2014; Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 0626-1, 26 June 2014; and Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 062-6, 26 June 2014.
57 Notification from the director of the Pharmaceutical Safety and Environmental Health Bureau No. 0328-1, 28 March 2017.
58 Section 13 of the PMD Act.
demanding a report that includes data about adverse reactions to the medical product, recall information, etc.

Further, criminal sanctions can be imposed in response to violations of certain regulations applicable to pharmaceutical business operating entities.

III PRICING AND REIMBURSEMENT

A universal healthcare system was introduced in Japan in 1961 and has been well organised thus far, although some financial problems still exist and could become more serious in the future. Under the universal healthcare system, most legal residents are covered. Costs for a substantial number of the medical services provided and prescription drugs sold, as well as certain medical supplies, are covered by this system.

In this regard, the national health insurance price list has an important role in Japan. For example, the costs for drugs prescribed by a doctor may only be reimbursed if the subject drugs are listed on the national health insurance price list. As such, this list is deemed to be very important for running businesses in the medical field.

Costs for medical services provided using a medical device are reimbursed if those services are covered by the national health insurance. Additionally, costs for certain expendable medical supplies can also be reimbursed if they fall within one of the classifications of the medical supplies that are listed on the price list. In the case of large pieces of medical equipment and non-expendable medical devices, however, the costs of the devices themselves are not reimbursed; only the cost for utilisation may be subject to reimbursement.

The scope of the medical services, drugs and medical supplies covered by national health insurance, and the prices designated for each, are determined by the MHLW in consultation with a specialists’ committee. Usually, there is a 10–30 per cent rule for patients to pay; however, there is an upper limit cap, which prevents patients from paying too much. As such, the actual costs for patients are limited and controlled.

Reimbursement under the national health insurance system is generally made through a benefit-in-kind system. A large portion of the cost of the medical services, drugs and medical supplies covered by the health insurance is directly paid to the hospitals, doctors or pharmacists providing the services, drugs or supplies to patients.

The amount of reimbursement is based on the price of the medical services, drugs or medical supplies specified on the respective price list. The patient is required to pay the hospital, doctor or pharmacist a designated portion of the cost of such services, drugs or supplies, which is not reimbursed under this system.

Discussion is continuing as to whether price alteration should be conducted every year instead of every two years to more closely reflect changes in the market.

With respect to pricing reform, the Japanese government has introduced drastic policy changes in the pricing system. Instead of a drug price revision every two years, Japan has introduced an annual revision system. In addition to the re-establishment of the evaluation system for innovation drugs, Japan has introduced a use of health technology assessment (HTA), including a cost-effectiveness evaluation system, when setting drug prices, particularly blockbusters. With respect to reference pricing lists overseas, currently those of the United...
States, France, the United Kingdom and Germany are considered, including Red Book. In 2018, Red Book will be excluded from consideration and, instead, ASP and NADAC will be considered.

**IV ADMINISTRATIVE AND JUDICIAL REMEDIES**

Generally speaking, an administrative disposition made by an administrative agency, such as an administrative remedial order or a revocation of a licence, may in principle be subject to an appeal to an administrative agency, in accordance with the Administrative Appeal Act; or a Japanese court, in accordance with the Administrative Case Litigation Act. Special provisions are provided by the PMD Act.59

The Administrative Appeal Act, enacted on 1 April 2016 and currently in force, is a result of renovation during the past 50 years. Under the new system stipulated by the amended Administrative Appeal Act, a person affected by an administrative disposition may file an application for review with the administrative agency that is superior to the agency that made the disposition, or, if no such superior agency exists, with the administrative agency that made the disposition. This type of appeal must be filed within three months of the day that the affected person became aware of the subject disposition (note that the date of the recognition is excluded and thus the calculation is made from the following date). Extensions are allowable only if there are reasonable grounds to justify such an extension. Generally speaking, extensions are not permitted, and it is therefore advisable to file an appeal as early as possible. In cases where an administrative agency renders a written disposition that is subject to such an appeal, the agency responsible for the disposition must inform the recipient, in writing, of the agency to which an appeal may be filed and the time limit for filing an appeal.

Additionally, a person affected by an administrative disposition may also dispute the disposition by bringing suit in a Japanese court pursuant to the Administrative Case Litigation Act. There are a number of types of administrative litigations under the Administrative Case Litigation Act, including an action for a revocation of disposition and an action for a declaration of nullity. An action for a revocation of disposition must, in principle, be filed within six months of the day that the affected person became aware of the subject disposition or within one year of the day of the subject disposition, whichever comes first, in the absence of reasonable grounds.

Generally speaking, the trial procedures resulting from an appeal are stipulated in the Administrative Appeal Act and are not as complicated as court proceedings performed in a litigation case before the court pursuant to the Administrative Case Litigation Act.

With respect to intellectual property examination, specific acts such as the Patent Act supersede the above-mentioned general procedure, and examination results of patent, utility model, industrial design and trademark applications shall be appealed to the Trial and Appeal Boards within the Japan Patent Office. If an applicant is not satisfied with the decisions made by the Trial and Appeal Boards, an appeal can be made to the Intellectual Property High Court of Japan, in Tokyo.

---

59 Articles 13 bis (5), 13 bis-7 (6), 14 bis (6), 23 viciester (5) and 80 decies (5) of the PMD Act.
V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The financial relationship between prescribers and payers is very restricted in Japan. The Act against Unjustifiable Premiums and Misleading Representations (the Premiums Act) controls the relationship, including wrongful inducement of customers through the provision of excessive premiums, incentives and other benefits; these acts are prohibited and controlled by the Premium Act. There are a couple of guidelines and codes established in accordance with the authority's order. In this regard, the Japan Fair Trade Commission (JFTC) and the secretary general of the Consumer Affairs Agency (CAA) has power to control trade in terms of medical products. With respect to pharmaceutical drugs, the Fair Competition Code Concerning Restriction on Premium Offers in the Ethical Pharmaceutical Drugs Marketing Industry has been established by the Fair Trade Council of the Ethical Pharmaceutical Drugs Marketing Industry (the Drugs FTC), and with respect to medical devices, the Fair Competition Code Concerning Restriction on Premium Offers in the Medical Devices Industry has been established by the Japan Fair Trade Council of the Medical Devices Industry (the Devices FTC). These codes set guidelines in relation to premiums or incentives provided not only to individual physicians but also to medical institutions. If a premium or incentive is offered to physicians or medical institutions in violation of these rules, the JFTC and CAA would be likely to consider such an offer to be in violation of the Premiums Act.

In this regard, the Drugs FTC and the Devices FTC include detailed descriptions of the standards on permissible premiums and incentives, giving specific upper-limit amounts for entertainment expenses. Additionally, a number of examples of excessive premiums or incentives that are unacceptable under the Premiums Act are exemplified in these codes.

With respect to public sectors, there are additional and specific regulations with respect to financial relationships. If a public servant, who may be a physician at a hospital managed by national or local government, receives excessive premiums, incentives or other benefits in relation to his or her official function and capacity, he or she can be criminally prosecuted for bribery and the party offering the bribe may also face criminal penalties for the violation. The above-mentioned financial relationships are not necessarily direct, but even an indirect relationship may be a problem; therefore care must be taken when dealing with a public servant. The relationship may be cross-border. For example, if an act of bribery such as an offer of excessive premiums or payment of money occurs in Japan, and the bribe is offered to a public servant of another country, the party offering the bribe may also face criminal penalties under the Japanese Unfair Competition Act, among others. The Act also stipulates a number of categories that fall within the scope of criminal penalties.

Payments made to physicians and medical institutions beyond certain criteria must be disclosed in principle, and that disclosure is regulated by industry rules established for the pharmaceutical industry and the medical devices industry. Specifically, each Japan Pharmaceutical Manufacturers Association (JPMA) member is encouraged to publicly disclose all such payments made for each fiscal year according to guidelines issued by the JPMA, a voluntary organisation formed by pharmaceutical companies. With respect to medical devices, the Japan Federation of Medical Devices Association, a voluntary organisation formed by medical device companies, issues similar guidelines.
VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Since medical products such as drugs and medical devices generally fall within the category of ‘products’, general rules relating to product liability under the Product Liability Act also apply with respect to tort principles or non-performance of contractual duties with some modification.

Specifically, adverse health effects arising from medical products are of note with respect to medical products, and the PMDA provides several relief services therefor. The pharmaceutical industry funds these services and the Japanese government subsidises the services. Relief benefits provided by the PMDA relating to health damage include those related to diseases and disabilities requiring hospitalisation that were caused by adverse reactions to prescription drugs prescribed at medical institutions, such as hospitals or clinics. Additionally, OTC drugs purchased at pharmacies or drug stores are also covered by the same system.

Certain anti-cancer and immunosuppressant drugs, however, are exceptions and health damage caused thereby may not be eligible for these benefits. Damage to health, including diseases, disorders and disabilities, caused by infections because of biological products are also covered by the relief benefits provided by the PMDA. These types of benefits are only applicable when the relevant medical products were used appropriately. Damages that are the result of inappropriate use of the medical products are not covered by these relief benefits.

It should be noted that any damages awarded under civil liability are, in principle, considered the main source of remedy, and thus the above-mentioned relief benefits are supplementary. That is, if a pharmaceutical business is held liable for the injuries caused by the use of a drug or biological product, the PMDA will not provide relief benefits, or the benefits will be reduced by the amount of the damages award.

With respect to adverse health effects resulting from statutory vaccinations, a different public relief system is available and thus the PMDA does not provide relief benefits therefor.

In addition to the relief services, there are certain special considerations for particular circumstances. Specifically, the PMDA provides the following relief benefits:

a SUMON: healthcare allowances and nursing-care expenses for subacute myelo-optico-neuropathy patients with respect to whom a settlement has been reached in court;  
b HIV: healthcare expenses or healthcare allowances for patients who have become infected with HIV because of treatment with blood products; and  
c HCV: financial assistance in accordance with the Act on special measures concerning the payment of benefits to assist individuals affected by hepatitis C through specified fibrinogen products and specified blood coagulation factor IX products contaminated by the hepatitis C virus.

These kinds of special remedies may be added in accordance with the updated adverse effects information.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The Antimonopoly Act provides a number of restrictions for promoting appropriate competition. Among others, in terms of the pharmaceutical industry, prohibition against maintaining resale prices often becomes an issue for drug manufacturers of prescription drugs. Specifically, in cases where a prescription drug is supplied by a drug manufacturer
to a distributor, and then to a wholesaler, the sale price of the drug is officially determined based on the price of the drug specified on the national health insurance price list. The price list is reviewed periodically. The frequency of the periodic review was every two years until 2017; however, this has been proposed to be changed to every year, as mentioned in Section IV. Between 2018 and 2020, the government will monitor the actual price for all the drugs and will decide whether revision of the price list should be every year or not. The price for a prescription drug may be lowered in view of a number of circumstances; for example, if the price at which wholesalers purchase and sell the drug decreases during the two-year period.

To prevent the drug price in the price list from being lowered, drug manufacturers are advised to maintain the price at which wholesalers actually purchase and sell their drugs. In addition, if the drug is protected under a patent, the price is generally maintained or the amount of reduction is minimised at the next review.

Additionally, the Antimonopoly Act prohibits a business entity from supplying goods or any other premiums to another party while, without justifiable grounds, causing said party to maintain the sale price of the goods as determined by the business entity, or otherwise restricting said party’s ability to freely decide on the sale price of the goods.

Although indicating a non-binding reference price is generally considered not to violate this prohibition if the manufacturer intends to restrict the resale price of the distributors by causing them to comply with the reference price, the manufacturer may be regarded as having violated the Antimonopoly Act. Generally speaking, whether resale prices have been restricted or not is determined based upon whether any unnatural or artificial measures have been taken to substantially ensure that the distributors will comply with the sales price indicated by the manufacturer. For example, such measures include imposing, or suggesting the imposition of, an economic disadvantage if sales are not made at the manufacturer’s indicated price, but are not limited thereto.

Price indications by a manufacturer are also strictly controlled: such indications may be made not only by indicating a specific (single) price, but also by indicating a specific price range or by requiring that a resale price be approved in advance by the manufacturer.

ii Transactional issues

It is important to proceed with much caution if any interested parties intend to conduct licensing and collaboration transactions in respect of drugs and medical devices in Japan. In this regard, the JFTC has established guidelines setting out its views on antitrust aspects relating to joint research and development (R&D), and the use of intellectual property, such as patents and clinical data.

There are two main sets of guidelines that pertain to transactional issues regarding R&D and intellectual property with respect to the Antimonopoly Act.

First, any transaction that may affect the Japanese market is subject to the Guidelines concerning Joint Research and Development under the Antimonopoly Act (the Joint R&D Guidelines). Such transactions are not limited and the Guidelines are applicable irrespective of whether the participants are Japanese or foreign (non-Japanese) business entities. The Joint R&D Guidelines stipulate that, if an arrangement made in respect of the implementation of a joint R&D project unjustly restricts the business activities of a participant, which may thereby impede fair competition, the arrangement may constitute an unfair trade practice prohibited under the Antimonopoly Act. In this regard, for example, in the case of contractual arrangements imposing restrictions on R&D with third parties, it is generally not considered to be an unfair trade practice to restrict R&D with third parties on the same theme as the

© 2020 Law Business Research Ltd
joint R&D project during the implementation period of that project. On the other hand, restrictions on R&D after completion of the joint R&D project are, in principle, considered impermissible under the Antimonopoly Act. This is because they would unjustly restrict the R&D activities of the participants and may significantly impede fair competition. In this regard, such restrictions may be permissible if the subject restriction is imposed on the same theme only for a reasonable period of time after completion of the joint R&D project, provided that the restriction is necessary to prevent a breach of faith or to ensure acquisition of rights.

Second, with respect to intellectual property rights, which are usually deemed an exception to the antitrust concept, there is a special measure. Specifically, there are the Guidelines concerning Use of Intellectual Property under the Antimonopoly Act, which are applicable to intellectual property related to technology, such as those technologies protected by patents, designs and copyrights under Japanese acts relating to intellectual property. These Guidelines define and state the principles by which the Antimonopoly Act is applied to restrictions pertaining to the use of technology. Particularly grant-back and assignment-back arrangements under licensing agreements are strictly controlled.

VIII CLINICAL TRIALS ACT

The Clinical Trials Act was enacted and promulgated on 14 April 2017, and was enforced on 1 April 2018. It was, however, still in the transition period until the end of March 2019. Any trials conducted before the end of March 2019 had to be processed according to the old regulation, in which no strict rules were applied. The Act controls any specific clinical studies, trials and research, which are not necessarily limited to those submitted to the PMDA for market authorisation. The types of clinical research at issue are classified as either (1) any clinical studies funded by a pharmaceutical company or the like, or (2) clinical studies on compassionate use of an approved drug, such as drugs marketed in Japan but for use other than the approved indications, and drugs that are not yet approved in Japan but marketed in a certain country outside Japan. Under the Act, monitoring and audit will be made compulsory. Currently, the regulation under the subject Clinical Trials Act is too strict, and thus chiken clinical trials for drug approvals are actually recommended in practice.

Since 2015, when the current international standards in accordance with IHC were implemented for clinical research conducted in Japan, it is expected that foreign researchers and practitioners will conduct clinical research in a more internationally harmonised manner, which may be easier for non-Japanese entities.

Additionally, amendments to the Act on Protection of Personal Information, which stipulates privacy under the Japanese practice, was promulgated in September 2015 and was enacted on 30 May 2017. This amendment is the first in the past half century to ‘replace’ existing legislation.

The amendment provides for various substantial reforms to the current legal framework, many of which will materially affect activities that involve personal information, such as clinical studies and the handling of patient information. In terms of clinical trials and data obtained therefrom, a new regulatory system will be introduced for anonymised data, which is currently not regulated under the previous law before the amendment. Under the new rules, anonymisation of personal information will need to be conducted in accordance with
a designated method, and anonymised data cannot be provided to a third party without first publicly disclosing the type of personal information contained in the anonymised data and information, as well as the method of providing the anonymised data.

From an international point of view, it is important to note that a new provision and requirements will be introduced for cross-border transfers of personal data. The new rule will prohibit personal information from being transferred out of Japan without the consent of the relevant individual, unless the transfer is made either to a jurisdiction designated under the subordinate ordinance as having an equivalent level of protection for personal information, or to a third party that has established protective measures satisfying the prescribed criteria. It is expected that under the new rules in Japan, more regulations will be required with respect to a number of activities involving personal information.

In view of the above two major aspects of updates in Japanese law, clinical trials and studies in relation to Japan and the Japanese market will see a drastic change in the next couple of years.

IX BIG DATA AND DATA PROTECTION

The Act Regarding Anonymised Medical Data to Contribute to R&D in the Medical Field (the Medical Big Data Act) was enacted on 11 May 2018. This act is intended to implement the necessary policies to enhance medical research using anonymised medical data, and to introduce a system in which only ‘certified anonymised medical data agents’ shall be entrusted with the medical information or medical big data. The agents shall be checked whether they have high security measures, and high technical and management abilities to anonymise the data for optimal use.

Before the Medical Big Data Act came into effect in 2018, revisions to the Act on the Protection of Personal Information came into effect in 2017. The amendment introduced legislation in which the use of clinical records for research can be performed without asking for a patient’s consent. However, to use such data, each hospital and clinic is responsible for making its data anonymous by deleting patients’ names and other privacy information, which is seen as cumbersome when their primary job is providing healthcare. The Medical Big Data Act facilitates the anonymisation. Further, the Big Data Act will allow hospitals and clinics to provide patient data to certified anonymised medical data agents to be accredited by the state. Such agents will be responsible for making the data anonymous and searchable. All clinical records, including a summary of conditions, prescriptions written by doctors and visual data such as MRI scans, are to be covered by the Medical Big Data Act.

Although the Medical Big Data Act was enacted in 2018, its implementation saw significant delay. In the Medical Big Data Act, it is necessary to designate entities that can process medical data with the necessary anonymisation of personal information. It was only on 19 December 2019 that such anonymisation entities were designated. Two entities (LDI and NTT Data) began operation on 6 January 2020.

X LIMITED PROVISION DATA

The Amendment to the Unfair Competition Prevention Act came into force on 1 July 2019. In the Amendment, a new framework to protect ‘valuable’ data was introduced. This valuable data is called ‘limited provision data’. In the new framework, the wrongful acquisition, use or provision of data that is protected by a management system (e.g., IDs and passwords) and
provided to limited users is an act of unfair competition. The Act provides civil remedies to victims; for example, rights to file a demand for an injunction or enjoy special treatments for compensation. It is, however, unclear as to what extent medical data will be covered by this regime, even after the publication of applicable guidelines in February 2019.

XI EXPECTED AMENDMENT TO THE JAPANESE PHARMACOPOEIA

The MHLW is currently working on the amendment to the Japanese Pharmacopoeia, which shall come into force in 2021. In the next revision, in addition to updating the items listed therein, modernisation and globalisation of the Pharmacopoeia are emphasised and additionally, the updating process should be more streamlined and open to the public as much as possible.

LATIN AMERICA OVERVIEW

Felipe Coronel C¹

I INTRODUCTION

The pharmaceutical industry in Latin America has historically represented a great challenge as its diversity is part of the rules of the game. Many actors in the life science sector have had to decipher such diversity to be able to penetrate these markets successfully, since it is not only based on different social, economic and political models, but also in heterogeneous legal systems. Consequently, the objective of this chapter is to drive the reader into understanding the complexity of the continent in terms of its regulations as well as the structure of its markets, main stakeholders, the challenges we have found in our practice and its normative evolution in recent years. This year's edition has some extra lines on the growing importance of the commercialisation of biological and biosimilar products in Latin America.

Though thorough, this chapter constitutes a summary of the most relevant aspects regarding life science in Latin America, and even includes some countries that do not have their own chapters in this publication.

II OVERVIEW OF THE REGION²

If we take as a reference for life science the global pharmaceutical market (global medicine spending), it currently exceeds US$1,000 trillion. Interestingly, 40 per cent of this amount corresponds to North America (the United States and Canada), while Europe has nearly 25 per cent of the total world market. Asia comes next with approximately 17.5 per cent.

In this global context, Latin America's share is between 7 per cent and 8 per cent of global drug spending, a figure that, taken as a whole, may seem insignificant, but from a market perspective, reflects a continent whose growth potential is extremely attractive, but equally challenging because of its diversity and complexity.

One of the first things to take into account to be able to decipher this region is that, within the total life science market in Latin America, Brazil and Mexico are particularly relevant because they are the countries with the largest population in the continent; hand

¹ Felipe Coronel C is founding partner at Latin Lex Consulting and Latin Lex International. This information in this chapter was accurate as at March 2019.
² We have been able to obtain the statistics referred to in this chapter as a result of our participation in the boards of multinational companies with presence in Latin America. We have also obtained data from IMS HEALTH, including the publication, Dinámicas y perspectivas del mercado farmacéutico en América Latina (Dynamics and Perspectives of the Pharmaceutical Market in Latin America), written by Juan Manuel Santa María, a distinguished participant in the 2015 IMS World Review Conference.
in hand with this, they have the greatest economic potential. Both countries represent approximately 60 per cent of the total life science market in Latin America, so it would be unfair not to start this chapter by dedicating a few words to these two players.

Brazil currently has a population of approximately 210 million, and is likely to represent a percentage close to 45 per cent of the total Latin American market, with a growing economy, particularly in the life science market. Many of the world’s leading stakeholders in the health sector have had a direct presence in Brazil for several years, and they measure the market signals with great rigour owing to their importance and complexity. However, getting a company in the life science sector to enter the Brazilian market and achieve a reasonable market share can take many years, depending on the commercial strategy chosen. On the other hand, as we will see later, the country is also very active regarding the enacting of new laws on life science, so acquiring an accurate understanding of the local reality is quite essential.

Mexico, the second-biggest country in the region, has a population close to 130 million and a market share in Latin America of approximately 15 per cent. Its operating costs are especially competitive compared with other markets and the inorganic growth (mergers and acquisitions) of its enterprises has played a predominant role in the past five years. The positioning, growth and expansion strategy for the different actors is probably different from that which might apply to the Brazilian market, but it also has material legal challenges to face.

Another particularly relevant country that deserves special treatment is Venezuela, which has a market share in Latin America of approximately 17 per cent, but also an especially complex economic and political reality in which many of the life science sector players have had to limit their investment and growth intentions. Following the same order of ideas, the legal challenges in the country are no less complex, and the institutions related to life science currently operate in a rather irregular manner. All these factors make Venezuela a highly important territory in terms of market size, but unfortunately it is also unattractive because of its current economic, political and social situation. The outlook is for a clear downward trend in the years to come as a result of the scarcity in the market and the lack of interest from investors in continuing their activities in the country. Hyperinflation in Venezuela rather distorts the macroeconomic figures and statistics on which we have based our assertions.

Argentina, with approximately 44 million inhabitants, shares a considerable 10 per cent of the total life science market in Latin America and, for the past few years, its economy seems to have been stabilising as a consequence of the change in the economic and political model. Therefore, the life science sector here also promises organic growth.

Life science markets in the rest of South America have also shown growth rates ranging from 1 per cent to 4 per cent per year, as is the case in Colombia, Ecuador, Peru, Chile, Bolivia and Uruguay. These smaller markets also have common business challenges, but radically different legal barriers.

Finally, there are the Central America and Caribbean markets, with a rather particular business model, where many international companies have an indirect presence and mostly operate through local distributors. These countries represent approximately 4 per cent of the total Latin American market. Nevertheless, it is an equally diverse and complex territory within the life science industry, where the realities of one market could be quite different to another.
III THE REGULATORY REGIME

As in other parts of the world, the regulatory regime in Latin America is increasingly rigorous, and the requirements from the local authorities differ from country to country. This aspect is material for the strategy of any company that intends to access the Latin American market.

The regional reference regulatory authorities for Latin America, qualified by the Pan American Health Organization (PAHO) and the World Health Organization (WHO), are the Colombian National Food and Medicine Surveillance Institute (INVIMA), the Brazilian Agency for National Health Surveillance (ANVISA), the Argentinean National Administration of Food, Drugs and Medical Technology (ANMAT), the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS), and the Cuban Centre for the State Control of Medicines, Medical Equipment and Devices (CECMED).

Some health authorities officially recognise marketing authorisations issued by health authorities of countries where medicine regulatory agencies have been certified as level IV by the PAHO, as well as those marketing authorisations issued by health authorities of certain countries, particularly the United States, Canada, Australia, Switzerland, Japan and the European Medicines Agency (EMA). However, special requirements may apply for biotechnological or biosimilar medicines and biological products.3

The participating members of the Central American Technical Regulation RTCA 11.03.59:114 are the Ministry of Health and Social Assistance of Guatemala, the Superior Council of Public Health and the Ministry of Public Health and Social Assistance of El Salvador, the Secretariat of Health of Honduras and the Ministry of Health of Costa Rica. The purpose of the RTCA is to establish the conditions and requirements for the marketing authorisation of medicines for human consumption. It applies to medicines manufactured or imported by natural or legal persons for commercialisation in the Central American territory (it does not include compounded medicines).

Even in Latin America there are some agreements for mutual recognition of marketing registration (e.g., between Panama and Mexico); nevertheless, in practice they are not fully honoured. Similarly, in Central America, a reciprocity agreement provides for acknowledgement in all the countries in the region of a product that has completed some of the stages of manufacturing (not necessarily the entire manufacturing process) and obtained the relevant marketing authorisation in one of those countries.

Based on the above, we consider that the optimum strategy for obtaining marketing authorisation in Latin America is to begin with the most complex countries (for instance, Venezuela, Ecuador, Brazil or Argentina, in South America; and Panama, the Dominican Republic, Guatemala or Honduras, in Central America). In the case of Brazil, for example, the first requirement is the qualification by ANVISA of the manufacturing plant of the relevant products, regardless of its location, which considerably lengthens the time required

3 For example, El Salvador: Decree No. 34, Special Regulation for the Acknowledgement of Foreign Sanitary Registries, published in the Official Gazette on 4 March 2013; Ecuador: Ministerial Agreement No. 586, Regulations for the Sanitary Registry of Medicines in General, published in the Official Gazette, Supplement 335 on 7 December 2010 (last amendment: 23 May 2016).
4 This document was approved by the Medicines and Similar Products Subgroup and the Standardization Subgroup as Central American Technical Regulation RTCA 11.03.59:11, Pharmaceutical Products, Medicines for Human Consumption. Requirements for Obtaining the Sanitary Registry. It was enforced through its ratification by the Council of Ministries for the Central American Economic Integration (COMIECO).
to complete the formalities. We also recommend studying those cases where any change in an existing marketing authorisation ultimately implies the processing of a new marketing authorisation (for example, Ecuador).

Regarding the renewal of marketing authorisations, some health authorities are particularly stringent. This is the case of INVIMA in Colombia, which is characterised by its special rigour and high standards. Hence, we suggest your strategy should also be term-based.

Among the many new developments in Latin American legislation on life science, the Regulation for Medicine Interchangeability in Peru, issued through Supreme Decree No. 024-2018-SA, will come into force in March 2019. It provides, among others, the acknowledgement of \emph{in vitro} and \emph{in vivo} therapeutic equivalency studies carried out and approved by institutions certified or authorised by the EMA, the US Food and Drug Administration, Health Canada, the Spanish Agency for Medicines and Health Products, the UK Medicines and Healthcare Products Regulatory Agency, the Swedish Medical Products Agency, the Swiss Agency for Therapeutic Products, ANVISA, WHO and bodies from other countries with high health vigilance standards. This Regulation is very relevant because countries such as Peru are accepting and taking over the work of international bodies, which is likely to become a trend in the coming years.

The increasing importance of biosimilar products during the past few years must also be mentioned. Biosimilar drugs are:

\ldots {\it products of biotechnological origin [that] are similar in structure, function, and clinical use as their \emph{reference} biological medicines. Biosimilars are a new step in biological drugs, they are very similar to the reference biological products and are obtained using new cellular sequences, so that they are similar, but not exactly identical to the reference products.}^{5}

For some time now, ANMAT, ANVISA and COFEPRIS have produced their own abbreviated regulations for these products, which are a combination of the biosimilar standards of WHO and the EMA, and their own political and economic requirements.\footnote{\textsuperscript{6}}

As evidence of this increasing importance of biosimilar products, it is sufficient to look at the number of marketing authorisations approved by the Latin American regulatory agencies, mostly in countries such as Mexico and Brazil, and in smaller markets such as the Central American countries, where the pharmaceutical industry has started to mark its territory. Nevertheless, along with the development of this market arises the need for a harmonious legislation, starting with elementary subjects such as nomenclature. The great challenge Latin America faces is to develop regulations fit for international application, as it has done in the case of intellectual property, for instance.


\footnote{\textsuperscript{6} GaBI Online – Generics and Biosimilars Initiative. Regulation on similar biotherapeutic products in Latin America (www.gabionline.net).}
IV  PRICING AND REIMBURSEMENT

i  Price control

The above-mentioned legislative diversity in Latin America applies equally to medicine price control in certain countries of the region, while in others such control does not exist, leading to significant differences in the cost of medicines from country to country.

Ecuador, Brazil, Argentina, Colombia and Venezuela have medicine price regulatory entities in place.

Ecuador

The General Regulations for Pricing of Medicines for Human Consumption were published in the Official Gazette on 1 June 2011. This regulatory framework aims to regulate the pricing procedures for medicines marketed within Ecuadorian territory.

The National Pricing Council for Medicine for Human Consumption is the entity in charge of fixing and reviewing medicine prices for sale and commercialisation throughout Ecuadorian territory. Medicine pricing is a fundamental requirement for medicine commercialisation throughout the national territory.

According to Article 19 of the aforementioned Regulations, the following criteria apply to pricing: (1) for companies requesting dealer pricing, including a 10 per cent mark-up for the dealer, the relevant auditing company should certify that the requesting company has deducted from its operating expenses the total amount delivered to the distributor whether in cash, in kind or in any other form whatsoever; and (2) for companies that do not request dealer pricing, a maximum 10 per cent will be accepted as part of operating expenses for bonuses and promotions regarding net sales income of the total amount submitted to the distributor, to cover the mark-up.

The commercial cost will be calculated on the actual costs and expenses incurred in the product, plus a percentage of operating expenses on the cost of sales for the last fiscal year, as duly audited.

Colombia

The Technical Secretariat of the National Pricing Commission for Medicines and Medical Devices, through the Integrated Medicine and Medical-Surgical Supply System (SISMED) is the regulatory entity for the control of certain medicines for human consumption in Colombia. Circular Letter 03 of 2013 establishes the methodology for the application of the direct price control regime for medicines traded in the territory. This methodology consists of four stages as detailed in the circular letter: (1) definition of the relevant market; (2) measurement of its concentration degree; (3) reference pricing; and (4) administrative fixing of the maximum sales price of medicines, if applicable.

On the basis of commercial integration, geographic proximity, similarity in the general economic intervention degree, membership of the Organisation for Economic Co-operation and Development, and information availability criteria, reference countries

7 Medicine price control in Ecuador has its legal basis on Executive Order/Decree 1290 for the creation of the Regulation, Control and Health Surveillance Agency (ARCSA), and the National Institute of Public Health Research (INSPI).

8 Medicine price control in Colombia has its legal basis mainly in Article 243 of Law 100 of 1993, Article 87 of Law 1438 of 2011, Decree 705 of 2016, and Circular Letter 03 of 2013.
for the Colombian authorities are Argentina, Brazil, Chile, Ecuador, Mexico, Panama, Peru, Uruguay, Spain, the United States, the United Kingdom, Australia, Canada, France, Norway, Germany and Portugal. The International Reference Price is calculated with consideration of the relevant information from all these countries, if available; otherwise, only those countries which information is available will be included in the calculation.

**Brazil**

The Executive Secretariat of the Medicine Market Regulation Chamber (CMED) is the inter-ministerial body in charge of regulating the medicine market and establishing the pricing criteria thereof. It works hand in hand with the Agency for National Health Surveillance (ANVISA). If a new product is acknowledged as having strong evidence of superiority over the standard therapy available, external reference prices should apply. If the CMED does not see any significant advantage compared with existing therapies, the new product will have a price comparable to the therapy. The group of countries taken as a source for price reference is made up of Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain, the United States and the country of origin. The price of the new medicine in Brazil will equal the lowest among the reference countries. The group will be changed in the near future, removing Greece and New Zealand and including a Latin American country. With regard to the above, here is a passage from the fifth edition of *The Life Sciences Law Review*:

*Given the complexities of the Brazilian healthcare system and considering that the government is the main purchaser of healthcare products and services, it is key that these be provided in an accessible and low-cost fashion. That being so, the government intervenes in the market by controlling prices and imposing mandatory discounts for medicines. Within this context, the ANVISA Drugs Chamber (CMED) is in charge of controlling the price for certain medicines in Brazil. After a given medicine is approved and registered by ANVISA, the marketing authorisation holder must obtain CMED’s approval for the respective price, before launch. The CMED-approved price is the maximum sales price in the private market. In any case, CMED also defines the final price for consumers and for the public market based on certain rules. Therefore, there is a price cap effective for suppliers and distributors in Brazil.*

In the case of Central America and the Caribbean, it is important to make particular note of the regulations of El Salvador, Honduras and the Dominican Republic.

**El Salvador**

Decree No. 1008 of 2 March 2012 contains the Medicines Law that defines the parameters to establish the mark-up. The maximum consumer price should be determined based on the International Reference Price establishing different mark-ups for innovative or generic medicines manufactured in or imported to the country.

The mark-up will be between three and five times the International Reference Price for each product according to the parameters of the WHO, but in no case should it exceed the average price of the Central American area and Panama, therefore becoming the maximum
consumer price. To establish the reference price, the National Medicines Direction will compare the prices of medicines offered by pharmaceutical chains of the same level in Central America and Panama. Generic medicine prices should be 30 to 40 per cent lower than the prices of innovative medicines. Authorized over-the-counter medicines are excluded from this regulation.

To determine the maximum consumer price of medicines, homogeneous groups are identified for price comparison with reference prices – the International Reference Price and the Average Price for Central America and Panama. The lowest of all will become the maximum consumer price. Medicine pricing is the responsibility of the Price Unit of the National Medicine Direction, and the enforcement thereof is the responsibility of the Inspection and Surveillance Unit, in coordination with the Consumer Protection Authority. Article 43(b) of the Consumer Protection Law qualifies selling goods or services at prices higher than those sanctioned by law as a serious offence, subject to a fine of up to 200 urban monthly basic minimum wages for the industry.

**Honduras**

Decree No. 65-91 of 28 May 1991 contains the Health Code for the Republic of Honduras. Its Article 134 (which was drafted in the terms of Decree No. 191-91, dated 11 December 1991, published in the Official Gazette No. 26659 of 3 February 1992) regulates medicine price control through the Secretariat of Economy and Commerce. It sets forth that the maximum percentage of gross profit in the sale or supply of pharmaceutical products will be determined based on the CIF price, in the case of products manufactured domestically. The aforementioned rule also indicates that the profit margin on the sale of generic products may be different from that established for the sale of commercial products under a trademark.

The gross profit on the sale or supply of pharmaceutical products by hospitals or private polyclinics to patients receiving medical treatment should not exceed 25 per cent of their cost; it is mandatory to issue a detailed invoice for the medicines for verification purposes.

Finally, although discounts to medicine prices are not regulated, they must adhere to the provisions of the Competition Defence and Free Promotion Law (Decree No. 357-2005).

**Dominican Republic**

Law No. 13 of 1963 states that medicines are essential items, and delegates their pricing to the Ministry of Public Health and Social Assistance (MISPAS). In practice, the regulations on this matter are not being enforced and, therefore, there is no updated or standardised price control. The only existing regulation that governs this aspect is the agreement executed in February 1972 by MISPAS, the Association of Representatives, Agents and Producers of Pharmaceutical Products, and the Association of Pharmacy Owners, which provides the following margins:

- **a** laboratory sales price (LSP): freely established by the producer;
- **b** distributor sales price (DSP): according to a domestic market survey, or the LSP plus 25 per cent if the distributor does not promote the drug, or the LSP plus 40 per cent if the distributor promotes the medicine, or the LSP plus 33.3 per cent when promotion costs are shared; and
- **c** retail price (RSP): DSP plus 30 per cent.
Advertising and promotion

As a general rule, public advertising of prescription pharmaceutical products is forbidden in virtually all the countries of Latin America, although enforcement is more rigorous in some countries than in others. In many cases, any promotional material for prescription medicines requires the approval of the regulatory authority. For this reason, before carrying out promotional activities for ethical products, the internal legislation for each country must be carefully reviewed to identify the requirements that the promotional material must meet. In general, these requirements are quite similar, and are contained and summarised in deontological codes such as the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Code, or ‘Business Principles for Promoting Integrity in the Pharmaceutical Sector in Latin America’, recently published by Transparency International.\(^{11}\)

As a general guideline, advertising of ethical products is acceptable if it meets the following criteria:

\(a\) phrases or words such as ‘wonderful’, ‘magical’, ‘infallible’, ‘insurmountable’, ‘the most effective’ that exaggerate the benefits of the products should not be included as they may imply unfair competition;

\(b\) the information contained in promotion and advertising materials must be based on verifiable scientific evidence, accurate, reliable and not abusive of the good faith and credulity of people;

\(c\) the advertising message cannot threaten a person’s dignity or violate ethical values;

\(d\) the advertising message must avoid any form of violence or discrimination;

\(e\) the promotion or advertising should not use expressions that may cause fear or anguish or suggest that health may be affected by not using the medication;

\(f\) advertising must contain accurate, balanced, honest information and it should be complete enough to allow the recipients the best choice for their clinical needs;

\(g\) advertising must be disclosed in Spanish, in clear and easily understandable terms for the target audience;

\(h\) statements or testimonials of users of the product that do not match the therapeutic indications approved in the registry thereof should not be included;

\(i\) the name and characteristics of the advertised medicine must be the same as those found in the actual product registry with the relevant authority;

\(j\) the advertising nature of the material and the name of the subject matter product should be evident;

\(k\) invitation to read carefully the instructions that appear in the indications of the medication should be express and clearly visible; and

\(l\) the advertising message should include the phrase, ‘Consult a pharmacist or a physician in case of any doubt’ or a similar expression.

In many countries, the direct or hired dissemination of misleading or false advertising is considered a serious offence, and is often regulated by both the health legislation and consumer protection laws.

V TRANSACTIONAL AND COMPETITION ISSUES

Latin America has not developed specific legislation on free competition exclusively focused on life science. Notwithstanding the above and considering that the subject of health is very sensitive, particularly from a political point of view, the legislation on free competition in countries where there is no price control becomes especially relevant and has gained prominence in the region during the past decade. For instance, in the famous Pharmacies case in Chile (2008–2012), in which the top three pharmacy chains in the country were charged by the National Economic Prosecutor’s Office with agreed increase or collusion to increase the price of 222 medicines, mostly for chronic diseases. The prices offered by the pharmacies exceeded those of the national supply office (Cenabast) by up to 3,000 per cent. In the end, two chains were sentenced by the Free Competition Defence Court to pay a fine for the maximum amount allowed by the law in force at that time (an amount close to US$19 million each), which constituted a major a milestone in Chile.

A similar case occurred in Peru in 2016, in which the National Institute for the Defence of Free Competition and Protection of Intellectual Property penalised in the first administrative instance five pharmacy chains for agreeing on prices for medicines and nutritional supplements. Additionally, the Commission for the Defence of Free Competition instructed the five chains, as a corrective measure, to implement a three-year programme that aimed to avoid the recurrence of antitrust behaviour. This conduct is categorised in Article 11.2 of the of the Anti-Trust Behaviour Law.

VI CURRENT DEVELOPMENTS

i Interaction with health professionals

Based on our experience, we can ascertain that the interaction with health professionals in the life science field is increasingly relevant not only for pharmaceutical laboratories, but also for the authorities of the region. In this sense, in recent years we have seen interesting legal reforms of which the main focus has been to ensure an ethical and transparent interaction between life science-related companies (especially pharmaceutical companies) and health professionals.

For example, the Colombian legislation has a considerable number of regulations related to interaction with health professionals, on which subject INVIMA plays a fundamental and active role. Additionally, Law 1438 of 2011 regulates physicians, health professionals and the healthcare industry. Article 106 prohibits pharmaceutical companies and other health-related entities from offering and providing any incentive or other rewards, either in cash or in kind, to any doctor or public or private health professional, or any employee or entity of the social security system, except when the delivery of such incentive or reward is provided under a contract executed by the health-related entity and the beneficiary. Fines may apply to companies or institutions that do not comply with these provisions.

12 Case File C 184-08: Requirement from FNE against Farmacias Ahumada SA and Others. Free Competition Defence Court. Filed on 9 December 2008 by the National Economic Prosecutor’s Office.
13 For further details on this case, see http://servicio.indecopi.gob.pe/buscadorResoluciones/getDoc?docID=workspace://SpacesStore/2b1b5306-38bd-469a-a612-8c73ac903e1c.
14 Law 1438, whereby the general social security system was reformed, including other provisions, was enacted on 19 January 2011.
In El Salvador, the pharmaceutical laboratories, drugstores and pharmacies are prohibited from granting or offering directly or through third parties, any gifts, commissions, bonuses, cash payments or any other type of royalties or incentives whatsoever, directly or indirectly to doctors, dentists, veterinarians, shop assistants, managers, employees of public and private institutions or owners of drugstores or pharmacies, in compensation for prescription, dispensation or retail sale of their products on a preferential basis.

In addition, the representatives of associations of pharmaceutical laboratories, pharmaceutical chemists, distributors of pharmaceutical products, laboratories, drugstores, pharmacies, law firms, the Central American Federation of Pharmaceutical Laboratories, the National Direction of Medicines, and the President of the Surveillance Board of the Pharmaceutical and Industrial Chemical Profession have executed the Self-Regulation Agreement for Ethical Practices in the Distribution and Dispensing of Medicines, whereby they undertook to avoid unethical practices regarding medicine advertising and promotion, committing not to directly or indirectly offer any type of incentive, discounts, bonuses, premiums or gifts made by those who have direct or indirect interest in the production, manufacture and marketing of medicines, to health professionals, with the purpose of promoting the prescription, dispensation and administration thereof. The signatory parties of the Agreement are committed to create corrective mechanisms to allow the rectification of any improper behaviour according to the provisions of the Medicines Law.

In this sense, public health professionals are also bound by the Government Ethics Law, which prohibits them from requesting or accepting, directly or through a third party, any goods or services of economic value or additional benefit to those received for the performance of their work. A public officer is prohibited from receiving benefits other than those he or she is entitled to receive by law, and must adopt the necessary measures to avoid any reasonable doubt about the legitimacy of his or her income and patrimony.

In line with the above, Article 228 of the Guatemalan Health Code establishes as infractions against health, among others:

8. Giving or offering economic or material benefits to the owners or shop assistants of medicine distribution or sale centres, in order to have them influence the consumer to replace the prescribed medicine.

9. Receiving economic or material benefits by the owners or shop assistants of medicine distribution or sale centres, in order to influence the consumer to replace the prescribed medicine.

With regard to the Dominican Republic, sections 13 and 69 of Article 268 of Decree 246-06 prohibit the direct or indirect offer of incentives, bonuses and gifts by those who have interests in the marketing of medicines to those involved in the prescription, dispensation or administration thereof.

15 Regarding El Salvador, we refer to the following regulatory bodies: Decree No. 1008, Medicines Law, Decree No. 245; General Regulation to the Medicines Law; Decree No. 776, Consumer Rights; Decree No. 417, Medicine Promotion and Marketing; Government Ethics Law and its Regulation.

16 Regarding Guatemala, we refer to the following regulatory bodies: Technical Regulation No. 39-2003, Medicine Marketing, Promotion and Information; Decree No. 90-97, Health Code; Decree No. 06-2003, Consumer Protection Law; Government Agreement No. 712-99, Regulation for the Sanitary Control of Medicines and Related Products; Regulation 53 of 2006, Advertising and Promotion of Related Products.

17 Regarding the Dominican Republic, we refer to the following regulatory bodies: Law 042 of 2001, General Health Law; Law 05 of 1988, medicines and controlled substances; Law No. 68 of 2003, creation of the
Although we have not identified a significant amount of legislation or express regulation on sponsorship to health professionals in Latin America, Argentina, through its Resolution 627/2007, allows pharmaceutical companies to sponsor health professionals to attend medical congresses and other scientific meetings in Argentina and abroad. However, in line with the above-mentioned IFPMA Code, many deontological codes prohibit companies from sponsoring offshore events, unless the venue is justified by security or logistics reasons (e.g., if most of the participants are foreigners). Hospitality in connection with sponsorship, including the payment of travel expenses, registration fees, accommodation and travel allowance, must be reasonable and limited to the days required to attend the event. Events must take place in places conducive to the scientific or educational objectives and the purpose of the event. Luxurious places should be avoided. The events should be focused on educational activities. Social and cultural activities should be limited to breakfasts, lunches, snacks or dinners. Entertainment or leisure activities, such as sporting events, should not be included.

VII CONCLUSIONS

The production of a brief review of the main issues regarding life sciences and the relevant regulations in Latin America is indeed a great challenge, as the continent is constantly evolving and its health authorities are increasingly prevailing. This is immediately apparent to anyone trying to obtain authorisation for marketing or promotional materials, facing pricing or market regulations, or interacting with healthcare professionals. The life sciences industry is highly regulated around the globe and new trends (e.g., compliance issues) are beginning to permeate this part of the world. A case in point is the regulatory evolution of biologics and biosimilar products, where international legislation should be applied rather than local or isolated constructs.

It is crucial for those who intend to enter the Latin American market to be able to discover and understand some of the key aspects developed in this chapter, which I expect to complement in future editions.

Dominican Medical Association; Law 340 of 2006, acquisition and contracting of goods and services and concessions; Decree 486 of 2012, creation of the General Direction of Government Ethics and Integrity; Decree 310 of 2005, Operating Regulations of the Ethics and Fight against Corruption Commission.
I INTRODUCTION

Malta has the second largest pharmaceutical trade balance per capita in the European Union (€614 million in 2016), the tenth in total, and was the EU’s fastest growing pharmaceutical exporter between 2001 and 2016 with an unprecedented increase of 45 per cent. More than 30 established international pharmaceutical brand names operate in Malta, including several US mega-cap corporations. In 2019, the Managing Director of Aurobindo Pharma (Malta) Limited, Frederick Schembri, announced the company will invest in oncology research and set up a highly specialised new oncology laboratory in Malta to test oncology medicines destined for the EU and African markets. Aurobindo Pharma, the tenth-largest generic company by sales globally, has been established in Malta for the past 13 years and now employs 150 people.

Companies must adhere to EU requirements in manufacturing, licensing and distribution of pharmaceuticals, active pharmaceutical ingredients and medical devices, and most companies also receive US Food and Drug Administration accreditation.

This chapter summarises the Maltese laws governing medicines and medical devices. Malta is the European Union’s smallest Member State and has implemented the EU medicines and medical devices regimes. We will therefore not repeat the substantive content of the EU chapter, but will only focus on unique, different, and significant features of the Maltese regime. This chapter should be read in conjunction with the EU chapter.

The principal regulatory authority to ensure the quality safety, and efficacy of medicines is the Superintendent of Public Health, which is the Licensing Authority for the purposes of the Medicines Act. The Medicines Authority is a body corporate having a separate and distinct legal personality and its functions are delegated to it by the Licensing Authority. It is responsible for assisting and advising the Licensing Authority on any matter relating to the regulation of medicinal products and related activities, as well as establishing licensing and marketing procedures.

The Medicines Authority is headed by a Chief Executive Officer who must be qualified and experienced in the medical, pharmaceutical or medical science sector and who is appointed...
by the Minister responsible for public health. The Chief Executive Officer is responsible for the overall management and performance of the Medicines Authority including the management of its day-to-day operations. The Medicines Authority has established five directorates and appoints its own officers and employees. The terms and conditions of employment are set by the Medicines Authority with the ‘concurrence’ of the Minister responsible for public health, given after consultation with the Minister responsible for finance.\(^5\) Since at least 2019, the Medicines Authority does not receive a government subsidy as its budget is funded exclusively from ‘user fees’ imposed on the industries it regulates, mainly the pharmaceutical industry. User fees may include registration fees for marketing authorisation applications, annual licensing fees for manufacturing and wholesale dealing facilities, and marketed medicinal products.

In Malta, to date, medical devices are regulated and authorised by the Malta Competition and Consumer Affairs Authority (MCCAA), although medical devices are planned to be regulated by the Licensing Authority and Medicines Authority instead in the future. This change is dependent on the passing of a bill and legal notice that are under way.

‘Medicinal products’ are defined and regulated by the Medicines Act (Chapter 458 of the Laws of Malta) and its subsidiary legislation. Medical devices are regulated by the Product Safety Act (Chapter 427 of the Laws of Malta), the Active Implantable Medical Devices Regulations (SL 427.10 of the Laws of Malta), the In Vitro Diagnostic Medical Devices Regulations (SL 427.16 of the Laws of Malta), and the Medical Devices Regulations (SL 427.44 of the Laws of Malta).

The Chamber of Commerce, Enterprise, and Industry based in Valletta represents the pharmaceutical industry in Malta through three sections, namely: the Healthcare Business Section, the Professional Community Lead Pharmacists Business Section, and the Pharmaceutical Manufacturers Business Section. The pharmaceutical manufacturers established their stakeholder group in 2003, before Malta’s EU accession, to lobby their interests during the transposition of EU legislation. The pharmaceutical industry has evolved considerably to date as Malta was able to leverage foreign investment, especially with English being an official language, and developed a strong reputation in manufacturing, batch-release to the EU market, day-one product launches, good engineering expertise, and favourable economic growth. The Chamber of Commerce members now include active pharmaceutical ingredient (API) manufacturers, finished dosage form manufacturers, repackaging and labelling companies, wholesale dealers, brokers, and pharmacists.

II THE REGULATORY REGIME

\(i\) Classification

The Medicines Authority’s Borderline Classification Committee distinguishes between medicinal and non-medicinal products.\(^6\) Assessments are made on a case-by-case basis. The Medicines Authority has issued borderline product classification guidelines and application forms. The guidelines explain the information and materials that must be provided for the

\(^5\) The Medicines Act (Chapter 458 of the Laws of Malta), Articles 4–8. Professor Anthony Serracino Inglott has served as Chief Executive Officer of the Medicines Authority since 2013.

\(^6\) The Medicines Authority Terms of Reference state that the Borderline Classification Committee is composed of the Licensing Director who chairs the group; a quorum of six members representing the Licensing Directorate, the Inspectorate and Enforcement Directorate and the Advertising Committee; a
classification to be undertaken, including dosage form, container type and packaging. The Borderline Classification Committee takes into account the medicinal claims made; intended use; mode of action; pharmacological properties; and similar authorised medicinal products that are on the market.

Medical devices are classified according to the degree of risk the patient is exposed to. Malta’s medical devices regulations establish standards to classify a medical device, centred on the level of invasiveness, mode of action, contact duration and impact on the patient. Active implantable devices are generally classified as high-risk medical devices, and the risk of in vitro diagnostic (IVD) medical devices is decided on the basis of use.

**ii Non-clinical studies**

The Good Laboratory Practice Regulations (S.L. 427.56) state that non-clinical studies must be carried out in conformity with the good laboratory practice (GLP) established by EC Directive 2004/10. The transposed regulations state that the inspection and verification of processes and conditions under which laboratory studies are planned, performed, recorded and reported for non-clinical testing shall be carried out in accordance with the rules and regulations, with respect to all chemicals (e.g., cosmetics, industrial chemicals, medicinal products, food additives, animal feed additives, pesticides) in order to assess the effect of such products on humans, animals and the environment.

The National Accreditation Body–Malta Standards Authority (NAB-MSA) is the competent authority responsible for verifying compliance with the principles of GLP of any testing laboratory in Malta claiming to use GLP.

The Animal Welfare Act (Chapter 439 of the Laws of Malta) establishes a Council for Animal Welfare comprising a chairperson and 11 members who advise the Minister responsible for veterinary services on all matters related to biotechnology in animals and animal experiments, and advise on the issuance of licences under the Animal Welfare Act. The Council, with the concurrence of the Minister, can also establish subcommittees for this purpose.

A licence issued by the Minister, acting on the advice of the Council, in conjunction with the Director for Veterinary Services is required to carry out animal experiments. The licence specifies the practice for which it is required and may include conditions and restrictions. Animal experiments must be authorised by the Council, may only be performed by competent authorised persons, or under the direct responsibility of such a person, and only if the experimental or other scientific project concerned is authorised in accordance with the provisions of the Animal Welfare Act to protect animal welfare.

---

7 The Medicines Authority has issued guidelines on what constitutes a medicinal product, which appears on the Authority’s website at http://www.medicinesauthority.gov.mt/classificationborderlineproducts.
8 Good Laboratory Practice Regulations (S.L. 427.56) Article 5.
9 Good Laboratory Practice Regulations (S.L. 427.56) Article 3.
10 Animal Welfare Act (Chapter 439 of the Laws of Malta) Article 32.
The Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations (S.L. 458.47) state that available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.\textsuperscript{11}

### Clinical trials

#### Medicines

**Legislation**

In Malta, clinical trials are governed by the Clinical Trials Regulations (S.L. 458.43), transposing European Directive 2001/20/EC regulating clinical trials on human subjects where such clinical trials involve medicinal products in interventional clinical trials. The Good Clinical Practice and Requirements Regulations (SL 458.47 of the Laws of Malta) supplement the Clinical Trials Regulations and outline good clinical practices to ensure the subject’s rights and safety. The Medicines Authority has issued guidance notes on good clinical practice, clinical trial applications and notifications, which were last updated in February 2018.

**Application and authorisation**

A clinical trial may be carried out if its benefits outweigh foreseeable risks. This is a decision that falls on the Ethics Committee set up by the Licensing Authority. A ‘sponsor’ – the person taking responsibility for the initiation, management and financing of the clinical trial – must be authorised on the basis of the Ethics Committee’s opinion. Approvals are granted for one trial at a time. Requests for clinical trial approval must be decided by the Licensing Authority no later than 60 days from the date of the request.

**Insurance policy**

Insurance or indemnity to cover the liability of the investigator and sponsor is a requisite to be able to carry out a clinical trial, and the adequateness of the insurance taken out is assessed by the Ethics Committee.

**Informed consent**

The Clinical Trial Regulations define ‘informed consent’ as a decision written in one of the official languages of Malta (English or Maltese) or in a language understandable to the clinical trial subject or his or her legal representative, dated and signed, to take part in a clinical trial, taken freely after being informed of its nature, significance, implications and risks, and documented by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative. If such person is unable to write, verbal consent may be given in the presence of at least one witness.

\textsuperscript{11} The Clinical Trial Regulations (S.L. 458.43) define an ‘investigational medicinal product’ to be ‘a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form’.
Medical devices

The Medical Devices Regulations require a mark of conformity (a ‘CE mark’) to market a medical device. A notified body must have carried out a conformity assessment procedure depending on the class of medical device. A technical file is submitted with documentation showing the medical device’s conformity with the regulations. As an EU Member State, the EU’s Clinical Trials Regulation (536/2014) will be directly applicable in Malta.

iv  Named-patient and compassionate use procedures

Unlicensed medicinal products

The Committee for Unlicensed Medicinal Products was established to permit the use of unlicensed medicines in Malta. The Pharmaceutical Unit within the Ministry for Health is responsible for the processing of individual requests for medicinal products by certified prescribers and for use in public and private hospitals.

The ‘Guidelines for the supply of medicinal products for human use through processes which are not covered by the Medicines Act, 2003 and its subsidiary legislation (unlicensed medicinal products)’ includes application forms. The supply and use of unlicensed medicinal products is restricted to circumstances where the licensed product cannot be obtained or the patient is not in a position to obtain the product directly from abroad for personal use under a doctor’s prescription (Annex 1 of the Guidelines).

‘Unlicensed products’ do not include products that are: undergoing clinical trials, approved for compassionate use under European Council Regulation 726/04; prepared in a pharmacy under prescription; prepared by division of authorised packs into smaller units in a pharmacy for dispensing to patients within the same pharmacy; reconstituted intravenous preparations and prepared in centralised intravenous additive services; or used outside the clinical indications of their marketing authorisation.

The request for the use of an unlicensed medicinal product must be submitted by a doctor or a dentist registered in Malta to the Superintendent of Public Health. The request must explain why a licensed product is not a suitable alternative and include a declaration that the prescriber takes direct personal responsibility for the use of the unlicensed product.

Requests on a named patient basis must include the patient’s signature confirming that he or she is aware that the medicinal product is unlicensed. The absence of the patient’s signature has to be justified.

Exceptional medicinal treatment

In March 2018, the Maltese legislature passed the Exceptional Medicinal Treatment (EMT) Committee Regulations (S.L.528.08). These regulations cater for medicinal treatment provided to patients suffering from diseases for which medicinal treatment is not listed on the Government Formulary List; or listed on the Government Formulary List but not according to protocol, indication or prescribed criteria; specifically branded medicines; or medicines for the treatment of rare diseases. The Exceptional Medicinal Treatment Committee (EMTC) assesses requests submitted to the Directorate for Pharmaceutical Affairs of the Health

12 Form I: request for the use of an unlicensed medicinal product on a named patient basis, for a specific patient (applies to both the government health services and the private sector); Form II: request for the use of an unlicensed medicinal product by a hospital department within the government health services; Form III: request for the use of an unlicensed medicinal product by a hospital or clinic in private practice.
Ministry by medical consultants by a prescribed application form. Department of Health Circular 15/2018 (DH 417/2018) comprises the policy addressed to healthcare professionals outlining the procedures, the EMT Request Form, the EMTC Terms of Reference, and the Schedule of Review Criteria.

v Pre-market clearance

Medicines

Medicinal products are approved and authorised for commercial distribution in Malta through the legal supply chain as follows:

a marketing authorisation according to Article 20 of the Medicines Act (Chapter 458 of the Laws of Malta) and Legal Notice 387 of 2004 as amended;
b marketing authorisation by centralised procedure (Regulation 726/2004);
c parallel import licence according to Legal Notice 437/2004;
e Licensing Authority approval of medicine to be put on the market in exceptional cases, subject to such conditions as the Licensing Authority may attach to it (Article 20(1) of the Medicines Act, 2003) on the ground of public health.

In the past seven years, the Licensing Directorate of the Medicines Authority processed 4,400 licensing applications that were granted a marketing authorisation in Malta. There are approximately 2,000 medicines in Malta licensed under the Article 126a procedure mentioned in (d) above. The Medicines Authority has set eligibility criteria for an Article 126a application, stating that ‘this procedure should in no way be considered as an easy way of circumventing the current procedures stipulated by the EU legislation’. However Malta, because of its small market size and availability challenges, has proven itself to be the biggest user of the Article 126a marketing authorisation. From around 5,400 national authorisations (inclusive of parallel importation licences), more than one-third have been licensed through the Article 126a procedure. A total of 572 new authorisations for medicinal products were issued in 2018; 372 of these authorisations were made under Article 126a. Malta is also a Reference Member State (RMS) or a rapporteur in European registration procedures. In 2018, Malta led 38 authorisation procedures, an increase of 12 procedures from 2017.13

A study published by senior authorised officers of the Medicines Authority identifying pharmaceutical issues encountered during regulatory review in European marketing authorisation application procedures found that applicants would benefit from following published guidelines to avoid delays in the registration of medicines.14

EU laws apply for the licensing of biologics, biosimilars and generic medicines, and the validity of marketing authorisations. In the case of homeopathic and herbal medicines,

the authorisation procedure is simplified and applications are received and reviewed by the Medicines Authority. The quality issues and regulatory challenges the pharmaceutical industry needs to consider when developing and producing biosimilars and in the submission of dossiers for marketing authorisations were studied and published by senior authorised officers of the Medicines Authority.  

**Medical devices**

The European Medical Device Regulation 2017/745 repealed the directives on medical devices: the European Medical Devices Directive 93/42 and the European Active Implantable Medical Device Directive 90/38. The Medical Device Regulation was published on 5 May 2017 and came into force on 25 May 2017. Approved medical devices have until 26 May 2020 to meet the new Medical Device Regulation requirements. At the time of writing, the Malta Competition and Consumer Affairs Authority Technical Regulations Division is responsible for the approval and authorisation of commercial distribution of medical devices.

**vi Regulatory incentives**

Malta applies European pharmaceutical law, including data and market exclusivity, orphan medicines and paediatric medicines. The EU and the US in particular have adopted regulations, incentives and policies targeted at improving orphan drug access to patients suffering from rare diseases. Malta has no additional national regulatory requirements beyond the EU requirements so as not to hinder the pharmaceutical industry.

**Data exclusivity**


**Generic medicines and Roche Bolar**

Malta is one of the few EU Member States that has a broad interpretation of the Roche Bolar provision, which has been incorporated in the Maltese Patents and Designs Act, and fully recognises the research exemption of the Patent Cooperation Treaty and European Patent Convention, by which generic companies can undertake development, but not commercialisation, of drugs prior to patent expiry.

---


16 In a University of Malta (Pharmacy Department, Faculty of Medicine and Surgery) study published as a research paper, out of 24 countries only 16 countries were found to have a national orphan drug (OD) or rare disease (RD) policy. Malta was found to have no national OD or RD plan, financial incentives or non-financial incentives. Malta’s pricing of OD is ‘free’ upon passing HTA through therapeutic programme scheme’. Abbas, Amar & Vella, Janis & Azzopardi, Lilian & Serracino-Inglott, Anthony (2019) Orphan drug policies in different countries. Journal of Pharmaceutical Health Services Research. 10.1111/jphs.12305.

17 The Patents and Designs Act (Chapter 417 of the Laws of Malta), Article 27.
Joint/multilingual labelling
The Medicines Authority recognises joint/multilingual labelling with other countries to be an incentive for retaining medicinal products on the Maltese market. The Medicines Authority has facilitated joint/multilingual labelling with the UK, Ireland and other markets, and continues to pursue collaboration opportunities with other European competent authorities for multilingual labelling.

Day zero mutual recognition procedure (simplified procedure)
To address medicines availability challenges in Malta, the Medicines Authority accepts the assessment of the RMS or the national competent authority (where the product had been authorised nationally), without any comments or questions. The approved product information will also be accepted without any comments. The Medicines Authority does not request any update of the assessment report or the dossier, nor are there any changes related to such procedure, except that in this simple way Malta joins a mutual recognition procedure (MRP). These procedures are finalised once the application has been accepted by the RMS and the Medicines Authority, known as an ‘MRP day zero procedure’. Day zero licensing procedures have already been executed successfully with various RMS countries.

vii Post-approval controls

Medicines
Pharmacovigilance
Pharmaceutical companies and regulatory authorities must honour their pharmacovigilance obligations according to EU law. The Medicines Act (Chapter 458 of the laws of Malta), and its subsidiary legislation namely the Pharmacovigilance Regulations S.L. 459.35, transpose the European Council Directive 2001/83 (as amended). The Medicines Authority has also published Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations and Adverse Drug Reaction (ADR) Reporting Requirements for Medicinal Products for Human Use (last amended in December 2019). There are no significant country-specific obligations provided for by Maltese law.

The Medicines Authority ensures patient safety by communicating with healthcare professionals, evaluating safety reports and conducting pharmacovigilance inspections to assess marketing authorisation holders’ (MAH) compliance with pharmacovigilance obligations. MAHs must comply with their pharmacovigilance obligations to maintain the marketing authorisation of a medicines product.\(^{18}\)

If there are concerns affecting the risk-benefit balance of an authorised medicinal product, the Medicines Authority may impose an obligation on a MAH to operate a risk management system and to submit a detailed description of the risk-management system that the MAH intends to introduce for the medicinal product concerned. The imposition of such obligations shall be duly justified, notified in writing and shall include the time frame for submission of the detailed description of the risk management system.\(^ {19}\)


\(^{19}\) The Pharmacovigilance Regulations, Article 8.
Staffing requirements for MAHs – the QPPV

MAHs in Malta must appoint a qualified person for pharmacovigilance (QPPV). The MAH shall submit the name and contact details of the QPPV to the Medicines Authority and the European Medicines Agency. The Medicines Authority may request the nomination of a contact person for pharmacovigilance issues in Malta (at national level) who reports to the QP responsible for pharmacovigilance activities.

Variations and transfer of ownership of product approvals

Post-authorisation procedures are handled by the Medicines Authority and include variations, notifications, renewals and withdrawals. Variations of marketing authorisations are governed by European Variation Regulation 1234/2008, amended by European Regulation 712/2012, which introduced work-sharing of different types of procedures, timelines, and takes into account the new European pharmacovigilance regulations. European Council Directive 2009/53 applies to variations submitted for nationally authorised medicines. The transfer of ownership of the marketing authorisation is made by filing the relevant request forms to the Medicines Authority depending on whether the marketing authorisation has already been issued or not.

Medical devices

The Medical Devices Regulations impose post-market surveillance obligations. Medical devices that compromise the health and safety of patients may be withdrawn from the market or prohibited or restricted by the Director of Market Surveillance after interim measures are taken. The Market Surveillance Directorate may carry out inspections, including the technical documentation and the CE conformity declaration. The Medical Devices Regulations specify that regulatory data must be uploaded to the European databank and made accessible to the national competent authorities.

viii Manufacturing controls

The main applicable legal instruments are the Manufacture and Importation of Medicinal Products for Human Use Regulations (S.L. 458.36); Good Manufacturing Practice in Respect of Medicinal and Investigational Medicinal Products for Human Use Regulations (S.L. 458.42); and the Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations (S.L. 458.47).

The manufacture of any dosage form of a medicinal product must be in conformity with the EU Good Manufacturing Practice (EU GMP) throughout the entire manufacturing process until the its release on the market. The applicant must hire qualified staff, particularly the qualified person (QP) responsible for manufacturing. The Medicines Authority Inspectorate and Enforcement Directorate carries out inspections to verify that the technical facilities and equipment is in place and that the manufacturing site fulfils all legal and EU GMP requirements.
The authorisation timeline is as follows: the application is vetted within 10 days of being submitted by the applicant; the assessment is then expected to take six months (unless further information or clarifications are needed); and the approval is issued within five days of conclusion of the assessment. The decision is then delivered within the following two days. The list of licensed manufacturers is published on the Medicines Authority website.\textsuperscript{20}

**Medical devices**

The production or manufacture of medical devices in Malta and the importation of medical devices into Malta are required to be in compliance with the Product Safety Act (Chapter 427 of the Laws of Malta) under penalty of law. Producers are obliged to only place safe medical devices on the market.\textsuperscript{21}

**Advertising and promotion**

**Medicines**

The advertising of medicinal products is governed by the Medicinal Products (Advertising) Regulations (S.L. 458.32), which transpose European Directive 2004/27 into Maltese law and regulate advertising to the general public and to healthcare professionals. The Medicines Authority has also issued guidelines, last updated in 2017. The system of medicines advertising is based on self-regulation as the Medicines Authority does not review advertising prior to its publication, but offers guidance and monitors advertisements. No advertising complaints were made to the Medicines Authority in 2018.

It is unlawful to advertise medicinal products that have not been granted marketing authorisation. The Licensing Authority may prohibit advertising of reimbursable medicinal products to the general public. The advertising to the general public of prescription-only medicines, and medicines that contain substances defined as psychotropic or narcotic under the First Schedule to the Dangerous Drugs Ordinance (Chapter 101 of the Laws of Malta) and the Third Schedule to the Medical and Kindred Professions Ordinance (Chapter 31 of the Laws of Malta), is forbidden.

Compliance orders issued by ‘qualified entities’ as defined by law, administrative penalties, and other administrative sanctions are made under the Medicines Products (Injunction to Advertising) Regulations (S.L. 458.51), which transpose European Directive 92/28 implementing it into Maltese law.

\textsuperscript{20} List of licensed pharmaceutical activities, Medicines Authority website http://www.medicinesauthority.gov.mt/licensed-pharmaceutical-activities.

\textsuperscript{21} Article 2 of the the Product Safety Act gives a wide definition of ‘producer’: ‘(a) the manufacturer of the product, when he is established in Malta, and any other person presenting himself as the manufacturer by affixing to the product his name, trade mark or other distinctive mark, or (b) the person who reconditions the product; or (c) the manufacturer’s representative, when the manufacturer is not established in Malta or, if there is no representative established in Malta, the importer of the product; or (d) others in the supply chain, in so far as their activities may affect the safety aspects of a product placed on the market’.
Medical devices
The Product Safety Act (Chapter 427 of the Laws of Malta) contains a definition of 'advertisement' and states that in the interest of public safety, the Director General (Technical Regulations) of the MCCAA may impose, by order in writing, conditions on product marketing, advertising, labelling and marking.

Other laws
The Broadcasting Act (Chapter 350 of the Laws of Malta) includes rules on the broadcasting of medicinal products advertising. The Commercial Code (Chapter 13 of the Laws of Malta) applies to all advertising in Malta.

Distributors and wholesalers

Medicines
The applicable legal instrument is the Wholesale Distribution and Brokering of Medicinal Products and Active Substances Regulations (S.L. 458.37). These Regulations also apply to homeopathic medicinal products. The Medicines Act (Chapter 458 of the Laws of Malta) defines 'wholesale distribution'. The Medicines Authority publishes a list of licensed wholesale dealers in Malta, last updated in December 2019.22

Application
The national competent authority (the Licensing Authority) shall grant the applicant a wholesale distribution licence (WDL) within 90 days of the date of receipt of the application provided the requirements listed in Article 8 of SL458.37 are met. This timeline is suspended if the applicant is asked to provide additional information. The application must also include the pharmaceutical forms of the medicinal products to be distributed, in particular whether they are sterile, require storage below 8º centigrade, details on whether they are narcotic or psychotropic substances, blood, immunological medicinal products or radiopharmaceuticals.

Responsible person
One of the requirements is that the applicant must engage a responsible person (RP). The RP is a registered pharmacist with the Malta Pharmacy Council and recognised as suitable by the national competent authority. The RP must be knowledgeable of proper conditions for the storage and distribution of medicinal products and have an understanding of good distribution practice (GDP) and must comply with the duties assigned to the RP as described

22 List of licensed pharmaceutical activities, Medicines Authority website http://www.medicinesauthority.gov.mt/licensed-pharmaceutical-activities.
in the Regulations. The RP can be a full-time employee, a part-time employee or work on a contract basis for the wholesale dealer. The Medicines Authority publishes a list of pharmacists accepted by the Medicines Authority to act as RPs.

**Marketing authorisation holder letter of access**

For each medicinal product distributed in Malta, the wholesale dealer must provide the Licensing Authority with an authenticated copy of the marketing authorisation together with a letter of access issued by the MAH granting the wholesale dealer the use of such marketing authorisation. The only exception is if the wholesale dealer is in possession of a valid parallel import licence.

**Patients’ needs and medicines supply obligations**

The Regulations also require every wholesale dealer, within the limits of their responsibilities, to ensure that ‘an appropriate and continuous supply of medicinal products is provided to pharmacies and persons authorised to supply medicinal products’ to satisfy patients’ needs.

**Good distribution practice**

The Licensing Authority requires full traceability of product quality throughout the entire supply chain and the wholesale dealer’s conformity with the EU Good Distribution Practice (EU GDP) standards. The Medicines Authority carries out EU GDP inspections. The licensed entity is given a list of findings after the Medicines Authority inspection, which they are required to respond to with proposals for corrective action within 28 days. Once all findings have been addressed with a satisfactory corrective action plan and measures, the renewal of the wholesale dealer’s licence is recommended to the Licensing Authority. Site re-inspection is performed at a frequency determined by the Medicines Authority by a systematic risk-based assessment.

**Medical devices**

The Product Safety Act (Chapter 427 of the Laws of Malta) regulates the wholesale dealing of medical devices. Wholesale dealers are obliged to cooperate in monitoring the safety of products on the market. Knowingly distributing unsafe medical devices is unlawful. The Director General (Technical Regulations) of the MCCAA may impose restrictions.

## Classification of products

### Medicines

The Borderline Classification Committee classifies borderline products into medicinal or non-medicinal products in line with the EU pharmaceutical law definition of medicinal product.

In Malta, medicines can only be dispensed to a patient from a licensed pharmacy. Medicinal products are either ‘prescription-only medicines (POM)’ (dispensed by a pharmacist to the patient under a physician’s prescription) or ‘over-the-counter products (OTC)’ (dispensed by a pharmacist to the patient without a prescription).

Classifying medicines as prescription-only or over-the-counter is part of the Marketing Authorisation process that licenses and ensures the quality, safety and efficacy of the...
medicinal product. The Medicines (Marketing Authorisation) Regulations (S.L. 458.34) specify the POM classification criteria. The Prescription and Dispensing Requirements Rules (S.L. 458.49) stipulate the content of the prescription and the dispensing regulations.

The Prescription Forms for Free Medicinals Rules (S.L. 458.24) govern the provision and prescription of medicinal products and medical aids to the patients at no cost to the end-user through the national health service (NHS) under the Social Security Act (Chapter 318 of the Laws of Malta).

**Medical devices**

Medical devices are classified in line with European law, on the basis of their risk to patients.

**Imports and exports**

Maltese legislation governing the import and export of medicinal products and medical devices generally reflects EU rules. Import regulations are enforced by the Customs Authority, and the Commissioner for Revenue also plays a part. Import tariff regulations are established by the Import Duties Act (Chapter 337 of the Laws of Malta). Product classification in Malta is made under the Harmonised Standard (the HS code number). The Dual-Use Items (Export Control) Regulations (S.L. 365.12) control dual-use export goods. European Council Regulation 428/2009, which governs the EU’s export control regime, applies to Malta.

**Medicines**

The main applicable legal instrument is the Manufacture and Importation of Medicinal Products for Human Use Regulations (S.L. 458.36). In Malta, an importer’s licence (IL) is required for the importation of medicinal products.23 ‘Imported medicinal products’ means medicinal products obtained from a source outside the European Union or the European Economic Area.24

All medicinal products for human use imported into Malta and the EU from a non-EU or non-EEA country, including medicinal products intended for export outside the EU and not intended for the Maltese market, are to be manufactured in accordance with the principles and guidelines of European Good Manufacturing Practice (EU GMP).25 It is the importer’s duty to ensure that medicinal products imported from third countries have been manufactured in accordance with standards equivalent to the EU GMP standards by authorised manufacturers.26

In Malta any licence holder (whether the holder of a manufacturing or importation licence, a wholesale dealing licence) must be a natural person or a legal person. ‘Licensee’ means any person who is the holder of a licence for a particular activity granted under the Medicines Act.27 Whichever entity within the EU or EEA first physically receives medicinal products entering the EU or EEA market from a non-EU or non-EEA country must be in possession of an IL.

---

23 S.L. 458.36, Article 3(3).
24 S.L. 458.36, Article 2.
25 ‘Good practice’ in relation to manufacturing practice, laboratory practice, distribution practice, clinical practice and dispensing practice means the standards for the proper execution of the relative activity as established by or under the Medicines Act, Chapter 458 of the Laws of Malta, Article 2.
26 S.L. 458.36, Article 7(5)(a)&(b).
27 The Medicines Act, Chapter 458 of the Laws of Malta, Article 2.
The IL is issued by the national competent authority following verification of the contents of the application, but no later than 90 days from the date of receipt of the application. This time period is suspended when additional information is requested from the applicant. The national competent authority may grant a conditional licence subject to the applicant’s fulfilment of the legal requirements. The IL shall only apply to the premises, medicinal products and pharmaceutical forms specified in the application.  

There must be a qualified person (QP) approved by the Maltese national competent authority for batch release, who ensures that each batch complies with the law, the GMP, the importer’s or manufacturer’s authorisation and the marketing authorisation.  

The Wholesale Distribution and Brokering of Medicinal Products and Active Substances Regulations (S.L. 458.37) state that wholesale distributors of active substances must comply with EU GDP, including active substances intended for export.

**Falsified medicines**

The Licensing Authority is responsible for taking the necessary measures to prevent medicinal products that are brought to the EU, but are not intended to be placed on the EU market, from entering into circulation if there are sufficient grounds to suspect that those products are falsified. These measures include applying the S.L. 458.37 regulations to warehouses in the free trade zones and customs bonded warehouses used to store medicinal products.

**Medical devices**

The import and export of medical devices is regulated by the Product Safety Act (Chapter 427 of the Laws of Malta).

**Controlled substances**


The importation, manufacture, exportation, purchasing and selling of any controlled drug is subject to the Drugs (Control) Regulations (S.L.31.18). These activities need to be authorised by the Superintendent of Public Health and registered and reported to the Superintendent at specified time frames. Importation and exportation procedures including details to be submitted and labelling requirements are at the Superintendent’s discretion. Dispensing of controlled must follow the applicable protocols.

According to the Medical and Kindred Professions Ordinance, the Health Minister, after consultation with the Council of Health, can amend, add to, revoke or substitute the list of psychotropic drugs. The Health Minister can also make regulations for controlling the manufacture, exportation, importation, possession, distribution and sale of psychotropic drugs, in the public interest.

---

28 S.L. 458.36, Article 5.
29 The qualifications for designation of a QP are outlined in S.L. 458.36 Articles 9 and 10. The QP’s responsibilities are listed in S.L. 458.36 Articles 11 and 12. The requirements of Directive 2001/83/EC as transposed into national legislation (the Medicines Act, Chapter 458 of the Laws of Malta, Article 38(1e) and S.L. 458.36, Article 9) must be fully complied with.
30 S.L.458.37, Article 12.
xiv Enforcement

The Licensing Authority has delegated its enforcement powers to the Medicines Authority. A dedicated Inspectorate and Enforcement Directorate within the Medicines Authority is tasked with enforcement and market surveillance. Article 101 and 101A of the Medicines Act (Chapter 458 of the Laws of Malta) establishes broad enforcement powers including right of entry, inspection, taking of samples, and seizure of goods and documents of any person duly authorised in writing by the national competent authority.

On production of his or her authorisation or credentials, such authorised person shall have a right to enter and carry out repeated and unannounced inspections at any premises (including any building, place or means of transport) at any reasonable time for the purposes of ascertaining whether there is, has been or is likely to be any breach of the provisions of the Medicines Act and its subsidiary legislation.

An authorised officer shall, on the production of his or her authorisation, have a right to board any ship or aircraft at any reasonable time to ensure that no substance or article is imported in contravention of the Medicines Act and its subsidiary legislation.

Offences and penalties

Article 99 of the Medicines Act establishes the penalties, in the form of fines and terms of imprisonment, in the event of conviction for failure to comply with any of the provisions of the Medicines Act or any regulations or rules made thereunder.

III PRICING AND REIMBURSEMENT

Malta has a unique ‘split’ medicines market, with two separate and distinct regimes:

i The National Health Service

Patients’ entitlement to medication on the public health market (national health services) outside a Maltese government hospital setting is based on the principle of social solidarity. Entitlement is assessed on the basis of disease or means by virtue of the Social Security Act (Chapter 318 of the Laws of Malta).

National health services are funded by taxpayers and managed by the Maltese government (responsible directorates within the Ministry of Health). Medicinal products listed in the government formulary are provided free of charge to eligible patients (end user). Under the entitlement programme, patients have no freedom of choice but are prescribed the medicinal products included in the government formulary.

Requests by medical practitioners (consultants) for medicinal products not included in the government formulary are made on a named-patient basis and may be accepted provided conditions are met and the medicinal product holds a valid marketing authorisation in an EU Member State.

32 According to the Medicines Authority 2018 Annual Report, in 2018 the Medicines Authority investigated four enforcement cases, coordinated by the Enforcement Committee (chaired by the Licensing Authority), and resulted in two court sittings concerning pharmacy issues, and two other court cases in which the Medicines Authority’s employees were summoned as witnesses.
Malta has transposed and implemented the EU transparency laws which apply to medicinal products procured via national health services (i.e., the national formulary). The applicable Maltese law is the Availability of Medicinal Products within the Government Health Services Regulations (S.L. 458.31).

ii The private market
This essentially services those areas of the healthcare sector that are not covered and supported by the Malta National Health Service. Medicinal products purchased on the private market (i.e., from a pharmacy at retail level) are an out-of-pocket cost to the patient or consumer and, in the case of prescription medicines, are prescribed by a doctor (prescriber) in private practice.

The Maltese private market enjoys a free-market pricing policy. There are no statutory price controls. Private market medicines prices (purchased by the consumer from a pharmacy at retail level) are not fixed by the government, but are determined by the licensed market players in the legal supply chain (pharmacy, wholesale dealer, manufacturer or MAH). A number of privately owned hospitals are licensed to operate in Malta.

The price of medicines at retail level are monitored by the MCCAA via a referencing mechanism aimed at benchmarking an average consumer price across 12 EU Member States and there have been negotiations between the Maltese government and the pharmaceutical industry that have led to price reductions of certain medicines.

iii Health technology assessment
In January 2018, the European Commission published a Proposal for a Regulation on Health Technology Assessment (HTA) amending Directive 2011/24/EU. The proposal establishes a Member State Coordination Group on HTA (Coordination Group) composed of representatives from national HTA authorities and bodies. The Coordination Group will be responsible for overseeing the joint clinical assessments. Joint clinical assessments (of medicinal products and medical devices) are limited to the most innovative technologies with the most potential EU-wide public health impact. A Maltese pharmaceutical expert, former Medicines Authority CEO Dr Patricia Vella Bonanno, spearheaded and significantly contributed to a paper that presents the consolidated views and considerations of policymakers, payors, pricing and reimbursement authorities, and academics on the original European Commission proposal.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES
The matter of legal interest is of paramount importance in litigation and judicial remedies. In Malta legal standing is apportioned based on legal interest (i.e., the test for being an interest party). Interest must be direct and personal, meaning that the right claimed or alleged should belong directly to the patrimony of a person. Interest has to be legal, meaning it must find a legal basis and be qualified as being based and founded on a legal principle or legal provision.

Interest must be actual, meaning that the party must demonstrate some actual benefit from the proceedings. This need not be economic benefit but it could be intangible such as reputation.

The Medicines Review Board hears appeals submitted by the applicant of a marketing authorisation on any recommendation of the Medicines Authority in relation to the safety, quality and efficacy of a medicinal product and to provide advice and make its recommendations to the Licensing Authority in this regard. An appeal may be filed with the Medicines Review Board within 14 days of receipt of a copy of the Medicines Authority’s recommendations and findings. The timelines and stages of the process are established by the Medicines Act. The Medicines Review Board appoints the matter for public hearing within 30 days of the day of filing the appeal or review request and shall decide the matter as expeditiously as possible.

It is possible to file a warrant of prohibitory injunction as an interim measure provided certain conditions are met. It is also possible to file other civil law proceedings on the basis of unlawful government action, for example under the Administrative Justice Act (Chapter 490 of the Laws of Malta), or the judicial review of administrative action under Article 469A of the Code of Organisation and Civil Procedure (Chapter 12 of the Laws of Malta).

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS


Gifts to HCPs must be inexpensive and related to the practice of medicine or pharmacy. Hosting HCPs is restricted to events organised around a scientific theme and the same invitation should not be extended to non-HCPs. The provision of free samples to medical prescribers needs to be documented and is conditional to a number of provisos, such as having to be in their smallest presentation on the market and prohibiting the prescriber from using the free samples in any commercial transactions.

According to the Ethics of the Medical Profession Regulations (S.L. 464.17), practitioners cannot publicly endorse any particular commercial product or service. Moreover, conducting commercial enterprise of medicines can result in erasure from professional registers. S.L. 464.17 stipulates that doctors ensure their professional independence and must not accept conditions that could jeopardise it.

The Pharmaceutical Research-Based Industry Malta Association (PRIMA) is a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and has established a national code applicable to all its members, based on the EFPIA HCP Code of Practice.

Anti-bribery and anti-corruption laws are governed by the Criminal Code (Chapter 9 of the Laws of Malta) and the Prevention of Money Laundering Act (Chapter 373 of the Laws of Malta).

34 S.L. 464.17, Paragraph 7(a).
36 S.L. 464.17 Paragraph 8.
VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The European Council Product Liability Directive was transposed into Maltese law by introducing the principle of strict liability to the Consumer Affairs Act (Chapter 378 of the Laws of Malta), enabling consumers to claim compensation when a product causes death, personal injury, loss, damage or destruction of any item of property. The producer is also able to raise defences under the provisions of the Act.37 Under Maltese law, liability may arise either in contract or in tort. Private actions for damages suffered as a result of a breach of competition law would usually be founded on tort. Tort is based on fault. The Maltese Civil Code (Chapter 16 of the Laws of Malta) states that every person shall be liable for the damage that occurs through his or her fault.38 A person shall be deemed to be at fault if in his or her own acts he or she does not use prudence, diligence, and attention of a bonus paterfamilias.39 Any person who, with or without intent to injure, voluntarily or through negligence, imprudence, or want of attention, is guilty of an act or omission constituting a breach of duty imposed by law, shall be liable for any resulting damage.40

VII  TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

The Competition Act (Chapter 379 of the Laws of Malta) governs competition law in Malta. As an EU Member State, Malta subscribes to the EU competition law regime. National antitrust or competition law litigation in Malta of special relevance to the life sciences sector in Malta is not commonplace.

ii  Transactional issues

Transactional issues in the pharmaceutical and medical device sectors, including mergers and acquisitions, joint ventures, and licensing and strategic collaborations, inevitably have a regulatory impact, especially in the transfer of marketing authorisations and meeting pharmacovigilance requirements. The complex interplay of provisions of Maltese codified legislation, including but not limited to the Product Safety Act, the Medicines Act, the Commercial Code, the Civil Code, the Companies Act, the Competition Act, the Data Protection Act, the Patents and Designs Act, the Trademarks Act and the Copyright Act, would feature prominently in any transaction.

38 Civil Code (Chapter 16 of the Laws of Malta), Section 1031.
39 Civil Code (Chapter 16 of the Laws of Malta), Section 1032.
40 Civil Code (Chapter 16 of the Laws of Malta), Section 1033.
VIII CURRENT DEVELOPMENTS

i Brexit
As a small island EU Member State, Malta has experienced medicines access and availability challenges in its national healthcare service.41 Malta’s national market is also expected to be affected by Brexit.42 The Medicines Authority has also seen a recent surge in applications to act as the RMS in medicines authorisation applications, partly due to the UK’s impending exit from the EU as Malta takes over as RMS in applications where it is the only EU CMS.

ii EU–US FDA mutual recognition of inspections of medicines manufacturers
On 1 November 2017, Malta became one of the first of eight EU Member States to begin mutual recognition of inspections of manufacturing sites for human medicines between the US and the EU.

iii Medical cannabis
The Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta) and its subsidiary legislation were enacted in 2018, legalising the production of cannabis for medicinal and research purposes. This initiative was led by the Medicines Authority’s Advanced Scientific Initiatives Directorate.43

Licensed medical practitioners are able to prescribe cannabis-based medicinal products with a valid marketing authorisation, and other cannabis products for medicinal use that are manufactured under EU GMP. The Medicines Authority reviews applications for the importation or wholesale distribution of such products. The first application was received in March 2018.

iv Medicines pricing – the Valletta Group
Headlined by the Deputy Prime Minister and Health Minister the Honourable Christopher Fearne, Malta hosted a Valletta Group meeting in July 2019 with a mandate to move forward on a collaborative framework for price-information sharing to undertake collective negotiations on regional prices for bulk purchases of medicinal products in Europe, with the ultimate objective of reducing prices. The Valletta group is named after the 2017 Valletta Declaration in which 10 EU countries, representing 160 million citizens, agreed to work together to leverage pharmaceutical industry negotiations.

42 The Medicines Authority has published a regulatory update regarding Brexit on its website: http://www.medicinesauthority.gov.mt/brexit?
Chapter 18

MEXICO

José Alberto Campos-Vargas

I INTRODUCTION

The Mexican Federal Constitution establishes health as a fundamental human right and provides the basis for the government to enact provisions related thereto. Article 73 of the Constitution grants the Mexican Congress authority to issue laws regarding health matters. Under this provision, the government has enacted diverse laws and regulations concerning medicines, pharmaceuticals, devices, food and beverages, dietary supplements, tobacco, vaping, cannabis and other goods and activities deemed to have an impact on human health.

The main law in this area is the Mexican General Health Law (the Health Law), which provides that certain products, including, inter alia, pharmaceuticals, narcotics, devices, food and beverages, dietary supplements, etc., and diverse processes related to these, are subject to sanitary control, this latter being comprehensive of manufacturing, packaging, handling, transportation, distribution, warehousing, etc.

The Health Law specifies that the authorities in charge of medicines, devices and most other regulated products are: the President of Mexico, the General Health Board, the Ministry of Health and state governments (on state jurisdictional matters).

The Ministry of Health has the broadest jurisdiction regarding these goods and activities. Moreover, the Health Law details the specific areas of competence for the diverse authorities in health matters, including the particular roles of the executive branch, the Health Board the state governments, etc.; other laws also establish particular competence for these authorities such as the Tobacco Law or the Federal Law on Metrology and Normalization.

In addition to Congress' authority to enact laws, the executive branch has the authority to issue regulations that clarify or specify the content of existing laws, without extending beyond or contravening the law being interpreted.

Among the most relevant regulations are the Health Law Regulations for Health-Related Goods (the Goods Regulations), the Health Law Regulations for Health Research (the Research Regulations) and the Regulations of the Health Law in Publicity Matters (the Publicity Regulations), etc.

Products and services imported, marketed or rendered in Mexico are also subject to Mexican official standards (NOMs). These are administrative guidelines that establish technical specifications, characteristics, processes, operation requirements, etc. in Mexican

1 José Alberto Campos-Vargas is a partner at Sánchez Devanny. The author would like to thank Juan Luis Serrano-Leets for his assistance with the chapter.

2 Through the Commission for the Protection Against Sanitary Risks (COFEPRIS).
territory. Before these are issued, the corresponding governmental entity, (e.g., COFEPRIS), prepares and issues draft guidelines that permit interested parties to participate in their creation or amendment.

Other provisions can be issued by the authorities as internal guidelines, decrees or accords, which may or may not be published in the Federal Official Gazette. Finally, although the Mexican legal system is not common law based, precedents regarding the nature of health provisions have been decided by the Mexican courts. Many of which focus on the interpretation of health as a constitutional and human right and its prevalence upon other such rights and vice versa.

II THE REGULATORY REGIME

In all cases, pharmaceuticals, devices and other products and services that have effects on human health are regulated at the federal level. These include, among others, research; food and beverages; human tissue and DNA; psychotropic and narcotics; toiletries and cosmetics; toxic substances; publicity; tobacco and alcoholic beverages; medical software and telemedicine; etc.

The Health Law and other provisions establish general licence, procedure and penalty requirements applicable to these goods and activities. Regulations, NOMs and guidelines establish additional or more specific requirements to each type of product and service.

i Classification

The Health Law, its regulations and other provisions provide specific definitions of medicines, medical devices and other products and services subject to sanitary control. In some cases, where specific legal provisions have not been enacted, it is quite common to have the competent authorities resort to provisions based on ‘similarities’ or broad general concepts within other provisions.

Medicines

The Health Law defines medicines as substances having therapeutic, preventive or rehabilitative effects identifiable on pharmacological, physical, chemical and biologic characteristics and classified based on diverse criteria as: allopathic; homeopathic; herbal remedies; prescription; controlled prescription; over the counter; vitamins; biotechnological; orphan drugs; traditional or indigenous medicines; etc.

In addition to the above, other regulated products include toxins, anti-toxins, vaccines, serums, parenteral preparations, blood products, microbial and fungal preparations, hormones, enzymes, etc.

Medical devices

The Health Law identifies six main types of medical devices (medical equipment; prostheses and functional aids; diagnostic agents; dental products; surgical material; and hygienic products), which are classified based on their risks, safety and efficiency into three classes: Class I: well-known in medical practice and not body-invasive; Class II: known in medical practice or body-invasive for periods shorter than 30 days; and Class III: new or recently accepted in medical practice or remaining in the body for periods greater than 30 days.

Certain NOMs and internal criteria include additional requirements for products that, although not formally medical devices under the Health Law or its Regulations, have
been included under its scope by the authorities, as possible new technologies (APPS and software), electric and electronic products used in ‘wellness’, holistic therapies and similar procedures, telemedicine services, etc.

ii Non-clinical studies
There is no specific restriction regarding the use of non-clinical studies. The party performing the non-clinical study is solely responsible for assuring good laboratory practices and that these studies do not represent a risk to human health. Under certain state legal provisions, including those regarding animal welfare, certain risks exist of interpretations that may lead to restrictions for these activities.

iii Clinical trials
In contrast with non-clinical trials, clinical trials are subject to extensive regulation. The Health Law, the Research Regulations and specific NOMs regulate clinical trials. These may involve research on prophylactic, diagnostic, therapeutic and rehabilitative resources; bio safety risks; DNA and biotechnology; and radiation.

Clinical trials are classified based on the risk they may pose to the test subjects and are divided into non-risk research; minimum-risk research; and greater-than-minimum-risk research.

Research involving human beings requires authorisation prior to its commencement. The performing parties must provide the authorities with information regarding the scope and purpose of the research, the main investigator, approval of the institution’s committees and informed consent of the subjects.

In principle, clinical research should only be carried out at health institutions under the direction of a principal investigator who is a health professional, member of such institution and the latter guarantees possible damages arising therefrom, medical treatment required and potential indemnification to subjects.

In the case of sponsorship or other forms of remuneration, measures to prevent conflicts of interest for protecting test subjects, preservation of results and assignment of resources should be implemented.

Certain legal concepts associated with clinical trials, such as CRT agreements and sponsorship and activities, are not regulated by Mexican law; however, in practice the authorities have issued internal criteria, compliance with which is required to obtain the authorisations, and included some references in NOMs or other administrative criteria.

Currently, it has become a fairly common activity for legal entities or individuals to carry out data and information collection of a medical or investigative nature thorough new technologies (apps, software and similar means) that are not specifically regulated as information considered as a clinical trial subject to permits and authorisations.

iv Named-patient and compassionate use procedures
Only one exception exits for using a product before it has received marketing authorisation (MA). This is in the case of clinical trials that may save a patient’s life or health, or eliminate pain, provided the patient has supplied written consent.

Notwithstanding, the Mexican courts have issued recent criteria establishing that irrespective of the restriction to import and use regulated products subject to MA, the health authorities must permit their use considering the greater relevance of the human right for life in relation to the general health protection and exclusivity of cleared products.
One these is the ‘Grace case’, which resulted in specific amendments to the provisions included in the Health Law regarding psychotropic substances derived from cannabis and their use in pharmaceuticals.

**Pre-market clearance**

Currently only medicines and medical devices require registration with COFEPRIS, the same that is granted based on available information regarding their safety among which is: technical and scientific data; therapeutic efficacy and safety; use and prescription; labelling; certificates from country of manufacturing; etc.

If the product is considered safe, the registration is issued and the products can be manufactured, imported and marketed in Mexico. As an alternative to the general registration process, this information can be pre-reviewed by a private authorised entity, and a fast-track registration may be granted. This kind of registration is also available for products holding MA in jurisdictions with which mutual recognition agreements have been executed.

Both Mexican and foreign laboratories that manufacture pharmaceutical products may obtain MA. For medical devices, it is not necessary to have manufacturing premises in Mexico or abroad to obtain MA, however the requesting party must be registered with COFEPRIS and provide the required documents.

**Regulatory incentives**

*Patent term extensions*

Mexico does not provide patent term extensions or grant delays. However, as a signatory of the Unites States–Mexico–Canada Agreement (USMCA), expected to be ratified and become mandatory at some point in 2020, it shall enhance intellectual property protection for pharmaceutical products, since under such agreement, the member parties must ‘make available an adjustment of the patent term to compensate the patent owner for unreasonable curtailment of the effective patent term as a result of the marketing approval process’.

*Link between regulatory approval processes and patent expiry*

The Regulations for the Industrial Property Law and the Goods Regulations establish a linkage mechanism to observe patent rights. This has been subject to a considerable number of litigation actions since its enactment.

The Mexican Patent Office (IMPI) issues a Gazette containing patents in force covering:

- Active ingredients (including polymorphs);
- Formulations;
- Biologics; and
- Some use patents.

Published patents do not have a correlation with approved products (patents can be published even if the corresponding product is still at a clinical trial stage, or the approval has been refused.

Upon receiving an MA application for a generic drug or biosimilar, COFEPRIS will formally request from the IMPI an opinion regarding whether the requested MA infringes patent rights. The applicant is informed of the IMPI’s opinion, without the involvement of the patent holder.
The Goods Regulations also establish a Bolar-type three-year exemption to apply for MAs associated to patents close to expiry.

**Data and marketing exclusivity**

Data and marketing exclusivity for pharmaceutical products is an obligation under NAFTA, which has only been regulated through an internal guideline from COFEPRIS, that includes a five-year period of data exclusivity.

**vii Post-approval controls**

Holders of MAs must maintain the conditions upon which such were granted while these are in force. Changes thereto may result in cancellation. Changes to the background upon which an MA was issued must be filed for approval. The health authorities may verify that premises where processes are carried out meet the necessary GMPs or sanitary conditions.

In the specific case of pharmaceutical vigilance, in addition to the general procedures set out by the Health Law, those of the applicable NOM must also be satisfied.

**viii Manufacturing controls**

Medicines, devices, food and beverages, tobacco and other regulated product’s manufacturing is subject to sanitary control and includes requirements regarding premises where related ‘processes’ are carried out. In some cases, laboratories or other kinds of premises may be authorised to process products subject to this requirement through the issuance of a sanitary licence. The Health Law establishes different types of premises that may be authorised to operate in Mexico, including factories or laboratories of medicines, homeopathic or herbal remedies or biological products for human use, etc.

Premises where pharmaceutical products are manufactured must as a general rule evidence ‘good sanitary practices’; have quality control laboratories; appoint specific individuals with the health authorities as representatives of the entity; provide, as required, information regarding products, services, processes and, as the case may be, specific administrative controls (e.g., narcotics and psychotropic).

Compliance with these requirements can be verified through inspections following the filing of an application or through an alternative verification process called an operation requirements compliance certification. Once approved, the Health Authority will issue the corresponding licence.

Additionally, these premises must meet specific operational and manufacturing requirements set out in certain NOMs depending on the kind of products to be manufactured, including, inter alia, materials handling procedures; lot controls and production; testing; raw materials and finished-product inventory control systems; SOPs for production controls; manufacturing processes’ validation; compliance with NOMs certifications; samples and documents preservation; labelling compliance; etc.

**ix Advertising and promotion**

The Publicity Regulations define the term ‘publicity’ as any activity that includes all creation, planning, playing and broadcasting processes of advertisements in communication media with the purpose of promoting the sale or consumption of products or services.

The Health Law differentiates between publicity intended for health professionals and for the public, the former being that regarding the characteristics and use of medicines,
medical devices and medical or scientific information used for publicity or promotional purposes restricted to specialised media and based on the content of the products’ MA and the latter intended for the public at large, which requires specific permits and is only applicable to OTC medicines and herbal remedies.

Promotional materials regarding pharmaceutical products and medical devices in Mexico are not subject to authorisation, provided these do not include information other than the names of the products and the entity manufacturing or distributing them or both. Likewise, activities carried out involving health professionals are generally not subject to restriction, because it is possible to organise or sponsor congresses, sessions, courses, etc. regarding products, and to provide sample products, gifts, hospitality and entertainment.

x Distributors and wholesalers
Distribution and wholesale of pharmaceutical products and devices are ‘processes’ subject to sanitary control by the Mexican health authorities and subject to restrictions and conditions depending on the specific type of sanitary licence.

The Health Law and applicable regulations establish different premises subject to sanitary control and specific requirements for each. Generally, premises for the wholesale and distribution of pharmaceutical products and medical devices is subject to compliance with specific requirements for warehousing, transportation and control.

xi Classification of products
The Health Law and corresponding regulations set the rules and conditions for classifying pharmaceutical products, medical devices and other regulated products and services. This classification determines the conditions for marketing goods and specific permits and authorisations for related processes. The specific criterion for products classification may be determined by the health authorities.

xii Imports and exports
The Health Law identifies importation and exportation of goods as a ‘process’ subject to sanitary control and general requirements. Specific requirements apply based on the product and its tariff classification.

For products imported into Mexico, the general requirements include registration of the importer of record with the General Importer’s Registry, the appointment of a customs broker or in-house broker, and registration with the Specific Sectors Importer’s Registry for clearance through specific customs houses.

Goods importation triggers general import duties at the rate for tariff classification number and value of goods. Most products exportation is exempt from export duties. Likewise, importation of goods triggers value added tax. For finished pharmaceutical products this is zero per cent or exempted. Medical devices are subject to the 16 per cent general rate under the Value Added Tax Law.

Non-tariff requirements are also applicable. For medicines and pharmaceuticals, these are generally subject to the issuance of an import or export permit by COFEPRIS. Medical devices are generally only subject to presentation to the customs authorities of the corresponding MA.
Other products subject to controls may include those bound for wellness purposes, certain kinds of food and beverage and other apparently unrelated items which may represent a health risk.

xiii Controlled substances

Controlled substances include all psychotropic and narcotic substances. The list of such goods is included in specific chapters of the Health Law, which establishes the general requirements applicable to these goods and their classification based on their use and effects.

Under the Health Law, psychotropic substances are divided into those:

a with minimum therapeutic value by virtue of their possible unlawful use and that constitute a particularly serious public health problem;
b with therapeutic value but that constitute a serious public health problem;
c with therapeutic value but that constitute a public health problem;
d with considerable therapeutic value that constitute a minor public health problem; and
e with no therapeutic value and that are generally used for industrial purposes.

Processes involving these substances and those considered as raw materials for manufacturing illegal drugs are subject to specific controls, set forth in the Federal Law for the Control of Chemical Raw Materials, Essential Chemical Products and Machinery for Tablet and Pill Manufacturing and its regulations. This also provides specific regulations regarding production, sale, acquisition, importation, exportation, transportation, warehousing and distribution of certain chemical products, and apparatus for the manufacture of tablets and pills, specific permits and control and reporting requirements.

In 2017, diverse amendments to the Health Law were published, including amendments establishing the possibility to obtain MA for pharmaceutical products deriving from cannabis. These amendments derive from the mentioned ‘Grace case’ and provide the possibility to import and marked in Mexico pharmaceutical products containing derivatives of this plant. Likewise, the amendments established the possibility to manufacture and market other industrial products derived from cannabis with certain maximum permissible amounts of THC.

xiv Enforcement

The Mexican health authorities may verify at any time the due compliance of applicable provisions of process involving these goods and services. COFEPRIS is generally in charge of these verification procedures, which must meet requirements in the Health Law and the Federal Law on Administrative Proceedings. These procedures must always be served in writing and the scope and purpose of the verification must be established clearly. Once such procedure notice is served, the authorities may initiate the review and verification of documents, premises and processes.

The verification procedures in health matters must meet the general guidelines and requirements for these types of matters included in the Constitution, Health Law and Federal Law on Administrative Proceedings.

All reviews and actions carried out by health authorities in these processes must be included in minutes and finalised with a written resolution in which the findings or potential
infractions committed are set out. The determination of the commission of an infraction must always set out the factual background and legal basis upon which it is considered as such, and may be challenged through the applicable legal remedies.

III PRICING AND REIMBURSEMENT

Pricing and reimbursement can be broadly divided into two sectors: the private sector and the public sector.

i Private sector

In sales to the private sector, there is an agreement between the National Pharmaceutical Chamber and the Ministry of Economy, called the ‘PROMIF’, which establishes a way to determine maximum sales prices for new drugs, taking into account reference to prices for new drug products in other countries. Reference pricing is not applicable to generic products or biosimilars.

ii Public sector

In Mexico the government is a direct provider of health services, through different institutions, including the Social Security Institute (IMSS); the Institute of Security and Social Services for State Workers (ISSSTE), which provides services for federal government employees; the Ministry of Defence (SEDENA); the National Oil Company (PEMEX); and the state health bodies.

The new administration has incorporated an Institute of Health for Well-Being (INSABI), which replaces the former Popular Insurance System (Seguro Popular), and is intended to provide health coverage for individuals not covered by other public health systems.

Medicines and devices used in these institutions are directly purchased by the Mexican government through a combination of public tenders and direct acquisition proceedings. Acquisition of products is based on the list included in the National Health Products Compendium, and inclusion in this compendium is based on analysis of pharmaco-economic considerations by the health authorities.

The Health Law includes some specific restrictions regarding the maximum prices for medicines offered for sale to the public at large, it being necessary to include these maximum prices in the labelling. As mentioned above, most medicine sales to governmental health providers are subject to specific bidding procedures under the Law on Acquisitions, Leases and Services of the Public Federal Administration; however, some exceptions to this general rule are applicable. Similarly, the Mexican social security system relies on the direct rendering of health-related services by the competent governmental agencies; no reimbursement procedures exist for goods directly acquired by the population covered by the public healthcare system.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Administrative infringements may be determined independently of possible criminal offences arising from acts or omissions set forth by the corresponding legal provisions. The applicable legal remedy depends mainly on the type of fine or penalty applied to a legal entity
or individual, as well as the reasons for such determination. In general, the penalties for failure to comply with obligations set out by the corresponding legal provisions can be fines, seizures, foreclosure of premises, destructions of goods, etc.

Various legal remedies exist for challenging decisions or determinations regarding possible infringements of health-related provisions. These are administrative appeal and the administrative litigious procedure.

i Administrative appeal
Under the Health Law, acts by the health authorities may be challenged through an administrative appeal. This should be attached with the power of attorney of the legal representative; challenged resolution; facts, legal arguments and evidence.

The administrative appeal may confirm, cancel, amend the resolution in specific terms, or order issuance of a new resolution. The resolution of the administrative appeal may be further challenged through the administrative litigious procedure before the Federal Administrative Justice Court.

ii Administrative litigious procedure
Alternatively, resolutions may be challenged through an administrative litigious procedure (nullity petition) before the Administrative Justice Court, based on the Federal Law on Litigious Administrative Procedures.

This nullity petition must be filed before the Administrative Justice Court during the 30 business days following the formal serving date.

The nullity petition may confirm the resolution, declare it null and void, declare partial nullity, or declare nullity for a specific purpose.

Unfavourable or partially favourable resolutions to a nullity petition may be challenged through a direct *amparo* or constitutional remedy before the Federal Court of Appeals. In specific cases, the resolution issued by an administrative authority may also be directly challenged through filing an *amparo* when the resolution implies the direct violation of constitutional principles.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS
Mexican law provides no specific rules regarding financial relationships between pharmaceutical and medical device companies with prescribers and payors, except in some very limited cases involving public health service officials. In the case of acquisitions by government agencies, the Federal Law on Public Servants is applicable in connection with the prohibition to provide any kind of gift to an individual who holds public office when the gift is directly related to his or her activities.

Based on the foregoing provision, it is not possible to provide prescribers or payors with any kind of financial benefit, gift or hospitality if they act as public servants. In the case of private practitioners these restrictions are not applicable. This restriction creates a considerable number of practical issues because many health professionals may hold governmental positions and maintain private practice.

Under the new administration, greater controls and provisions regarding corruption and control of benefits and hospitality have been formally and practically enacted. This has resulted in a more complex regulatory environment when dealing with the supply and sale of pharmaceutical, devices and other goods to the federal and local governments.
In addition, the National Pharmaceutical Chamber (CANIFARMA) and the Mexican Association of Innovative industries of Medical Devices (AMID) are both part of the National Council for Ethics and Transparency for the Pharmaceutical Industry (CETIFARMA). CETIFARMA has issued codes of ethics that follow international guidelines for interactions with prescribers and physicians.

In addition to the above, a considerable number of new provisions and guidelines regarding administrative controls in this connection have been enacted by the new administration. Likewise, new provisions interacting with the existing ones have been enacted and several regulations and interpretations are still awaiting enactment.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Under Mexican law, there is no specific procedure or system for the compensation of possible injuries or damages arising from use of medicines or medical devices. Individuals who are affected or damaged by a medicine or medical device may file a lawsuit (ordinary civil procedure) to request the compensation of damages. Under Mexican law, only direct damages may be requested, if a direct relationship between the product and the damage can be duly evidenced.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The Law of Economic Competition (the Competition Law) does not include specific provisions regarding medical devices and pharmaceutical products in Mexico. These product types are subject to the general provisions of the Competition Law. Owing to the nature of the pharmaceutical and medical devices business in Mexico, however, these industries tend to be severely scrutinised by the competition authorities, especially in the case of sale to governmental agencies.

In the case of medicines, the National Competition Authority (COFECE) has taken two major actions:

a a broad-scale investigation on possible collusion activities associated with manufacturing, production, distribution and sale of products, which led to formal sanctioning proceedings announced in 2019; and

b a study on competition conditions associated with patent expiry, published in 2017.

ii Transactional issues

Under Mexican law, no specific provisions or regulations pertain to transactional issues regarding legal entities engaged in the pharmaceutical or medical devices business. In practice, however, various issues may be encountered in the event of mergers, acquisitions, spin-offs and sales of assets in connection with these industries. Thus, the transfer of MA, licences and authorisations by virtue of the aforementioned transactions may take considerable time to be finalised. Likewise, any change to the manufacturing processes or the grounds on which an MA was issued must be duly reported to the health authorities and, in some cases, may be considered a ‘change’ or amendment to the conditions upon which a such authorisation was granted.
The foregoing may imply delays in transactions involving these types of products and may represent a challenge for legal entities carrying out these transactions to avoid the total or partial impossibility of carrying out the importation, manufacturing or marketing of pharmaceutical products or medical devices post-transaction.

VIII CURRENT DEVELOPMENTS

Mexico is the second-largest medicine market in Latin America after Brazil, and one of the most developed, with high regulatory standards and a well-developed life sciences industry. With the change of government after the 2018 election, several public policy changes have been enacted that considerably affect the life sciences sector. These include a change in government procurement rules, banning distributors from participating in the largest centralised tender proceedings to acquire medicines and devices, and amendments to rules regarding national treatment for entities from countries with which Mexico has entered into free trade agreements, etc.

These amendments have forced life sciences companies to participate in a more active manner in these kinds of proceedings as well as to evaluate with greater care their participation in business with the Mexican public sector. Among these matters we can mention an investigation ordered by the Mexican President of the three major drug distributors in the country that has generated concern in the industry.

Another change was the replacement of the Seguro Popular with the National Institute for Health and Well-Being. In addition, it has been established that there is a necessity to create a National Drug Formulary for a National Health Compendium, which is expected to have a broader scope than the current one.

The new administration has taken very specific positions in connection with life sciences industries and health-related matters, the most relevant being those regarding the following topics:

i Cannabis
Currently there is a law awaiting finalisation by Congress. This will, in essence, regulate the recreational use of cannabis and the decriminalisation of its use; however, the industrial and pharmaceutical use and processes have not yet been addressed or properly included in this proposal.

ii Software as a medical device
Software as a medical device has just been included as a regulated concept. Unfortunately, its proposed regulation lacks the necessary formal procedures and is in general a mere reference contemplated in a NOM whose enforcement and legality is debatable.

iii Vaping
One of the most controversial subjects currently being addressed by the health authorities is vaping.

The restriction and control of vaping is a global trend. Because of Mexico’s legal structure, vaping is not contemplated within the products regulated by the applicable provisions; however, the health authorities have considered a national health emergency in this regard and thus have attempted to restrict the importation, sale and use of these products.
These restrictions, owing to their nature and characteristics, have been challenged by diverse entities and individuals engaged in this industry having obtained favourable results from the competent courts.

Another relevant matter during the new administration is rules and provisions regarding food and beverage labelling. During the last quarter of 2019, Congress amended the Health Law and added diverse articles specifically related to food and beverage products’ labelling. The main purpose of these amendments is to provide, in the clearest manner possible, information to the consumer as to the actual caloric content of products and possible elements of risk for their health such as salt, sugars, fats, caffeine, etc.

iv Dietary supplements
The importation and marketing of dietary supplements was less restricted during the past administration; however, the current administration has given special attention to their importation and marketing requirements. It is very likely this new attention to these products derives from the obesity emergency in the country and the publicity strategies of some entities engaged in the sale of these kinds of products.

v Wellness
Wellness is a concept that has been progressively increasing its presence in diverse jurisdictions. Mexico is no exception and a very noticeable increase in the marketing of these kinds of products has taken place during the past couple years.

Many of these ‘wellness’ products fall within the grey line of a ‘medical’ device, since many times these allege that their use may help improve certain medical conditions or bodily functions or that their use may improve an individual’s general health and are, in the end, machines or apparatuses that are in contact with the human body.

The health authorities have increased their review and enforcement of these kinds of goods; however, due to their nature and marketing strategies, on many occasions it is difficult to enforce the applicable provisions and when enforced these may go beyond the actual scope of the applicable provisions.

Finally, it is worth noting that many of the health-related authorities are being restructured by the current administration, thus practical issues in the day-to-day relationship with these are a definitive trend, which it is hoped will diminish once these restructures are implemented.
Chapter 19

PAKISTAN

Arlin Merchant¹

I  INTRODUCTION

The Drugs Act, 1976 (the 1976 Act) is the underlying legislation for the import, export, manufacture, distribution and sales of drugs in Pakistan. The Drugs Regulatory Authority of Pakistan Act, 2012 (the 2012 Act) was subsequently passed for the effective coordination and enforcement of the 1976 Act and for the endorsement and systematic implementation of international treaty obligations, including with respect to ‘therapeutic goods’.² The 2012 Act is the controlling statute, operating as unified law across all provincial boundaries.³

The 2012 Act established the Drug Regulatory Authority of Pakistan (DRAP), which comprises the Policy Board,⁴ the Central Licensing Board (CLB), the Registration Board (RB) and the Provincial Quality Control Board. DRAP is recognised as the national competent authority for medicines and medical devices.

II  THE REGULATORY REGIME

Following the 18th amendment to the Constitution of Pakistan 1973, drugs and medicines do not fall within the ambit of federal legislation. However pursuant to Article 144 of the Constitution, Parliament may legislate on provincial matters by invitation and to the extent so conferred. The provincial governments may therefore amend or repeal any law in respect of competences that are exclusive to the provinces, or otherwise curtail or withdraw the invitation.

Each of the provincial assemblies has validly conferred the power to legislate in respect of drugs and medicines to Parliament, which promulgated the 2012 Act.

¹ Arlin Merchant is an associate at Kabraji & Talibuddin.
² This term is defined in Section 2 of the 2012 Act to include drugs, alternative medicine, medical devices and biologicals and such related products as may be notified by DRAP.
³ Messrs Azfar Laboratories Private Limited through Directors and others versus Federation of Pakistan through Secretary Ministry of National Health Services and 4 others (PLD 2018 Sindh 448).
⁴ The general direction, administration and monitoring of DRAP vests with the Policy Board; Section 9 of the 2012 Act.
i Classification
The term ‘drug’ is defined widely to include:

- any substance or mixture of substances that is manufactured, sold, stored, offered for sale or represented for internal or external use in the treatment, mitigation, prevention or diagnosis of disease, an abnormal physical state, or the symptoms thereof in human beings or animals;
- abortive and contraceptive substances, agents and devices, surgical ligatures, sutures, bandages, absorbent cotton, disinfectants, bacteriophages, adhesive plasters, gelatin capsules and antiseptic solutions;
- substances intended to be used for the destruction or repulsion of such vermin, insects, rodents and other organism as cause, carry or transmit disease in human beings or animals or for disinfection in residential areas or in premises in which food is manufactured, prepared or kept or stored; and
- any substance mentioned as a monograph or as a preparation in the Pakistan Pharmacopoeia, the Pakistan National Formulary, the International Pharmacopoeia, the British Pharmacopoeia, the British Pharmaceutical Codex, the United States Pharmacopoeia or the National Formulary of the United States, whether alone or in combination with any substance exclusively used in the Unani, Ayurvedic, homoeopathic or biochemic system of treatment, and intended to be used for the above purposes (a) to (c).

Medical devices include: instruments, medical equipment, implants, disposables and software, used mainly for the purpose of diagnosis, monitoring and treatment of disease. The 2012 Act also extends in scope to biologicals, as well as to health and over-the-counter non-prescription products such as probiotics and disinfectants, nutritional products, food supplements, baby milk and foods, medicated cosmetics, medicated soaps and medicated shampoos. A determination as to whether a product falls within the scope of the applicable legislation is factual and based on the purported health related purpose thereof and whether it is presented in pharmaceutical dosage forms.

The Medical Devices Rules, 2017 (the MDR Rules) govern the manufacture, import and sale of medical devices. The Alternative Medicines and Health Products (Enlistment) Rules, 2014 (the Alternative Medicines Rules) govern the licensing and registration of alternative medicines (such as Chinese, Unani, Ayurvedic and homeopathic) and health and over-the-counter non-prescription products. All other drugs are registered and licensed in accordance with the Drugs (Licensing, Registering & Advertising) Rules, 1976 (the Licensing Rules).

ii Non-clinical studies
The Drugs (Research) Rules, 1978 (the Research Rules) govern the research, development and evaluation of drugs. Any research in drugs is required to be conducted at such places and by such persons as are approved by the federal government and are categorised as: (1) clinical trials; and (2) other than clinical trials.
The Division of Quality Assurance and Laboratory Testing of DRAP is responsible for the enforcement of good manufacturing practices and for the testing and research of drugs, with an aim to implement guidelines respectively of the World Health Organization (WHO), International Conference on Harmonization and the Food and Drug Administration.

Any research on aspects other than clinical trials are to be conducted under the supervision of a person who possesses postgraduate qualifications and experience in the relevant field and has sufficient background to conduct scientific investigation. Progress regarding the investigation is to be submitted to the federal government at regular intervals, not exceeding six months. Further, experts authorised by the federal government must be allowed to visit the premises where the research is being conducted.

iii Clinical trials

The Bio-Study Rules, 2017 (the Bio-Study Rules) regulate the safety, quality, efficacy, handling and use of investigational products in clinical trials. A clinical trial requires a licence for the trial site and the clinical studies. An approval must also be sought from the National Bio Ethics Committee of Pakistan Health Research Council (NBC-HRC). Additionally, the institutional review board or the institutional review committee of public or private health institutions is responsible for ethical clearance and periodic review of the clinical trial being carried out at the institution, as well as for submission of reports to the committee formed under the Bio-Study Rules.

Conditions for a clinical trial include:

a each investigational product or trial material must be labelled as ‘caution: for investigational use only’ and ‘not for sale’;

b quarterly reports of results obtained and the final results from the clinical trials are required to be furnished to the clinical studies committee; and

c a database of subjects recruited or enrolled for the study or trial must be maintained.

In addition to the requirements set out for non-clinical studies (above), research during clinical trials is to be conducted in stages as follows: stage 1 – on human beings to determine the single and short-term multiple dosing for tolerance, side effects, toxicity, metabolism, preferred routes of administration, safe dosage range and other pharmacological actions of the drug; stage 2 – to determine the safety and effectiveness, including the effective dose range, the common side effects of the drug on both clinical and laboratory parameters and, where possible, the level of the drug in biological fluids in relation to therapeutic response; provided that these studies shall be undertaken if studies in stage 1 of the investigation demonstrate satisfactory results, and shall involve initial and limited use of the drug in the treatment or prevention of the disease for which the drug is intended, which shall be administered to carefully supervised patients; and stage 3 – to be conducted under controlled conditions in order to expand knowledge of potential use and hazards and shall be undertaken if the data obtained in the above stages provides reasonable assurance of safety and effectiveness, or

---

8 Rule 6 of the Research Rules.
9 Rules 3 and 7 of the Bio-Study Rules, respectively.
10 Conduct of Clinical Trials Guidelines.
11 Rules 8 and 10 of the Bio-Study Rules.
12 Rule 8(3) of the Bio-Study Rules.
13 Rule 8(18) of the Bio-Study Rules.
suggests that the drug may have a potential value of conducting several trials outweighing its hazards; provided that these studies shall be carefully monitored and all possible precautions shall be taken to prevent unnecessary exposure of the patient to the risk.\textsuperscript{14}

Studies on children shall not be undertaken unless there is a possibility of benefit to them and adequate studies of safety and efficacy are available in adults.

Small quantities of medical devices, components or raw materials for the purpose of clinical investigation may be imported and an application for such import is required to be made.\textsuperscript{15} A clinical investigation using a medical device cannot be carried out unless the appropriate label has been provided.\textsuperscript{16} Labels must be in English, but some labels for devices intended for use at home may be in Urdu.

**iv ** **Named-patient and compassionate use procedures**

A licence for import, manufacture and/or sale of drugs does not apply to drugs for personal use.\textsuperscript{17} Further, anti-cancer drugs, cardiac drugs and any essential life-saving drugs imported for use in hospitals and institutions are not required to be registered under the 1976 Act provided, inter alia, that such drugs:

\begin{itemize}
  \item[a] have the prior approval of the CLB;
  \item[b] are not sold or distributed in the market;
  \item[c] are on free sale in the country of origin, except for life-saving vaccines and anti-sera for human use only, where pre-qualification by the WHO or approval of any regulatory authorities as defined by the RB is provided; and
  \item[d] are used for therapeutic purpose in hospitals or institutions only and not for clinical trials, examination, test or analysis.\textsuperscript{18}
\end{itemize}

Small quantities of medical devices may be imported for the use of hospital patients, including those that are not enlisted or registered with DRAP, subject to conditions, including:

\begin{itemize}
  \item[a] the medical device shall form part of a passenger’s bona fide baggage and shall be intended for exclusive personal use;
  \item[b] the quantity shall be restricted to meet personal requirements only; and
  \item[c] any medical device whose import is prohibited on account of lack of enlistment or registration may be imported for hospital use subject to prior approval from the Medical Device Board of DRAP (MDB) and upon compliance with conditions imposed by it.\textsuperscript{19}
\end{itemize}

**v ** **Pre-market clearance**

Where there is an unmet need for unregistered drugs, an application may be made to DRAP for: (1) consideration of such drugs on a priority level; and (2) conditional registration or marketing authorisation.\textsuperscript{20}

\textsuperscript{14} Rule 7 of the Research Rules.
\textsuperscript{15} Rule 22 of the MDR Rules.
\textsuperscript{16} Rules 38 and 42 of the MDR Rules.
\textsuperscript{17} Section 23(2) of the 1976 Act.
\textsuperscript{18} SRO 142(I)/2018 from the Ministry of National Health Services, Regulations and Coordination dated 7 February 2018.
\textsuperscript{19} Rule 24 of the MDR Rules.
\textsuperscript{20} Drug Regulatory Authority, Priority Review and Accelerated Approval of Registration/Market Authorization, 1st Ed.
The following criteria must be met for expediting the assessment of a drug:

a. benefit-risk balance of the product is positive;
b. unmet medical needs will be followed;
c. the benefit to the public health of the drug product’s immediate availability on the market outweighs the risk; and
d. it is likely that the applicant will be able to provide comprehensive data.

To be eligible for a priority review, the drug must be:

a. for the treatment of rare diseases;
b. a new drug molecule or new indication drug;
c. short in availability; and
d. for a severe condition (e.g., outbreak of a disease).

Drugs that are not registered may apply for conditional marketing authorisation if: (1) the drug is aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases; and (2) required in a public health emergency.

vi Regulatory incentives

An invention is patentable if it is new, involves an inventive step and is capable of industrial application. Invention, as defined in the Patents Ordinance, 2000 (the 2002 Ordinance), includes any new and useful product, including chemical products and any substance, article, apparatus, and machine. The rights holder can derive exclusive benefits and exclude others from making, selling, stocking, using, etc., their invention for 20 years. During this period, the rights holder can use their invention or, if they so desire, license it to others.

vii Post-approval controls

Section 6 of the 1976 Act provides that the provincial governments shall regulate the sale of drugs and may, for this purpose, make orders and issue directions to importers, manufacturers, stockists, retailers and other dealers of drugs.

Under the MDR Rules, a manufacturer must establish, maintain and implement a post-market surveillance system. The conditions of an establishment licence include that the manufacturer establish an independent quality control department and maintain separate staff, premises and adequate laboratory equipment for carrying out tests of safety, quality and performance of the medical device being or to be used in the manufacture. Additionally, the manufacturer shall, on demand from the MDB, direct that every batch, or specific batches, of medical devices specify a sample for examination and if required, furnish full protocols of the tests applied. Furthermore, a manufacturer is required to comply with all applicable good manufacturing practices, good distribution practices and good storage practices.

The Alternative Medicines Rules provide that each enlistment holder (manufacturer or importer) is responsible for and liable for the quality, safety and efficacy of the authorised
enlisted product, and is responsible for following the principles of good manufacturing practices. Additionally, manufacturing, quality control, sale and distribution records are to be maintained for one year after the expiry of the finished product.26

viii Manufacturing controls

A licence from the Health Department of the relevant provincial government is required to manufacture drugs in Pakistan.27 The manufacture of drugs is regulated under the Licensing Rules. Rule 3 of the Licensing Rules sets out the different types of licences to manufacture, which are: (1) basic manufacture;28 (2) semi-basic manufacture;29 (3) formulation;30 (4) repacking;31 and (5) for experimental purposes. Specific conditions are set out in detail in the Licensing Rules.

Rules 26 and 28 of the Licensing Rules provide the mechanism for registration of a drug. If drugs are manufactured on more than one set of premises, a separate application shall be made and a separate licence shall be issued in respect of each.32 Any licence granted under the Licensing Rules is valid for a period of five years, unless suspended or cancelled earlier, and may be renewed for another period of five years.33

An application for registration shall be made to the Secretary of the RB. The Licensing Rules set out certain conditions that must be met for a registered drug, including:

\[\text{a} \] the import, manufacture and sale of drugs shall be in accordance with the information contained in the applications in respect of those drugs or in any supplementary information or, where such information was amended by the RB, in accordance with such amended information (provided deviations may only be made after obtaining prior approval of the RB);

\[\text{b} \] the indications, contra-indications, side effects, the dosage and cautions, if any, as have been approved for the purpose of registration of a drug, are clearly specified in the labelling and promotion;

26 Rule 8 of the Alternative Medicines Rules.
27 Rule 14 of the Licensing Rules.
28 Basic manufacture is defined in the Licensing Rules as the ‘manufacture of a drug from basic raw material to a product which is ready for use as a starting material for the formulation of a finished drug or for repacking and such manufacture may involve chemical, bio-chemical, photochemical, microbial or such other processes or a combination of any of such processes’.
29 The term ‘semi-basic manufacture’ means the ‘manufacture from an intermediate substance of a drug to be used as a starting material for the formulation of a finished drug or to be used for repacking’.
30 The Licensing Rules define ‘formulation’ as the ‘all operations involved in converting a drug into a final pharmaceutical dosage form ready for usage as a finished drug including compounding, processing, formulating, filling, packing, finishing, labelling and other like processes’.
31 Repacking, in the Licensing Rules, means ‘all operations involved in the transfer of a drug from a larger container or packing into smaller containers or packings including filling, packing and labelling with a view to make it ready for retail sale or wholesale, but does not include any compounding, or processing with a view to formulate it in any dosage form.’
32 Rule 4 of the Licensing Rules.
33 Rule 6 of the Licensing Rules; the application for renewal is made within 60 days of the expiry of the initial licence.
every drug is produced in sufficient quantity so as to ensure its regular and adequate supply in the market; and

manufacture of a drug may not be discontinued without prior approval of the RB.\textsuperscript{34}

A licence to manufacture medical devices must be procured from the MDB.\textsuperscript{35} Any licence issued by the MDB shall be subject to conditions, including:

- manufacturing to be conducted under the active directions and personal supervision of competent technical staff consisting of at least one person, being the production in-charge, who shall be a full-time employee and who has a degree in either pharmacy or bio-engineering and at least four years of experience in manufacturing medical devices or pharmaceuticals; and

- establishment of a quality control department and to maintain separate staff, premises and adequate laboratory equipment for carrying out tests of the safety, quality and performance of the medical device being, or to be used in the manufacture.

With respect to alternative medicine, an application is required to be made to DRAP for enlistment.\textsuperscript{36} The following are eligible to apply for enlistment: (1) manufacturers with manufacturing and quality control facilities; (2) ‘givers’ of manufacturing contracts (if applicable); (3) importers authorised by the overseas principal manufacturer; and (4) manufacturers with existing manufacturing licences.\textsuperscript{37}

Baby milk and foods, nutritional products and probiotics shall be manufactured and tested in accordance with internationally recognised standards, codes of practice, guidelines and recommendations of the Codex Alimentarius.\textsuperscript{38} A warranty is required to be issued by the enlistment holder or authorised agent stating that the products do not contravene the 2012 Act.\textsuperscript{39}

ix Advertising and promotion

No person may advertise any drug, any substance used or prepared for use in accordance with the Ayurvedic, Unani, homeopathic, or bio-chemic system of treatment (or any other substance or mixture of substances as may be prescribed), or any remedy or treatment, or offer a treatment for any disease, without prior permission.\textsuperscript{40} The term ‘advertise’ means to make any representation by any means whatsoever for the purpose of promoting (whether directly or indirectly) the sale or disposal of a drug, a substance or a mixture of substance, a remedy or a treatment.

Rule 31 of the Licensing Rules provides that the federal government may, after seeking advice of the Committee on Advertising, allow the advertisement of a drug, any substance or remedy, and may approve the contents of such advertisement subject to certain conditions. An advertisement cannot contain any direct or indirect comparison in any way with any other

\begin{itemize}
  \item \textsuperscript{34} Rule 30 of the Licensing Rules.
  \item \textsuperscript{35} Rule 3 of the MDR Rules.
  \item \textsuperscript{36} Rule 3 of the Alternative Medicines Rules; an application is addressed to the Director of Division of Health and OTC Products (non-drugs).
  \item \textsuperscript{37} Rule 3(2) of the Alternative Medicines Rules.
  \item \textsuperscript{38} Rule 10(2) of the Alternative Medicines Rules.
  \item \textsuperscript{39} Rule 10(3) of the Alternative Medicines Rules.
  \item \textsuperscript{40} Section 24 of the 1976 Act.
\end{itemize}
drug, substance or remedy for any disease, for the purpose of attracting customers or with a view to discrediting another product. 41 Further, no advertisement, sampling or promotional activity in respect of drugs shall exceed 5 per cent of the turnover of the manufacturer. 42

Lastly, a retailer’s discount is capped at 15 per cent of the maximum retail price. 43

An application to the MDB is required to be made before advertising a medical device to the general public. 44 The MDB may permit the advertisement of a medical device, approve the contents of the same and specify conditions subject to which such advertisement may be made, including that no direct or indirect comparison can be made with any other medical device for the purpose of attracting customers or with a view to discrediting the other product. The advertisement shall include information or any risks or other precautions as may be necessary for the protection of public health, as well as the maximum retail price. 45 No approval from the MDB is required if a medical device is advertised to the medical, pharmaceutical and allied professions, through medical representatives or through professional journals and publications that are meant for circulation exclusively among the members of these professions; provided, however, that a copy of such journal or publication shall be sent to the Division of Medical Devices and Medicated Cosmetics.

The Alternative Medicines Rules provide that no person may issue or cause to be issued any advertisement without obtaining permission for the content of the advertisement material. 46

x Distributors and wholesalers

In Pakistan, drug manufacturing companies do not generally sell medications directly to retail outlets. They instead appoint distributors and wholesalers to supply drugs to the retailers from where drugs are dispensed to the patient. Pursuant to Section 23 of the 1976 Act, no person can sell any drug without a licence or without a warranty in the prescribed form, bearing the name and batch number of the drug issued. Further, a drug cannot be distributed as a sample except in accordance with any conditions as may be prescribed by DRAP. 47

A medical device cannot also be placed in the market unless it has been appropriately labelled. 48

With respect to alternative medicines and health products, enlistment holders may authorise distributors as authorised agents for the supply and sale of finished alternative medicine and health products and such distributors are required to issue a statement, on behalf of the enlistment holder, that the products do not contravene the 2012 Act. 49

41 Rule 31(6) of the Licensing Rules.
42 Rule 33 of the Licensing Rules.
43 Rule 35 of the Licensing Rules.
44 Rules 64 and 65 of the MDR Rules.
45 Rule 66 of the MDR Rules.
46 Rule 11 of the Alternative Medicines Rules.
47 Section 25 of the 1976 Act.
48 Rule 38 of the MDR Rules.
49 Rule 10(5) of the Alternative Medicines Rules.
xi Classification of products

Based on the Essential Medicines List of the WHO, the National Essential Medicines List of Pakistan provides a core list of the minimum needs of a basic healthcare system. The medicines are classified based on symbols, which indicate:

- **a** clinical performance within a class of pharmaceuticals;
- **b** any age or weight restrictions;
- **c** medicines that require specialist diagnostic or monitoring facilities;
- **d** individual medicine or strength of medicine to be restricted when used for children; and
- **e** medicine recommended for use at primary, secondary and tertiary level.\(^{50}\)

The Drugs (Labelling and Packing) Rules, 1986 set out separate requirements for the labelling of products, which depend on the intended consumer.

Classification and grouping of medical devices has been harmonised with international guidelines of the WHO, the International Medical Devices Regulators Forum and the Asian Harmonization Working Party.\(^{51}\)

xii Imports and exports

A licence from DRAP is required by a manufacturer to export, import or manufacture for sale, or sell any drug.\(^{52}\)

The Drugs (Import and Export) Rules, 1976 (the Import and Export Rules) provide the mechanism for obtaining licences for the import and export of finished drugs. Licences are also issued for a period of two years, unless suspended or cancelled earlier, for the import and export of: drugs other than finished drugs; and for small quantities of drugs for the purpose of clinical trial, examination, tests or analysis.\(^{53}\)

A medical device may be imported subject to the condition that the importer:

1. shall possess a valid medical device establishment licence and medical device enlistment or registration; and
2. have premises for proper storage to preserve its properties.\(^{54}\)

General conditions (except where such import is for personal or hospital use), include:

1. to supply a copy of the test report of the medical device or component or raw material from the manufacturer; and
2. provide an undertaking that the quality and safety of the medical devices, components or raw materials and their genuineness is in accordance with the MDR Rules.\(^{55}\)

---

52 Section 23 of the 1976 Act.
53 Rules 8 and 21 of the Import Export Rules.
54 Rule 21 of the MDR Rules.
55 Rule 25 of the MDR Rules.
Medical devices cannot be exported without the approval of the MDB. A permit to export medical devices, unless suspended or cancelled earlier, shall be valid for three years. A permit for the export of medical devices is subject to certain conditions, including that:

a. the permit holder shall furnish to the MDB (if so demanded) from every batch or lot, as may be directed, samples in such quantity as the authority may consider adequate for any examination, test or analysis to be made and the permit holder shall, if so required, furnish full protocols of such tests as may have been applied; and

b. the permit holder shall, on being informed by the MDB that any part of any batch or lot of a medical device has been found not to conform to the required specifications and on being directed so to do, withdraw the remainder of that batch or lot from export.

xiii Controlled substances

The Control of Narcotic Substances Act, 1997 (the Narcotics Act) regulates controlled substances, narcotics and psychotropics in Pakistan. Controlled substances are defined as any substance that may be used for the production or manufacture of narcotic drugs or psychotropic substance. A ‘narcotic drug’ includes all manufactured drugs. A comprehensive list of ‘psychotropic substance[s]’ is included in the Narcotics Act.

The possession, manufacture, extract, preparation or any offer for sale, purchase, distribution or delivery of a narcotic drug, psychotropic substance or a controlled substance is prohibited unless it is for medical, scientific or industrial purposes. Additionally, the import, export, transport or transhipment thereof is prohibited, unless in accordance with special rules framed by the government of Pakistan in this regard.

Pursuant to the 2012 Act, the Controlled Drugs Division of DRAP, in consultation with the federal government, is responsible for regulating and allocating quotas for narcotic drugs, psychotropic substances and precursor chemicals and to perform other functions connected therewith.

xiv Enforcement

The federal government or a provincial government may, by notification in the Official Gazette of Pakistan (the Gazette), appoint such persons as it thinks fit, having the prescribed qualifications to be federal inspectors, or as the case may be, provincial inspectors within such local limits as it may assign to them.

Section 18 of the 1976 Act provides that an inspector may: (1) inspect any premises wherein any drug is manufactured, stored, exhibited for sale, or distributed; the plant and process of manufacture and the storage arrangements; the means employed for standardising and testing the drugs and all relevant records and registers; and (2) take samples of any

---

56 Rule 27 of the MDR Rules.
57 Rule 30 of the MDR Rules.
58 Section 2(j) of the Narcotics Act.
59 Section 2(a) of the Narcotics Act.
60 Section 2(za) read with Schedule of the Narcotics Act; entries from the list include: (1) alprazolam; (2) brolamfetamine; (3) cloraepate; (4) dexamphetamine; (5) fencamafamin; (6) flurazepam; (7) lefetamine; (8) medazepam; (9) phenobarbital; and (10) vinybital.
61 Section 6 of the Narcotics Act.
62 Section 7 of the Narcotics Act; to the best of our knowledge, no rules have been framed thus far.
63 Section 17 of the 1976 Act.
drugs that are being manufactured, sold, stocked or exhibited. In event of a contravention, a provincial inspector shall refer the matter to the provincial quality control board and seek orders as to the action to be taken in respect of such contravention; in the case of federal inspectors, such referral shall be made to the CLB or the RB.\(^6^4\)

The Drugs (Federal Inspectors, Federal Drug Laboratory and Federal Government Analysts) Rules, 1976 (the Inspectors Rules) set out the qualifications and duties of a federal inspector.

The duties of a federal inspector include, to:

- inspect, at least twice a year, all premises licensed for the manufacture of drugs including the plant and the process of manufacture and the methods and places of storage;
- take samples of any drugs that are suspected to be manufactured, stocked, sold or exhibited for sale in contravention of the provisions of the 1976 Act;
- institute prosecutions in respect of breaches of the 1976 Act; and
- conduct surveillance of marketed drugs for ensuring quality control.

### III PRICING AND REIMBURSEMENT

The federal government may, by notification in the Gazette, fix the maximum price at which any drug specified is to be sold.\(^6^5\) The mechanism for the fixation of prices of various therapeutic goods and the regulation thereof is carried out by DRAP.

Rule 3 of the Drugs Discounts and Price Adjustment Rules, 2006 (the Pricing Rules) provides that ‘[n]o company or firm or proprietor shall allow a sum of all discounts, in cash, kind or both, exceeding forty percent of the maximum retail price printed on the pack of the drug.’ Rule 4 of the Pricing Rules provides that the adjustment of prices of registered drugs shall be subject to the following conditions:

- downward or upward adjustments of the drug prices shall take place within the maximum retail price fixed;
- the company shall make upward or downward adjustments in prices, if they so desire, after the expiry of one year from the date of last adjustment;
- the Ministry of Health shall be informed in advance of the adjustment in prices and the effective date for such adjusted price; and
- there shall be no other change in the approved labelling of the drug.

Further, the Pricing Policy, 2018 (the Pricing Policy) sets out the pricing mechanism with respect to allopathic drugs, including biologicals for human use only, which are to be divided into two categories: (1) drugs and biologicals on the National Essential Medicines List; and (2) all other drugs.\(^6^6\)

The price of a drug cannot exceed the maximum retail price.\(^6^7\) Further, the price of a generic drug cannot exceed the maximum retail price of the respective originator brand,

\(^{64}\) Section 19(6) and 19(7) of the 1976 Act.
\(^{65}\) Section 12(1)(a) of the 1976 Act.
\(^{66}\) Section 3(2) of the Pricing Policy.
\(^{67}\) Section 3(5) of the Pricing Policy.
except when the originator brand has made a request for de-registration or it has been confirmed from the manufacturer or importer of the originator brand that it can no longer ensure adequate availability of the drug, due to non-viability of the same.68

With respect to medical devices, Rule 14 of the MDR Rules states that when making an application for enlistment and registration of a medical device, the applicant shall propose a maximum retail price for the medical device sought to be registered.

IV  ADMINISTRATIVE AND JUDICIAL REMEDIES

Any export, import, manufacture for sale, or sale of any spurious drug or unregistered drug, or manufacture for sale or import of any drug without a licence, is punishable with imprisonment and a fine. Additionally, the drug court may order forfeiture of any stock of drug or substance or any implements used in the manufacture or sale of such drugs and any receptacles, packages or coverings in which such drug is contained and the mode of transporting such drugs.69

Any contravention of the 1976 Act in relation to the import, export, manufacture or sale, which in the opinion of the licensing authority or the CLB is likely to endanger public health, may result in a cancellation or suspension of a licence.70 Any contravention may also lead to cancellation of the registration of the drug or suspension of the same for a specified period.71

Further, if a corporate entity is guilty of an offence, then each director, partner and employee of the corporate body with whose knowledge or consent the offence was committed, is also be guilty.72 If any person is convicted of an offence, the Drug Court may publish the offender’s name, place of residence, offence and penalty in a public newspaper, at the expense of the offender.73

The MDR Rules also stipulate that any contravention may result in suspension or cancellation of a licence for enlistment or registration of medical devices, being declared guilty of an offence under the 2012 Act and conviction thereunder.74 Any contravention in relation to narcotics is punishable with imprisonment and a fine.

V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

There is nothing to report.

68 Section 3(4) of the Pricing Policy.
69 Section 29 of the 1976 Act.
70 Section 41 of the 1976 Act.
71 Section 42 of the 1976 Act.
72 Section 34 of the 1976 Act.
73 Section 35 of the 1976 Act.
74 Rule 46(2) of the MDR Rules.
VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS
Laws pertaining to clinical negligence and medical malpractice are underdeveloped in Pakistan and there are, as such, no special systems required to be set up under the legal framework to compensate persons injured by medicines or medical devices. The remedy would lie in tort, with a claim for damages.

VII  TRANSACTIONAL AND COMPETITION ISSUES
i  Competition law
Competition in all sectors is regulated by the Competition Commission of Pakistan (CCP) established pursuant to the Competition Act, 2010 (the Competition Act) and the rules and regulations framed thereunder.

Certain agreements are prohibited under Section 4 of the Competition Act, including exclusivity agreements. However, the CCP may grant individual or block exemptions.

ii  Transactional issues
There are no transactional issues as such.

VIII  CURRENT DEVELOPMENTS
The National Health Vision 2016–2025 serves to align Pakistan's vision and international health priorities and aims to provide a unified national direction to harmonise provincial, federal, inter-provincial and inter-sectoral efforts to achieve the desired health outcomes.
I  INTRODUCTION

Law No. 29459 on Pharmaceutical Products, Medical Devices and Sanitary Products, enacted in November 2009, is the principal legislation that regulates pharmaceutical products, medical devices, sanitary products, pharmaceutical establishments (laboratories, storehouses, drugstores and pharmacies) and activities related to the marketing, promotion, advertising and prescription of the aforementioned products.

This Law has been complemented with the issuance of several supreme decrees that regulate specific requirements and conditions for said products and activities, the most important of which are Supreme Decrees Nos. 16-2011-SA (Rules on the Registration, Control and Sanitary Surveillance of Pharmaceutical Products, Medical Devices and Sanitary Products) and 014-2011-SA (Rules for Pharmaceutical Establishments).

The General Directorate of Medicines, Supplies and Drugs (Digemid) – a public entity that is part of the Ministry of Health – is the national competent authority in charge of granting all types of marketing authorisations regarding the above-mentioned products and their corresponding authorisations in order to carry out activities as pharmaceutical establishments. Digemid is also in charge of sanitary control and surveillance.

II  THE REGULATORY REGIME

Law No. 29459 sets forth the conditions for granting marketing authorisations of pharmaceutical products, medical devices and sanitary products.

There are two principal authorisations for the manufacture and importation, and commercialisation and storage of pharmaceutical products and medical devices that can only be granted to individuals or companies duly incorporated in Peru: a health operating authorisation, which must be granted in order to carry out activities as a pharmaceutical establishment (laboratories, drugstores, warehouses and pharmacies); and a marketing authorisation of the product.
In this sense, medicines and medical devices manufactured locally or in a foreign country can only be traded with the corresponding marketing authorisation issued by Digemid to local companies.

i Classification

Law No. 29459 includes a subclassification of the products that are included under the following main categories:

a pharmaceutical products:
   • medicines (which include pharmaceutical specialities, diagnostic agents, radiopharmaceuticals and medicinal gases). Pharmaceutical specialities are subclassified into specialities whose active pharmaceutical ingredient is: (1) included in the unique national list of essential medicines (Category 1); (2) not included in the unique national list of essential medicines but registered in high health surveillance countries\(^4\) (Category 2); and (3) not included in categories 1 and 2 (Category 3);
   • dietary and sugar substitutes;
   • biological products;
   • herbal medicines; and
   • galenic products;

b medical devices of low, moderate, high or critical risk; and

c sanitary products (cosmetic, household cleaning and products for personal hygiene and protection).

Cosmetic and household cleaning products are regulated under the applicable international rules (Andean Decisions)\(^5\) for the member countries of the Andean Community (Bolivia, Colombia, Ecuador and Peru).

ii Non-clinical studies

Law No. 30407, enacted in January 2016, forbids any experiment and research involving living animals that may cause them unnecessary suffering, injury or death, unless the aforementioned is essential for study and scientific advances. The results of such experiments cannot be obtained through other procedures, or said procedures cannot be replaced by cell cultures or tissues, or computerised methods or videos, when such experiments are necessary for:

a the control, prevention, diagnosis or treatment of diseases affecting human beings or animals;

b the assessment, detection, regulation or modification of the physiological conditions in human beings and animals;

c the preservation of the environment and the maintenance of biodiversity;

d investigation of productive parameters in animals; and

e medical-legal research.

---

\(^4\) France, the Netherlands, the United Kingdom, the United States, Canada, Japan, Switzerland, Germany, Spain, Australia, Denmark, Italy, Norway, Belgium, Sweden, Republic of Korea, Portugal, Ireland, Hungary and Austria.

\(^5\) Decision 516 will be applicable until 27 May 2020, the date on which Decision 833 will enter into force.
The Institutional Research Ethics Committee for the Use of Animals, part of the National Health Institute (INS) within the Ministry of Health, is the national competent authority that approves investigation protocols involving animals. Since there are many gaps in the regulation of studies on animals, the second complementary transitory provision of Law No. 30407 indicated that within a term of 90 days counted from 8 January 2016, the Ministry of Health should issue an ethics code for the use of animals in research. However, no such code has yet been issued.

### iii Clinical trials

Supreme Decree No. 021-2017-SA enacted in 30 June 2017 is the principle regulation regarding clinical trials, and the entity in charge of regulating and approving clinical trials is the INS.

Clinical trials must obtain prior authorisation issued by the General Office for Research and Technology Transfer, which is part of the INS. The authorisation can be requested by the sponsor or contracted research organisation and both need to be registered with the INS. The sponsor can be a foreign company but must have a legal representative in Peru duly empowered to act on its behalf with respect to any matter related to clinical trials.

It is only possible to request authorisations for clinical trials if the products under investigation comply with one or more of the following conditions:

a. they have an authorisation for investigation in human beings issued by the corresponding drug authorities from high health surveillance countries;

b. they are manufactured in Peru, have undergone preclinical investigation and are in accordance with the investigation policies or priorities determined by the Ministry of Health;

c. they are used to establish therapeutic equivalence of pharmaceutical products or similarity of biological products;

d. they are considered a priority for public health in Peru or part of the investigation policies or priorities determined by the Ministry of Health; and

e. they need to have clinical trials, according to the Ministry of Health, to support their efficacy and safety in order to grant the marketing authorisation.

For the importation of products under investigation, it is mandatory to obtain a sanitary importation authorisation granted by Digemid. This authorisation can only be granted to companies duly incorporated in Peru and after the company has been granted the authorisation to conduct the clinical trial.

### iv Named-patient and compassionate use procedures

Article 20 of Supreme Decree No. 016-2011-SA states that Digemid may provisionally authorise the importation and use of pharmaceutical products without sanitary registration or under conditions different from those ones stated in the sanitary registration for individual prevention or treatment. To obtain this authorisation, it is necessary to file an application submitting a medical report issued by a Peruvian doctor with a report stating the characteristics of the product.
The regulations state that the authorisation should be requested by the ‘person with interest’; therefore, it should be the patient who performs the procedure. Nevertheless, the patient could delegate the rights to another person or entity to perform the procedure on his or her behalf.

v Pre-market clearance

The general rule is that all medicines and medical devices must be previously registered with Digemid for their commercialisation in the market and this is achieved by obtaining a marketing authorisation. The holder of the marketing authorisation is responsible for the quality of the product.

There are some exceptions to the general rule and in certain specific cases it is possible to manufacture, import or use pharmaceutical products and medical devices without a marketing authorisation as long as Digemid gives prior approval. Exceptions are only applicable for:

a use in urgent situations or if an emergency is declared;

b research and training purposes;

c prevention and individual treatment with the corresponding medical justification; and

d public health situations where the need and unavailability of the product in the national market is demonstrated.

vi Regulatory incentives

Patent legislation in Peru does not allow for granting extensions of patents and there are few incentives for the research and study of new chemical entities.

Marketing authorisations are independent of patent procedures and the two are not linked in any way.

Until 2009, there was no protection of test data submitted during the procedure for obtaining a marketing authorisation. This situation changed with the issuance of Legislative Decree No. 1072 on the protection of test data and other undisclosed data relating to pharmaceuticals, and now it is possible to protect undisclosed test data or other data on safety and efficacy for five years. The information that will be protected is related to the safety and efficacy of a pharmaceutical product containing a new chemical entity.

vii Post-approval controls

Digemid is legally authorised to permanently, and without prior notice, conduct technical inspections at pharmaceutical establishments as well as to monitor and perform tests of products to ensure their safety. These actions could result in cancellation of authorisations and even suspension of activities or closure of establishments.

The holder of a marketing authorisation of pharmaceutical products or medical devices should periodically submit security summaries (reports) in line with good pharmacovigilance practices according to the following agenda: (1) each six months during the first two years following the first commercialisation; (2) annually during the following three years, after the first two years have elapsed; and (3) every five years from the sixth year.

Likewise, before its commercialisation and distribution, the holder of the marketing authorisation must submit the results of the product’s quality control for each and every batch. The quality control of the first batch that enters into the market, after registration of the product, must be conducted within the National Centre of Quality Control of the INS or in a laboratory duly authorised by Digemid.
viii Manufacturing controls

Manufacturing laboratories need to comply with good manufacturing, laboratory, storage, pharmacovigilance, distribution and transportation practices, and must include independent areas for manufacture, quality control and storage. Digemid conducts periodic supervisions to control the conditions and quality of the manufacturing processes as well as the quality of the products.

All manufacturing laboratories must function under the supervision of a technical director, who must be a qualified pharmaceutical chemist and who is in charge of the laboratory’s manufacturing and quality control, among other responsibilities.

By means of Ministerial Order No. 796-2019-MINSA, the Technical Standard for Health (NTS) No. 156-MINSA/2019/DIGEMID was approved and regulates the preparation of the Pharmaceutical Products Risk Management Plan. This Technical Standard is enforceable on the holder of sanitary/health registration of pharmaceutical products. It does not apply to medical gases, herbal medicines, dietetic products, sweeteners and galenical products. It will come into effect as of March 2020.

Also, by means of Ministerial Order No. 779-2019MINSA, the Good Manufacturing Practice Inspection Technical Guide to Pharmaceutical Products was approved. The Inspection Guide will be applied to domestic and foreign laboratories manufacturing pharmaceutical products. It does not apply to herbal medicines.

ix Advertising and promotion

Advertisements do not require authorisation or supervision before dissemination by any authority. The supervision and control takes place after the advertisement is released (ex-post control) and it is supervised by Peru’s National Institute for the Defence of Competition and the Protection of Intellectual Property (Indecopi). The promotion and advertising of medicines and medical devices for sale with a medical prescription must be addressed exclusively to professionals who prescribe and dispense said products.

Advertising for non-prescription medicines must include legible and accurate information of the technical specifications. In the case of advertising panels and advertising on television, the information about the principal precautions and warnings must be clear, legible and perceptible to the public.

Samples must be duly labelled with all the technical and approved information included in the product’s marketing authorisation and only physicians are allowed to directly provide samples to their patients.

x Distributors and wholesalers

Pursuant to Supreme Decree No. 014-2011-SA, all pharmaceutical establishments dedicated to the manufacture, importation, distribution, storage and commercialisation of medicines, medical devices and sanitary products, such as drugstores, warehouses and pharmacies, must necessarily obtain a health operating authorisation. Any of these establishments must appoint a permanent technical director or a pharmaceutical chemist (or both).

Laboratories and drugstores cannot commercialise pharmaceutical products or medical devices to end user consumers. Likewise, prescription medicines must only be sold in pharmacies, although some non-prescription medicines (with low sanitary risk) can be sold in commercial establishments (over-the-counter) as long as the establishment has been authorised by Digemid when granting the marketing authorisation for the product.
xi Classification of products
The general classification of products is outlined in Section II.i. Regarding pharmaceutical products (medicines), there is a subclassification depending on how the products will be dispensed. There are four subcategories that involve products that (1) require a specialised, numbered medical prescription; (2) require a simple medical prescription; (3) do not require a medical prescription but can only be sold in pharmacies; and (4) do not require a medical prescription and can be sold in commercial establishments.

A marketing authorisation will not be granted for a pharmaceutical product that has a commercial name that is identical or similar to another product already registered with a different formula. Likewise, a marketing authorisation will not be granted for a pharmaceutical product that has a trade name that corresponds to an international non-proprietary name (INN) or another term that could be confused with an INN.

xii Imports and exports
Besides the general information required by the customs authorities for the importation of pharmaceutical products, medical devices and sanitary products, it is necessary to provide the following:

a a copy of the resolution that authorises the marketing authorisation;
b identification of the shipment by the product’s manufacturing batch and expiry date;
c an analysis certificate or protocol analysis conducted over the product’s batch; and
d a good manufacturing practice (GMP) certificate granted by Digemid.

With regard to (d), it is possible to submit GMP certificates issued by competent authorities from high health surveillance countries or countries that have a mutual recognition with Peru. It is also possible to submit GMP certificates issued by the competent authorities of the country of origin as long as the importer had previously requested it from Digemid and until 28 February 2019, to conduct the certification of the laboratory and the same is pending to be performed.

xiii Controlled substances
Narcotics and psychotropic drugs are subject to the control and supervision of Digemid. For the importation or exportation of said products, it is necessary to obtain an official certificate issued by Digemid.

The prescription of certain narcotics and psychotropic drugs must be undertaken in accordance with special numbered prescriptions that must comply with strict requirements related to the content of the drugs. Likewise, laboratories, importers and pharmacies must have a suitable record whenever substances or medicines that include narcotics or psychotropic drugs are dispensed.

xiv Enforcement
Digemid is duly empowered to adopt security measures, such as preventive retention, seizure, withdrawal or destruction of products or materials and equipment used. These measures can be executed without warning and are imposed regardless of other administrative sanctions that could also be applied, such as fines, cancellation of authorisations or closure of establishments.
Digemid promotes different campaigns to inform consumers about the dangers of falsified medicines and provide general recommendations to prevent the acquisition of said products.

Digemid constantly issues alerts to the national scientific community and to the public in general, with the objective of controlling and minimising the risk related to the sale of a certain product.

III PRICING AND REIMBURSEMENT

The Consumer Protection Commission has stated on several occasions that within a social market economy, price-fixing must be free, based on supply and demand, and that ‘excessive’ or ‘exploitative’ prices cannot be penalised. The only prices that may be fixed administratively are public services fees.

On the other hand, it has been stated that excessive prices generate incentives for other bidders (i.e., competitors with respect to whom exploitative conditions are imposed) to enter into the market and offer better prices. Therefore, the idea is that competitors should reduce prices to capture users’ preferences.

In relation to drug prices, it has been stated that Peruvian legislation does not regulate the government’s intervention in the price-fixing of drugs traded by private companies; however, the government has adopted different policies and measures with the purpose of helping to improve the access thereto by users of medicines.

In this regard, on 31 October 2019, the government issued Urgent Decree No. 07-2019 by which access to drugs and biological products included in the national list of essential medicines was declared as an essential right to health. By means of Supreme Decree No. 026-2019-SA, the Rules on the mentioned Urgent Decree were enacted, establishing that pharmacies must keep available or demonstrate the sale of generic essential drugs.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The procedures to obtain a health operating authorisation or marketing authorisation do not require the application to be published in a legal gazette or on Digemid’s website. For this reason, it is very difficult for third parties to be aware of new applications. Even if the third parties obtain information about a product that might infringe patent rights, it would not be possible to oppose or impede registration as the law does not foresee a specific procedure for a third party to do so. The registration application is a two-party procedure (the applicant and the administration).

If an authorisation is rejected, the applicant can either file a writ of reconsideration or a writ of appeal against the decision. The reconsideration writ must be supported by new evidence and will be resolved by the same authority that issued the decision. The appeal is resolved by Digemid’s general director, who acts as second and last administrative instance.

The decisions adopted by Digemid’s general director acting as second instance can be challenged before the judiciary. For such purposes, it is necessary to file a lawsuit within a term of three months after the issuance of the final decision and the judicial case could reach up to three instances (a judge specialised in contentious matters, the Superior Court
and the Supreme Court). Filing a lawsuit does not suspend the effects of the resolutions that are challenged. To do so, it is necessary to obtain a precautionary measure, but these are frequently rejected.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

According to Article 31 of Law No. 29459, the prescription of medicines must necessarily include the INN, pharmaceutical form, dose, term of the treatment, form of administration and, optionally, the trade name. Not including the INN in the prescription is considered an administrative infringement and economic fines could be imposed.

Administrative Directive 208-MINSA/DIGEMID-V.016 is the legal norm that regulates the activities of medical representatives. According to this Directive, medical representatives should not encourage healthcare professionals to perform unethical prescription practices by offering, inter alia, courses, trips, rewards and presents. Travel and accommodation expenses are not prohibited but they should be granted in accordance with the ethical criteria for medicinal drug promotion approved by the World Health Organization. The Directive also prohibits the installation of stands, modules and offices at public or private health establishments. It is also not permitted for advertisements to be posted on the walls of medical offices.

Any support to healthcare professionals to participate in any domestic or international symposium should not be conditional upon any obligation to promote any pharmaceutical product and must be announced as a conflict of interest, when applicable.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Under Peruvian law, product liability is ruled under the Consumer Protection Code (CPC) and the Civil Code. The CPC applies to any consumption relationship (relationships established between a consumer and a supplier, as defined below) entered into in the Peruvian territory or whose effects are performed therein. If the CPC is thus not applicable, then product liability shall be regulated by the Civil Code. General rules provide, however, that Peruvian law is applicable.

Consumers are defined as individuals or legal entities that purchase products as end users (i.e., not for business or professional activities). An individual or legal entity that purchases a product for business purposes shall not be considered a consumer. On the other hand, small businesses evidencing a situation of information asymmetry with the supplier in respect of certain products that are not part of their own course of business shall also be considered as consumers. By contrast, suppliers are defined as individuals or legal entities that regularly manufacture, process, handle, mix, pack, store, prepare, dispense or supply products of any kind to consumers. Suppliers may be, among others, distributors, producers or manufacturers, importers, or vendors.

 Suppliers that cause damage to consumers with defective products are subject to strict liability and must pay compensation in accordance with the provisions of the Civil Code in the corresponding judicial process. When there are several suppliers of a product (e.g.,

---

6 Approved by Ministerial Resolution No. 413-2015-MINSA on 1 July 2015.
manufacturer and distributor), they shall all be jointly liable. Notwithstanding the foregoing, each supplier has a right of recourse against the supplier that provided the defective product or caused the defect.

A supplier is also administratively liable for any breach of the CPC. The proceeding shall be conducted before the Consumer Protection Commission of Indecopi, which may impose fines of up to 1,867,500 soles and impose remedial and complementary corrective measures.

The Civil Code does not contain specific product liability rules. Nonetheless, general principles of civil liability contained in the Civil Code empower the victim of damage caused by a defective product to claim the corresponding compensation.

When there is no contractual relationship between seller and buyer (e.g., between the manufacturer and the end user), the seller may also be liable under tort liability. Article 1970 of the Civil Code provides that if a person causes damage to another person by means of a risky or dangerous product, or the exercise of a risky or dangerous activity, that person must compensate the victim of the damage. This article incorporates the strict liability principle in the Peruvian tort system, under which no degree of fault must be demonstrated. Peruvian scholarship argues that a defective product is a risky product and, therefore, when there is no contractual relationship between the seller and the buyer and the defective product causes damage to the buyer, the seller is subject to strict liability.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

There are no specific competition regulations in Peru that apply exclusively to the pharmaceutical industry. However, there is a general Antitrust Law that promotes and protects free competition for all markets.

The regulations governing free competition are contained in Legislative Decree No. 1034 on the Repression of Anticompetitive Conducts (LRCA).

The authority in charge of enforcing the general legal framework governing free competition is Indecopi, which through its Commission on Free Competition, investigates and sanctions anticompetitive behaviour in the markets, with technical and functional autonomy.

Peruvian antitrust regulations apply to all practices that produce or may produce anticompetitive effects in all or part of the Peruvian territory, even if the practice originated abroad. The LRCA prohibits and sanctions three types of anticompetitive conduct, namely abuse of dominant position,7 horizontal collusive practices8 and vertical collusive practices.9

With regard to the nature of these prohibitions, some qualify as absolute prohibitions and others as relative prohibitions. According to Article 8 of the LRCA, the former refers

7 Holding a dominant position, with or without affecting real or potential competitors, does not constitute an illegal conduct. Monopolies or dominant position are not rejected per se, but rather the abusive use thereof.
8 Horizontal collusive practices imply the joint action of several competitors as if they were one. According to the LRCA, such practices may consist of concerted agreements, decisions, recommendations or practices among competitors with the aim or effect of restraining, preventing or forging competition.
9 These are collusive practices among economic agents operating at different levels of the production, distribution or marketing chain, aimed at restricting, preventing or forging free competition.
to a behaviour that is forbidden per se and thus the competition agency will only have to prove the existence of the practice to determine the offence. However, in the case of relative prohibitions, to verify the existence of the offence, the existence of the practice must be proved and, additionally, it must be proved that it has or may have negative effects for competition and the well-being of consumers.

### ii Transactional issues

There are no specific rules on transactional issues for pharmaceutical products and medical devices. Whether foreign laboratories are holders of the marketing authorisation of pharmaceutical products or medical devices must always be taken into account when analysing any transaction because there is always a dependence on the holder’s will (usually local importers or drugstores companies that only have a commercial relationship with the laboratories) to transfer the marketing authorisation. Holders are even entitled to renounce the marketing authorisations and this could delay the commercialisation of products in the country as it would be necessary to obtain new marketing authorisations.

On 19 November 2019, the government issued Urgent Decree No. 13-2019, which approves a prior control regime for all business transactions that: (1) involve a change in control; (2) meet the thresholds set forth in the Urgent Decree; and (3) have effects in all or a part of the Peruvian territory.

The new prior merger control regime will be conducted by the Peruvian Antitrust Agency (INDECOPI) and will enter in force within nine months of its issuance date. Furthermore, the Urgent Decree will be in force for a period of five years and is subject to INDECOPI’s review in order to recommend its definitive extension.

The Urgent Decree’s main aspects are as follows:

a Business concentration transaction: any act or transaction that involves a permanent transfer or change of control in a company or part of a company. Among others, the following will be considered as business concentration transactions: (1) mergers; (2) acquisitions of shares; (3) the formation of a joint venture or any other similar arrangement involving the acquisition of joint control over one or more economic agents; and (4) the acquisition of assets that involve the transfer of control.

b Business concentration transactions subject to prior control: transactions that meet the following characteristics are subject to the new prior merger control regime:

- those that imply a permanent transfer or change of control in a company or part of it; including the acquisition of productive assets (control transfer);
- those executed in Peru or abroad but that have effects in all or a part of the Peruvian territory; and
- those that meet the thresholds established in the Urgent Decree.

c Thresholds: business concentration transactions will be subject to the new prior merger control regime when the following thresholds are jointly met before its execution:

- the total sales or annual gross income, in the country, reported by the companies involved in the transaction during the past tax year has reached an amount equal to or greater than 118,000 tax units (approximately US$141.5 million); and
- the annual sales or gross income, in the country, reported by at least two of the companies involved in the transaction during the past tax year has reached an amount equal to or greater than 18,000 tax units, each (approximately US$21.6 million for each company).
In the event of a merger or acquisition of joint control, all economic agents involved in the transaction must submit a joint authorisation application before INDECOPI. In all other cases, the authorisation application must be submitted by the economic agent that is acquiring control over all or a part of one or more economic agents.

VIII  CURRENT DEVELOPMENTS

i  Cannabis for medical purposes

The legality of medical cannabis in Peru arose in October 2017 pursuant to Law No. 30681, regulating medical and therapeutic cannabis and by-products. On 23 February 2019, the Rules of Law No. 30681 were enacted by means of Supreme Decree No. 005-2019-SA. A cannabis fact with respect to the variety of cannabinoids is provided by the Rules, identifying psychoactive and non-psychoactive substances. Therefore, psychoactive cannabis end products shall be for medical purposes only. In the case of non-psychoactive cannabis end products, they shall not have restrictions. In fact, non-psychoactive cannabis refers to cannabis of less than 1 per cent THC dry weight as set forth in the Regulations. Thus, they are non-controlled substances and are excluded from the Narcotic Drugs and Psychotropic Substances Regulations enforcement.

According to the Rules of Law No. 30681, patients shall directly import cannabis products by obtaining a special prescription and the authorisation issued by Digemid. Also compounded drugs (compounded drugs are pharmaceutical preparations tailored for an individual patient by a licensed pharmacist or under their supervision in strict compliance with a detailed medical prescription or the active ingredients as per technical and scientific standards in terms of pharmacy) should be prepared upon presentation of the pertinent prescription and are exclusively dispensed by the pharmacy receiving such prescription. They must not be kept in stock and their mass creation is forbidden. For compounded drugs, wholesale or end products must not be used as supplies. Compounded drugs containing substances subject to health control shall comply with the Regulations on Narcotic Drugs, Psychotropic Substances and Other Substances.

By means of Ministerial Order No. 1969-2019-IN, Directive No. 006-2019-IN the guidelines to approve the security protocols on the use of medical and therapeutic cannabis and its by-products were published. Security protocols aim to ensure physical intangibility of cannabis and to avoid drug diversion. Said protocols must be duly verified and approved by the representative of the Peruvian Police Force Anti-Drug Division (DIRANDRO).

The authorisation of the Agricultural Production Plan issued by the General Division of Agriculture (DGA) of the Ministry of Agriculture and Irrigation (MINAGRI) is a requirement for medical cannabis agricultural production licensing that laboratories authorised by Digemid must obtain. Pursuant to Ministerial Order No. 0499-2019-MINSAGRI published on MINAGRI’s website, it is set forth to approve the Guidelines for Agricultural Production Plan that includes sowing, cultivation and harvesting of cannabis for medical and therapeutic purposes.

ii  Electronic medical records

On 8 July 2019, the Ministerial Order published the Technical Document named Implementation Plan of the National Registry of Electronic Medical Records (RENHICE). This plan aims to implement the technological infrastructure specialised in health allowing the patient or their legal representative and health professionals being previously authorised
by them, to access to the medical data contained the electronic medical records. The plan shall be implemented progressively. The use of electronic medical records will favourably contribute to provide quality healthcare services to the benefit of patients. It should be mentioned that any person managing the information contained in RENHICE is liable to non-disclosure.
Chapter 21

POLAND

Ewa Skrzydło-Tefelska and Jacek Myszko¹

I  INTRODUCTION

The majority of the activities within the pharmaceutical sector in Poland are regulated by the Pharmaceutical Law of 6 September 2001 (PhL). The PhL is the basis for a number of Polish executive regulations laying down detailed rules on specific issues (such as good distribution practice, good manufacturing practice and advertising of medicinal products). Medical devices are regulated independently under the Act on Medical Devices of 20 May 2010 (AMD), soon to be replaced by new legislation on medical devices implementing into Polish law the EU Medical Devices Regulations 2017/745 and 2017/746. Other important regulations in the pharmaceutical or medical device sector include, besides EU legislation, the Act on Counteracting Drug Addiction of 29 July 2005 (CDA), stipulating rules of manufacturing and marketing of narcotic and psychotropic substances, and the Act on Reimbursement of Medicines, Foodstuffs for Particular Nutritional Uses and Medical Devices of 12 May 2011 (ARM).

The main authorities in charge of the pharmaceutical and medical device sector are the Ministry of Health (MoH), the Pharmaceutical Inspectorate (the main pharmaceutical regulator – MPI) and 16 local voivodeship pharmaceutical inspectors. Marketing authorisations (MAs) are issued by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (ORMP). Public funding of healthcare services and products is still operated by the National Health Fund (NHF). The most important changes to Polish legislation in the past year are the amendment of the PhL, which aims to combat illegal trade and exports of medicines and the implementation of the EU Falsified Medicines Directive; further changes regarding, inter alia, wholesale distribution models are being considered.

II  THE REGULATORY REGIME

i  Classification

The definitions of ‘medicinal product’ and ‘medical device’ under Polish law are essentially the same as those adopted under EU legislation. Polish law also follows the general EU rule regarding ‘borderline products’ – if a product falls within the definition of a medicinal product and, at the same time, of another type of product (in particular, a food supplement, a cosmetic or a medical device), the medicinal product’s regime applies. Most of the aforementioned products are regulated in Poland under separate pieces of legislation; for example, cosmetics are regulated under the Act on cosmetic products of 4 October 2018 (which reconciles

¹ Ewa Skrzydło-Tefelska and Jacek Myszko are partners at Sołtysiński, Kawecki & Szlęzak.
Poland

Polish legislation with Regulation (EC) No. 1223/2009 on cosmetic products), and dietary supplements and foodstuffs are regulated under the Act on the Safety of Foodstuffs and Nutrition of 25 August 2006 (which needs to be reconciled with Regulation (EU) No. 609/2013 on food intended for infants and food for special medical purposes).

ii Non-clinical studies

Non-clinical (i.e., pharmacological and toxicological) studies should be carried out in accordance with the rules of good laboratory practice (GLP), as regulated under the Act of 25 February 2011 on Chemical Substances and their Mixtures and under the Executive Regulation of the MoH of 22 May 2013 on Good Laboratory Practice and Performing Research in Accordance with the Rules of GLP. Consequently, non-clinical studies should be carried out by research entities that have been granted a GLP compliance certificate.

The means of protection of animals used in the course of studies is regulated under the Act of 15 January 2015 on Protection of Animals Used for Scientific and Academic Purposes. Tests on animals may only be carried out by authorised ‘users’ and only with consent from the local ethics committee. The register of authorised suppliers, breeders and users is kept by the Ministry of Science and Higher Education (available online). Records of experimental animals must be kept by the research centres.

iii Clinical trials

Clinical trials are regulated by the provisions of the PhL. All clinical trials (including bioavailability and bioequivalence studies) should be planned, carried out, monitored and reported in accordance with good clinical practice (GCP), as set out in the regulation of the Ministry of Health on Good Clinical Practice dated 2 May 2012. The sponsor of any clinical trials (a person responsible for initiating, conducting and financing a clinical trial) may be a natural person or an entity with the registered office in the territory of the European Union or the European Economic Area (EEA) – if the sponsor does not have its registered office in the territory of a EEA state, it may act solely through a legal representative with a registered office in this territory. As a principle, clinical trials may start only after obtaining a positive opinion from the bioethics committee and the authorisation of the president of the ORMP – at this stage, the trials are also entered into the Central Register of Clinical Trials. The president of the ORMP may refuse to authorise a clinical trial when submitted documents are incomplete, the trial constitutes a threat to public policy or is contrary to the rules of social conduct, or when the concept of the trial is not compliant with the requirements of GCP.

No financial encouragement should be offered to participants of clinical trials unless they are healthy adults (over 18 years old) who may give informed consent. This ban does not preclude reimbursement of the costs of participation.

Before conducting a clinical trial, the informed consent of participants is required. The PhL provides for specific requirements in this respect. Additional requirements apply to clinical trials that involve minors or incapacitated individuals.

The sponsor and the investigator are liable for damages caused in connection with clinical trials and are obligated to take out an adequate insurance policy. Specific requirements are set out in the regulation of the Ministry of Finance dated 30 April 2004 on compulsory insurance of the sponsor and investigator.

The products used in the trials should be prepared in accordance with good manufacturing practice. The principal documentation of the trials should be kept by the
sponsor and investigator for at least five years from the beginning of the calendar year following the year in which the clinical trial ends and should be made available to the ORMP upon request.

The national regulation on clinical trials is still in force but it will be replaced by Regulation (EU) No. 536/2014 on Clinical Trials, which is expected to become applicable in 2021. The draft amendment of the PhL implementing the necessary changes is still not ready.

Medical devices and active implantable medical devices should undergo a clinical analysis based on clinical data. The specific rules for such trials are regulated under the AMD. Clinical trials must be authorised by the bioethics committee and the president of the ORMP and conducted according to the protocol for clinical trials. The informed consent of participants is required. They also have the right to physical and psychological integrity, privacy and personal data protection; they may withdraw from the trials without sustaining damage or injury. The sponsor and investigator are required to obtain a civil liability insurance policy. Restrictions on offering financial incentives apply, similar to those that apply in trials regarding medicinal products.

Please note that there will be major changes with regard to the regulation of medical devices. On 26 May 2020, Regulation (EU) No. 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices will come into force. The national law will be also replaced by a new act, the draft of which is currently being subject to legislative works.

iv Named-patient and compassionate use procedures

The PhL allows for importation of medicinal products that have no MA in the territory of Poland, where it is necessary to save the life or health of a patient. A medicinal product must be authorised in the country from which it is imported (country of origin) and have a valid MA in that country (a targeted import procedure). The basis for a targeted import procedure is the requisition of a hospital or a physician carrying out therapy outside the hospital, confirmed by a national or regional medical consultant qualified in the relevant field of medicine. Detailed rules governing the distribution of medicinal products imported through the targeted import procedure were set out in the MoH regulation dated 21 March 2012 but, on 31 December 2016, the regulation was revoked and no new regulation has been enacted.

The following cannot be placed on the market under the targeted import procedure:

- medicinal products in respect of which a decision refusing an MA, non-extension of the validity period of an MA or revocation of an MA was issued in Poland;
- medicinal products containing the same active ingredients, dose and form as products that have already obtained MAs in Poland; and
- products that, owing to the safety of use or the volume of import, should be placed on the market in accordance with the general provisions of the PhL.

Pursuant to Article 39 of the ARM, medicinal products imported under the targeted import procedure may be reimbursed.

Poland has not expressly implemented legislation specific to compassionate use in the meaning set out in Article 83 of Regulation (EC) No. 726/2004. Currently, the proposal of specific regulations is included in the bill amending the ARM. This draft is at the stage of governmental work and it is difficult to assess when the new regulation will enter into force.

The PhL also provides extraordinary procedures for the importation of medicinal products applicable in the event of a natural disaster (or other similar life- or health-threatening events).
The AMD allows for the introduction into the Polish market of single medical devices that have not yet undergone a compliance assessment procedure if they are necessary to achieve required preventive, diagnostic or therapeutic purposes. Devices may be marketed on the basis of a decision of the president of the ORMP issued when it is necessary to protect the life or health of a patient, or for the protection of public health. A request for a decision may be filed by a healthcare provider, national, regional or military healthcare consultant, the president of the Health Technology Assessment Agency or the president of the NHF.

Moreover, custom-made medical devices may be distributed without a CE marking provided that the device is accompanied by a statement by the manufacturer or its authorised representative that it fulfils its essential requirements (or indicating which requirements are not fulfilled and why).

v Pre-market clearance

Medicinal products covered by a Polish national MA and products covered by an MA issued by the EU Council or the European Commission are eligible to be marketed in Poland. There are four ways of obtaining an MA that is effective in Poland: through a national procedure, a centralised procedure, a decentralised procedure and a mutual recognition procedure.

The marketing authorisation holder (MAH) may be an entrepreneur in the meaning outlined in the Polish Entrepreneurs’ Law, or an entrepreneur conducting business activity in the European Union or the EEA.

The national procedure is regulated under the PhL. The authority competent to issue an authorisation is the president of the ORMP. The authorisation should be issued within 210 days of submission of the application for a period of five years (which may be subsequently extended). The authorisation may be issued following verification of an application by the ORMP and after preparing an assessment report with a scientific opinion on the medicinal product. The application for authorisation must include extensive documentation, which reflects the requirements provided in Directive 2001/83/EC. The expedited path for generic products also reflects EU legislation (as a rule, eight years’ data exclusivity and 10 years’ market exclusivity periods apply). The results of non-clinical and clinical studies are not required for products with active substances that have a well-established use or well-established effectiveness and an acceptable level of safety and use in EU or EEA Member States.

The PhL provides for a simplified authorisation procedure for traditional herbal medicinal products and homeopathic products.

Some products do not require MAs to be distributed in Poland, including magistral formulae, official formulae, selected radiopharmaceutical products, whole blood, plasma and blood cells of human origin, advanced therapy medicinal products (according to Regulation (EC) No. 1394/2007); neither are authorisations required for products used solely for scientific research, products used by manufacturers, products used in registered clinical trials and intermediate products to be used by manufacturers. The PhL also regulates a parallel import procedure.

Medical devices may generally be marketed only if they have a CE marking (see the European Union chapter). The essential requirements for devices, as well as the specific procedure for compliance assessment, are set out in a number of executive regulations of the MoH. The manufacturer is responsible for compliance assessment and introduction of medical devices to the market. The manufacturer must be domiciled or have registered offices in the European Union or appoint an authorised representative who is responsible for a given
product. When the manufacturer does not appoint a representative, or the manufacturer or representative is not responsible for introducing the product to the market, the entity that places the product on the market bears responsibility for its compliance with law.

Medical devices should be notified to the ORMP by the manufacturer or its representative, domiciled or with registered offices in Poland, at least 14 days before the product is first put on the Polish market. Distributors and importers with a domicile or registered office in Poland who introduce medical devices to the Polish market must notify the ORMP without delay, and certainly no later than seven days following the first introduction of the products on the market.

vi Regulatory incentives

Supplementary protection certificates for medicinal products are granted in Poland according to Regulation (EC) No. 469/2009 (executive measures are implemented into the Polish Industrial Property Law).

Article 15 of the PhL implements into Polish law the data exclusivity and market exclusivity periods (eight and 10 years, respectively) provided by EU law.

The Polish government is still planning to introduce the Innovative Development Mode – a reward programme for pharmaceutical companies that conduct their economic activity and run the research and development centres in Poland and employ Polish nationals. The details of the Innovative Development Mode are still not specified. As a principle, qualifying companies could rely on easier reimbursement negotiations and other reimbursement-related incentives. The Innovative Development Mode has been included in the Polish Medicine Policy announced in 2018.

vii Post-approval controls

The obligations stemming from the EU pharmacovigilance system apply in Poland. The Polish implementation of the EU Directive on Falsified Medicines for Human Use entered into force on 8 February 2015.

After the lapse of a five-year period of validity of an MA, the authorisation may be indefinitely extended after examination of documents regarding the product’s quality, safety and effectiveness, as well as any side effects. At this stage, the ORMP may refuse to extend the authorisation or extend it only for a further five years (if, for safety reasons, the ORMP deems prolongation of the authorisation for an indefinite period to be inappropriate).

Any amendments to an MA may be made upon request of the MAH and requires a decision by the president of the ORMP. The procedure varies depending on the type and scope of the amendments.

The MA may be withdrawn because of, inter alia, serious adverse reactions related to the product, insufficient therapeutic effectiveness, infringement of provisions of the medicinal product’s marketing or failure to notify required new information regarding the product. Violations not resulting in a direct threat to public health may result in suspension of the authorisation. Furthermore, the MA expires if the product is not marketed for three years.

The AMD uses the term ‘medical incident’ for malfunctions, defects, improper labelling or contents of any manuals as well as other technical or medical causes related to medical devices that may result in death or deterioration of the health of a patient. Healthcare providers are obliged to report any such incidents without delay to the device manufacturer or its representative, and to send a copy of that notification to the ORMP. The manufacturer
(or its representatives) must carry out field safety corrective action. The president of the ORMp may issue a decision prohibiting or suspending the marketing of unsafe medical devices.

viii Manufacturing controls

The manufacturing of medicinal products is understood broadly and requires a permit from the MPI. There are certain exceptions to the obligation to obtain a permit; these exceptions are generally consistent with EU legislation.

Manufacturers of medicinal products must comply with provisions of good manufacturing practices (set out in the MoH regulation, reflecting the respective EC guidelines). Manufacturing permits may cover the manufacturers’ own products and any products manufactured for third parties (as a contractor). A manufacturing permit allows a manufacturer to undertake any of the activities expressly mentioned in the permit and with respect to the products listed in the permit. If the manufacturer wishes to expand the list of medicinal products or the scope of its activities, it must apply for the relevant amendment of the permit. The processing of controlled substances requires additional authorisation (see Section II.xiii).

Manufacturing permits are issued for an unspecified period of time. The MPI also issues a separate certificate confirming compliance of the manufacturing facility with the GMP requirements, which is valid for three years from the date of the latest inspection carried out by the MPI (the date of the inspection is stated on the certificate).

Depending on the legal form of the transfer of ownership of a manufacturing facility, manufacturing permits may be transferred with the facility (e.g., in the event of a merger). New permits may be required in the event of the sale of the facility to another entrepreneur.

ix Advertising and promotion

Advertising of medicinal products is regulated under the PhL and under the MoH executive regulation dated 21 November 2008. Applicable restrictions for advertising and promotion are generally consistent with the applicable EU legislation. Only the MAH (or a parallel importer) and any entity authorised by the MAH may undertake advertising of medicinal products (in practice written authorisation is required by the MPI). Reimbursed medicinal products cannot be publicly advertised. Violation of the applicable rules may trigger various sanctions, including criminal sanctions or a fine.

The regulations regarding advertising of medical devices are very limited. Under the AMD, promotional materials, presentations and information on devices may not be misleading as to the properties and operation of devices by:

a attributing properties, functions and operations to a device that are non-existent;
b giving the impression that treatment or diagnosis with the device is guaranteed to be successful;
c failing to inform of the expected risks connected with using the device in accordance with its intended use or for a period longer than intended; and
d suggesting use or properties other than those declared during the conformity assessment.

The new Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices will apply in 2020. Therefore, the Polish government has prepared a new draft of the Medical Devices Act, which regulates in more detail the issues related to advertising of medical devices. The draft regulates, among others, (1) what activities
constitute an advertisement; (2) what elements should be included in the advertisement; as well as (3) claims that must be included in the advertisement and the manner of their presentation. The authority responsible for supervision over advertising of medical devices will be the President of the Office of the Competition and Consumer Protection. The new law is currently subject to legislative works.

The ARM prohibits manufacturers and distributors of reimbursed products (including medicinal products, medical devices and reimbursed foodstuffs) to offer any encouragement regarding such products to patients or healthcare professionals authorised to issue prescriptions. In particular it is prohibited to offer conditional sale, rebates and bonuses, packages, loyalty programmes, donations, prizes, small gifts, trips, lotteries, any form of lending, tied transactions, facilitations, acquisitions or sponsored services, vouchers, coupons or other benefits not expressly named. Various sanctions apply for violation of this ban.

Pharmacies in Poland may not advertise. This prohibition includes a broad range of promotional activities such as loyalty programmes and the publication of price lists.

Distributors and wholesalers

Wholesale is defined in accordance with EU legislation. Wholesale trade may be undertaken by pharmaceutical wholesalers and pharmaceutical manufacturers (in the latter case, limited to their products). Before 8 February 2015 (when the amendments to the PhL entered into force), customs and consignment warehouses had also been authorised to carry on a wholesale trade in medicinal products. However, by operation of the amendment to PhL, such entities were automatically transformed into pharmaceutical wholesalers. Wholesalers must obtain an authorisation issued by the MPI, except for manufacturers (a manufacturing permit already encompasses authorisation for the sale of manufactured products). All wholesalers are required to follow the rules of good distribution practice (as regulated under the MoH Regulation dated 13 March 2015). The regulation implements EC Guidelines of 2013, but the Polish implementation is more strict than the requirements stemming directly from the Guidelines. Also the findings of pharmaceutical inspectors prove that the interpretation of law is not consistent and changes quite often. Under the new supervision system, periodic inspections are carried out in each wholesale premises at least once during a three-year period. There is also rather limited understanding of the pharmaceutical authorities for the more advanced business models (e.g., logistic operators running wholesale premises or transporting medicinal products for third parties); in most cases they tailor their expectations based on the ‘regular’ buy-sell business model. As a result, the standard for running a pharmaceutical wholesale business in Poland is set much higher than in most other EU countries.

In 2018 there was further limitation of the entities eligible for running wholesale activity. Namely, the authorities will deny permits for running wholesale pharmaceutical operations if an applicant simultaneously runs (or applied for a permit to run) a pharmacy, is brokering with regard to medicinal products or is entered into the register of medicinal activity.

Retail trade may be undertaken by pharmacies (the PhL distinguishes between generally accessible pharmacies and hospital pharmacies) and pharmacy outlets. Some over-the-counter products may also be sold in herbal medicine stores, medical supplies stores and general stores.

Distribution of medical devices does not require any specific authorisation and may be undertaken by any entrepreneur (provided they comply with the requirements of the AMD).
xi  Classification of products

Under the PhL, there are the following categories of dispensing medicinal products:

a  those dispensed over-the-counter without a physician's prescription (OTCs);

b  those dispensed on a physician's prescription;

c  those dispensed on a physician's prescription for restricted use;

d  those dispensed on a physician's prescription, containing narcotic agents or psychotropic substances defined in separate regulations; and

e  those for hospital use only.

The criteria for classifying medicinal products into one of the categories are specified in the MoH executive regulation dated 14 November 2008. The dispensing category must be indicated in the MA and may only be changed by an amendment of the MA. The main consequences of classification are limitations on the allowed channels of distribution (only OTCs may be sold in general stores) and limitations on the advertising of products other than OTCs directed to patients.

Medical devices are classified as Class I, IIa, IIb or III depending on the risk connected with their use. The factors relevant to classification are the time of contact of the device with an organism, the place of contact, the level of invasiveness, local and systemic effects, and the function and technologies used. Medical devices for in vitro diagnostics are classified as Class A or B in accordance with Directive 98/79/EC.

xii  Imports and exports

The import of a medicinal product from third countries (non-EEA) requires an import authorisation that is issued in a procedure similar to the granting of a manufacturing authorisation by the MPI.

The parallel import of products authorised to be marketed in Poland requires the importer to obtain an authorisation for the import of each specific product. This authorisation is valid for five years and may be renewed for subsequent five-year periods.

In order to remedy problems with shortages of state-reimbursed medicines, Poland has introduced new restrictions on the export (understood as every export of medicinal product outside the territory of Poland) of some products listed as being in danger of shortages (the list is compiled on the basis of information provided by the MPI, collected in the Integrated Monitoring System for Trade in Medicinal Products or other information concerning the availability of medicinal products, and is published by the MoH). An exporter must file a notification to the MPI at least 30 days prior to the export of any listed products. The MPI may then issue an opposition to the export. If such opposition is issued, the wholesaler is obliged to sell the products in Poland. If the MPI does not issue an objection to the export, the exporter may export medicinal products within 30 days. The entrepreneur shall inform the MPI within seven days about actual export. The sale of a medicine product, included in the MoH’s list (1) without prior notification to the MPI; (2) before the expiry of the opposition period; or (3) contrary to the MPI’s opposition, is invalid.

The same rules apply to medical devices listed as being in danger of shortage. However, importers of medical devices are obligated to ensure that the compliance assessment for the device was performed, that the manufacturer has appointed an authorised representative and that the CE marking, with the identification number of a notified body, are included in the product’s labelling (if required). An importer domiciled or with a registered office in Poland is also obliged to keep a declaration of conformity or required statements and
certificates regarding the device. The president of the ORMP, at the request of a manufacturer or authorised representative domiciled or with a registered office in Poland, may issue a certificate of free sale to facilitate the export of devices with a CE marking or custom-made devices.

**xiii Controlled substances**

The marketing of narcotic drugs and psychotropic substances (controlled substances) is governed by the CDA. Drug precursors are additionally governed by EU regulations.

Under the CDA, the importation and exporting (from or to EU and non-EU Member States) of controlled substances may be carried out only by businesses with authorisation to manufacture or wholesale trade. These authorisations are issued by the MPI. As a general rule, the importation and exporting of controlled substances require consent from the MPI and the competent authorities in the country of export. When the controlled substances are in transit through Poland, they must be accompanied by an export authorisation granted by the authorities in the country of origin and they cannot be stored in customs warehouses. There are exceptions to these rules with regard to controlled substances imported for personal medicinal needs.

The wholesale trade in controlled substances and drug precursors also requires authorisation granted by the MPI. The retail trade in these products (which are also medicinal products) may be undertaken by pharmacies and pharmacy outlets.

There are further specific requirements regarding storage, handling and issuance of controlled substances, keeping pertinent records and documentation, and so on.

**xiv Enforcement**

The MPI supervises the manufacture, importation, quality and distribution of medicinal products. When an instance of non-compliance is detected, the MPI generally issues a decision ordering the contravener to remedy the breach. If there is a direct threat to life and health of the population, the MPI may immediately close the manufacturer’s or distributor’s operations.

The president of the ORMP is the competent inspection authority for medical devices manufactured, marketed, used and assessed in Poland. The president of the ORMP may issue decisions prohibiting, suspending or restricting the marketing and use of devices for reasons regarding patients’ safety, public health, safety and order, etc.

The PhL and the AMD provide for criminal liability for infringement of some of the rules regarding labelling, compliance assessment, marketing or failure to perform some duties by the entities responsible for product compliance. In such a situation, enforcement is carried out by the police, public prosecutors and courts.

**III PRICING AND REIMBURSEMENT**

Under the ARM, medicinal products listed in the Register of Reimbursed Products (Register) are reimbursed. Under certain conditions, medicines without an MA and medicines for use exceeding the scope described in the characteristics of the medicinal product may also be reimbursed.

Reimbursement of a medicinal product already entered into the Register cannot be automatically extended to the equivalent generic or medicinal product or parallel imported medicinal products; they need to be separately entered into the Register.
The Register is compiled on the basis of reimbursement decisions issued by the MoH and is updated every two months. The application for reimbursement may be filed by the MAH, its representative or holder of parallel import authorisation. The medicinal product, medical device or foodstuff for a particular nutritional use covered by an application must meet the following requirements at the moment the application for reimbursement is filed:

\[ \begin{align*}
    a & : \text{it must have a valid MA or remain on the market as specified in the PhL;} \\
    b & : \text{it must actually be available on the market (the evidence thereof must be attached to the application); and} \\
    c & : \text{it must be granted a GTIN number in accordance with GS1 or another code that uniquely identifies the medical device or foodstuff for a particular nutritional use.}
\end{align*} \]

Prices (sale price, wholesale price and retail price) of reimbursed products are regulated (either by way of fixing the actual sale price or fixing the maximum price margin that may be added to the fixed sale price at a given stage). Prices are negotiated by the applicant and the MoH and only when a consensus has been reached may the product be subject to reimbursement.

The decision on reimbursement encompasses the category of reimbursement availability (i.e., under which category the medicine is reimbursed),\(^2\) the level of payment (whether the patient receives the product for free or against some payment),\(^3\) the regulated (fixed) price of sale and the specification of the limit group to which the particular product belongs.

There is also the possibility of reimbursing medicinal products under the emergency access to the drugs technologies procedure. Namely, a patient may obtain an extraordinary reimbursement of a medicinal product that is not on the reimbursement list, provided that use of that particular medicinal product is necessary because of the inefficiency of a standard therapy. Contrary to compassionate use, emergency access to the drugs technologies does not apply to medicinal products that do not have an MA.

\section*{IV \quad ADMINISTRATIVE AND JUDICIAL REMEDIES}

In general, decisions made by administrative bodies in Poland are subject to appeal. The appeal may be examined by the supervisory body or by the same body (the latter ‘re-examination procedure’ applies to decisions issued by ministries, such as the MoH, and heads of central governmental bodies, such as the MPI and the ORMP). After completion of the appeal procedure, the decision may still be subject to judicial (administrative court) review. The judicial review procedure has two stages: the basic complaint is adjudicated by the voivodeship administrative courts, whereas a cassation complaint against the decision of such court is adjudicated by the Supreme Administrative Court. If the Supreme Administrative Court finds that the decision is inconsistent with the law, in most cases it will quash the decision and state that it must be re-examined. Parties may request a stay of enforcement of the administrative decision during the period of the judicial review.

\(^2\) The specific categories are listed in the ARM.

\(^3\) Different levels of payment are possible.
V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

Under the PhL it is forbidden to address the advertising of medicinal products to persons qualified to prescribe and to persons trading in medicinal products involving inducements. The infringement of this provision may result in criminal liability. It is also prohibited to accept any advantages or benefits. An exception is made for gifts of small value (not exceeding 100 zlotys) related to a medical or pharmaceutical practice, bearing advertising or branding for the specific company or medicinal product.

The ARM provides for administrative and criminal sanctions for certain marketing practices. In general, it is prohibited to provide any benefit tied with reimbursed products, addressed in particular to patients, entrepreneurs or authorised persons (in particular physicians authorised to issue prescriptions), particularly by way of conditional sale, rebates and bonuses, packages, loyalty programmes, donations, prizes, small gifts, trips, lotteries, any form of lending, tied transactions, facilitations, acquisitions or sponsored services, vouchers, coupons or other benefits not expressly named.

Financial relations between companies and healthcare professionals is a very sensitive subject in Poland and a careful approach to the subject is generally recommended. Special care should be exercised in relation to healthcare professionals who perform administrative functions at hospitals and other entities, who also place orders for medicinal products and medical devices. People in these professional positions should not be offered any incentives or gifts as it may trigger various types of liability for both the healthcare professional and the person or entity offering the incentive (criminal sanctions may also apply). Such actions may also be perceived as bribery or violation of public tenders, which may result in criminal liability for individuals and trigger significant fines for companies.

VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There is no specific liability regime relating to the use of medicinal products or medical devices. The general principles apply – in particular, principles on the liability for the use of defective products (mirroring EU legislation in this respect).

Apart from the general possibility of seeking compensation in court, there is a special system of compensating personal injuries introduced by the Act on Patient Rights and the Patient Ombudsman. The Act introduces the term ‘medical event’, which is an infection of a patient with a biological pathogen, bodily injury or health disorder, or the patient’s death following a diagnosis, if it led to improper treatment or delayed appropriate treatment, contributing to the development of the disease; treatment, including surgery; or use of a medicinal product or a medical device that did not follow current medical knowledge. The term ‘medical event’ only applies to hospital healthcare services. A patient may apply to the regional commission for evaluation of a medical event. When the commission rules that a medical event has occurred, the ruling is binding for the hospital’s civil liability insurer, which is obliged to offer a sum of proposed damages within 30 days (300,000 zlotys for death.

---

4 The supply, offer or promise of pecuniary advantages, gifts and various types of facilitation, prizes, trips, and organising and financing medicinal products’ promotional meetings at which hospitality manifestations are not limited to the main purpose of the meeting.
and 100,000 zlotys for other injuries), which may be accepted or rejected by the applicant. This system, however, deals with medical incidents and not directly with defective medicinal products or medical devices.

There are also plans to introduce a special regime for damages caused by obligatory vaccines. This was one of the aims set out in the Polish Medicine Policy that was announced in 2018. One of the suggestions in this document was the creation of a special fund for adverse post-vaccinal reactions. The Polish legislature has not started work on this matter.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Competition law in the life sciences sector is regulated and enforced in accordance with EU law. The body responsible for supervision of practices restricting competition is the Office of Competition and Consumer Protection. Since the pharmaceutical market is already thoroughly regulated, there have been no significant antitrust decisions issued in this field during the past year.

Mergers and acquisitions within the pharmaceutical and medical devices sector are subject to notification to the antimonopoly authorities (standard provisions apply).

ii Transactional issues

There is a specific procedure for a change of MAH, in which the agreement on the transfer of rights and obligations of the MAH must be submitted to the ORMP with a statement that only a change of MAH has occurred (i.e., the MAH is the only element of the authorisation or documentation that has changed).

Most other authorisations under the PhL (e.g., MAs, wholesaler and pharmacy authorisations, licences to trade in controlled substances) cannot be transferred by agreement. However, according to the general rules of the Commercial Companies Code, administrative authorisations and licences may be transferred, via an acquisition or a merger by or with another company. This rule, however, is expressly waived with regard to permits for running pharmacies. Currently such permits may only be held by pharmacists (or two types of companies exclusively trading in medicinal products whose partners are exclusively pharmacists). Therefore, currently the permits to run pharmacies are, as a principle, non-transferable (this also applies in cases of mergers, demergers and sale of enterprise, etc.). This is an effect of further tightening of the anti-concentration rules in the pharmacy sector.

Please note that the market regulator is very active. If it traces any irregularity in terms of compliance with the anti-concentration rules in the pharmacy sector, it may instigate proceedings aiming at termination of the permits for running pharmacies that are not compliant with the above rules. There are also associations of independent pharmacists that investigate pharmacy concentration cases and publish on their websites reports regarding their compliance with the law. They also notify the market regulator of their findings.

VIII CURRENT DEVELOPMENTS

The most discussed developments at the moment are the amendments to the PhL – both past and current. The PhL is currently subject to a number of legislative works. On 11 September 2019, the Polish parliament adopted an act implementing the EU Falsified Medicines Directive. The act defines MPI supervisory and management competences
in relation to medicinal products databases, specifies and supplements the provisions of Commission Delegated Regulation 2016/161 in the scope of responsibilities of individual participants in the chain of distribution of a medicinal product (which are left to the decision of the competent authorities of the Member States of European Union), in particular by:

\[a\] introducing subjective exemption in the scope of the obligation to verify safety features by some entities and placing this obligation on the entrepreneur conducting wholesale trade;

\[b\] defining new MPI competences for supervision of the database system;

\[c\] extending the obligations of entrepreneurs by expressly referring to Commission Delegated Regulation 2016/161;

\[d\] indicating administrative sanctions (pecuniary sanctions) for failure to comply with the obligations under Commission Delegated Regulation 2016/161; and

\[e\] introducing provisions enabling the conclusion of written agreements between a MAH and the wholesaler, regarding the storage and distribution of medicinal products.

Another important development was the introduction of new provisions enabling the authorities to more effectively combat the ‘medicinal products mafias’, which illegally exported medicinal products out of Poland. By way of an Act of 26 April 2019, Parliament passed a law that introduced additional control competences in this area. The main changes are:

\[a\] the introduction of a prohibition on pharmaceutical wholesalers obtaining supplies from entities other than those specified in the PhL;

\[b\] the limitation of the catalogue of entities to which pharmacies may supply medicinal products;

\[c\] the introduction of criminal liability for the ‘reverse distribution chain’;

\[d\] granting persons authorised to conduct inspections the right to order the opening of the facility, premises or parts thereof and the lockers therein, as well as their inspection; and

\[e\] the institution of distance selling of medicinal products by pharmacies or pharmacy outlets was expanded and supplemented with regard to supplying people with disabilities.

The big challenge for the Polish legislature, but also for the pharmaceutical companies, could still be the application of Regulation (EU) No. 536/2014 on Clinical Trials. This Regulation brings in a series of amendments to the existing system. The essential issue is the proper preparation of sponsors for clinical trials, the pharmaceutical companies, the investigators and the institutions to perform clinical trials under the new regulations. Currently, the PhL is not yet in line with Regulation (EU) No. 536/2014; the new draft law on clinical trials is awaiting further legislative works.

There is also a very vivid discussion regarding biosimilar medicines in Poland. Since the patent protection for certain biological medicinal products is due to expire in Poland in the near future, manufacturers of the biological (reference) medicinal products are taking various steps to de facto ensure continuation of the previous market share and of the therapy with the up-to-date patented products, despite expiry of the patents. The most controversial part of the discussion is in regard to the bioequivalence and interchangeability of reference products and biosimilar products during the course of a therapy that has already been initiated. The Polish reimbursement regime encourages the introduction of cheaper, biosimilar products,
thus creating price pressure on both the reference biological products and the new biosimilar
products. In the past year the discussion has been focused on patients’ right to express their
informed consent before switching the products (reference to biosimilar and vice versa). The
discussion was even stronger after the Supreme Administrative Court’s landmark decision
regarding patients’ rights in view of purchasing medicinal products by hospitals and automatic
switching into biosimilars.

The next challenge for Polish legislators is also adapting Polish regulations on medical
devices to Regulation (EU) 2017/745 of the European Parliament and of the Council of
5 April 2017 on medical devices, which will apply in 2020, and Regulation (EU) 2017/746
of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical
Polish legislature is working on a new draft of the Medical Devices Act, which is still under
public consultation. Work is also under way to provide pregnant women with free access to
medicine products for the treatment of pregnancy-related illnesses, thereby improving their
financial condition to ensure the mother’s health and proper child development.

As regards IP-related developments, there was an amendment to the Polish industrial
property law introducing a more flexible approach towards the Bolar exemption in Poland,
waiver of an obligation to demonstrate the ‘legal interest’ when applying for invalidation
of a patent and a possibility to limit a patent by modifying patent claims in the course
of the invalidation proceedings. All of the above constitute important practical issues for
pharmaceutical companies in Poland.
Chapter 22

PORTUGAL

Francisca Paulouro and Inês Caldas de Almeida

I INTRODUCTION

The life sciences sector in Portugal is heavily regulated, with the legal framework applicable both to medicines and medical devices closely following the EU regulatory framework. Nevertheless, in some areas national legislation goes beyond what is provided in the relevant directives; this is particularly noticeable, for example, in matters related to promotion, wholesale distribution and clinical trials. Pricing and reimbursement are exclusively dealt with at national level, as they are outside the scope of EU legislation, with the exception of transparency measures and procedural requirements set out in the Transparency Directive.2

The National Authority of Medicines and Health Products, IP (Infarmed), is the national regulatory agency for medicines and medical devices. In addition to its competence for technical health regulation, Infarmed’s powers also cover pricing, reimbursement and market access. Price approval of prescription products, including products for hospital use, is also attributed to this agency. Infarmed plays a significant role in relation to reimbursement and market access of medicines, as it is the entity responsible for conducting the relevant procedures and proposing decisions to the Minister of Health.

II THE REGULATORY REGIME

The Medicines Act3 consolidates in a single legal act the regime applicable to, among others, the marketing authorisation, manufacture, import, export, marketing, labelling, promotion and pharmacovigilance of medicines; transposing into Portuguese law several directives, including Directive 2001/83/EC,4 as amended (the Directive).

Medical devices, in turn, are governed by the Medical Devices Act,5 which, further to transposing several directives related to the manufacture, marketing and vigilance of medical devices (including Directive 93/42/EEC,6 as amended), establishes the regime applicable to promotion. With regard to promotion, the Medical Devices Act closely follows the regime

1 Francisca Paulouro is of counsel and Inês Caldas de Almeida is a senior associate at Vieira de Almeida.
set out for medicines. In early 2017, Decree-Law No. 5/2017\(^7\) introduced general principles applicable to the promotion of medicines and medical devices, and further implemented specific rules for scientific, educational and promotional events that take place in National Health Service entities.

i Classification

The definitions of a medicinal product for human use and of a medical device are identical to those arising from EU legislation, with the distinction between them being made on the basis of the intended use and the mechanism through which this is achieved. As is the case under the Directive, where any doubt arises, the classification as a medicinal product prevails.

ii Non-clinical studies

Directive 2010/63/EU\(^8\) on the protection of animals used for scientific purposes was transposed into Portuguese law in August 2013.\(^9\) This regime follows closely the one set out in Directive 2010/63/EU, thus establishing several requirements applicable to the use of animals for scientific or educational purposes, namely in what concerns the accommodation, care and use of animals in procedures; the origin, breeding, marking and killing of animals; licensing of breeders, suppliers and users; and the procedures for evaluation and authorisation of scientific or educational projects.

In addition, and similarly to what happens at EU level, the testing of finished cosmetic products and cosmetic ingredients on animals is prohibited, with the same applying to the marketing thereof if animal testing was conducted for cosmetic purposes.

iii Clinical trials

In April 2014, a new legal regime for clinical research was approved,\(^10\) consolidating in one legal act the provisions applicable to clinical studies, whether interventional or not, and covering medicines, medical devices and cosmetics. The regime encompasses the provisions of Directive 2001/20/EC\(^11\) regarding the conduct of clinical trials on medicinal products for human use and the provisions of Directive 2007/47/EC\(^12\) on clinical investigation with medical devices.

All clinical studies are subject to a prior favourable opinion from the competent ethics committee. In addition, interventional clinical trials with medicines depend on authorisation from Infarmed, with the same applying to interventional studies with Class III medical devices, implantable medical devices and long-term invasive devices falling within Classes

\(^7\) Decree-Law No. 5/2017 of 6 January 2017.
\(^9\) Decree-Law No. 113/2013 of 7 August 2013.
\(^10\) Law No. 21/2014 of 16 April 2014.
IIa or IIb. For the remaining classes of medical devices, interventional studies depend only on the favourable opinion from the ethics committee and on notification to Infarmed. The conduct of clinical interventional studies with cosmetics should also be notified in advance to Infarmed, with the sponsor being entitled to initiate the study should Infarmed not issue an unfavourable decision within 30 days of the notification.

Both the sponsor and the investigator are jointly and severally liable, regardless of fault, for material and non-material damage suffered by subjects – liability that must be covered by insurance. Should an interventional study be at stake, there is a legal presumption that damage that affects the health of subjects during the study and for a one-year period following its term (which may be extended by the ethics committee) is caused by the study. This reverses the general rule on burden of proof, subject to which whosoever alleges damage should demonstrate the causal relationship between the damage and the act (in this case, the study).

iv  Named-patient and compassionate-use procedures

Similar to what happens under EU legislation, the general rule is that medicines can only be marketed following the granting of a marketing authorisation. In exceptional circumstances, however, Infarmed may authorise the use of non-approved medicines, such as when the product is, subject to a clinical assessment, considered indispensable for the treatment of a given pathology and there is no therapeutic alternative among authorised products.

Within the context of interventional clinical studies, following the conclusion of a study, the sponsor is under an obligation to supply the investigational medicinal product or device under clinical investigation for free until its marketing should the investigator consider that continuation of its use by the former participant is indispensable and that there are no therapeutic alternatives with an equivalent degree of safety and efficacy.

v  Pre-market clearance

The Medicines Act reflects EU rules in this regard and thus medicines can only be placed on the market following the granting of a marketing authorisation – Infarmed being the competent authority for authorising medicines that follow national procedures.

The marketing in Portugal of medical devices bearing a CE mark does not require any authorisation from Infarmed. Nonetheless, Infarmed must be notified of all medical devices marketed by a given entity prior to its commercialisation.

vi  Regulatory incentives

The Medicines Act reflects the regime established in the Directive regarding regulatory data protection and market exclusivity. Generic applications cannot be submitted for a period of eight years following the first authorisation in the European Union. After this eight-year period has elapsed, the generic cannot be launched on the market for an additional two years. This period may be extended for one supplementary year should the innovator, within the data exclusivity period of eight years, obtain a marketing authorisation for one or more indications of significant clinical benefit.

Patent linkage is not permitted. The Medicines Act expressly provides that marketing authorisation applications cannot be dismissed on the grounds of the potential existence of industrial property rights of the reference product. A similar rule exists for pricing and reimbursement decisions.
There are no special provisions to encourage the development or market launch of innovative products, including orphan drugs. On the other hand, special provisions to encourage the sale of generics exist in a variety of areas; for example, generics benefit from a simplified regime regarding pricing and reimbursement, and prescription is mandatorily made by active substance once a generic is launched in the market, the rule being that of generic substitution, save in very limited circumstances expressly provided for by law. Incentives of a similar nature also exist in the case of biosimilars.

vii Post-approval controls
Pharmacovigilance rules applicable to medicinal products were modified in 2013 with the transposition into Portuguese law of Directive 2010/84/EU and Directive 2012/26/EU.\(^\text{13}\) In the same year, the provisions of Directive 2011/62/EU\(^\text{14}\) regarding prevention of entry into the supply chain of falsified medicinal products were also transposed, with the Medicines Act currently closely following EU legislation on these matters, such as the placing of safety devices on the packaging of certain medicinal products, to identify and authenticate them. Detailed rules for these safety devices were to be adopted through Delegated Regulation 2016/161,\(^\text{15}\) including a repository system containing information on the safety features. These rules were to be implemented by marketing authorisation holders up until 9 February 2019. In 2018, the Medicines Act was amended, to adapt local legislation to Delegated Regulation 2016/161.

A similar regime applies regarding medical devices, with the vigilance requirements stemming from the relevant directives. In addition, a vigilance system has been implemented that is similar to the system applicable to medicines.

viii Manufacturing controls
In line with the Directive, the manufacture of medicinal products is subject to prior authorisation by Infarmed, even if products are intended for export. An authorisation will only be granted if the applicant has adequate premises that comply with the applicable legislation and with the European Commission Guidelines on Good Manufacturing Practice (in 2018, the Medicines Act was amended to transpose Directive 2017/1572)\(^\text{16}\) and has a qualified person permanently and continuously at its disposal. The qualified person, who is responsible for all manufacturing activities performed, must be a pharmacist registered with the Portuguese Order of Pharmacists.

Any change to the manufacturing authorisation requires prior authorisation by Infarmed.

In 2013, the Medicines Act was amended, transposing Directive 2011/62/EU and thus requiring that the manufacturers of active substances established in Portugal register their activity with Infarmed.

The manufacture of medical devices, as well as the assembling, packaging, processing, fully refurbishing, labelling or assigning to them a purpose different from that of its original intended use, among others, is subject to prior notification to Infarmed. The engagement


\(^{15}\) Commission Delegated Regulation 2016/161 of the European Commission, of 2 October 2015.

in these activities is dependent on the applicant having adequate premises and equipment with capacity to ensure the manufacture, storage and conservation of medical devices and a technician responsible to ensure the quality of the activities performed.

In addition, and in line with what is set out in EU directives, manufacturers or their authorised representatives placing medical devices on the Portuguese market should notify Infarmed, providing in the notification the required level of information depending on the classification or nature of the device concerned.

ix Advertising and promotion

The regime applicable to the advertising of medicines closely follows the regime set out in the Directive. The major differences relate to the definition of advertising, to the scope of the prohibition on granting benefits to healthcare professionals and to the prohibition on granting any kind of benefit to patients, matters in respect of which the Medicines Act goes beyond what is established in the Directive.

The definition of advertising is broader than that set out in the Directive, advertising being considered, under the Medicines Act, as any kind of information, canvassing activity or inducement that has as its object or effect the promotion of the prescription, dispensation, sale, purchase or consumption of medicines. Contrary to what is foreseen in the Directive, Portuguese law does not require that the conduct be designed to promote a given product for it to qualify as advertising. It suffices that the conduct at issue has that effect.

Second, the Medicines Act extends the scope of the prohibition on pharmaceutical companies granting gifts, pecuniary advantages or benefits in kind to healthcare professionals to also include bonuses – a notion that is associated with the granting of discounts in kind, such as free products. The broadening of this prohibition is particularly relevant to the relationship between pharmaceutical companies and pharmacies, being hardly in line with the EU legal framework and with the principle that promotion rules do not apply to measures or trade practices related to prices, margins and discounts – provided for in both the Directive and the Medicines Act.

Finally, pharmaceutical companies are prevented from granting any kind of benefit to patients. Similarly to what happens in relation to healthcare professionals, companies cannot grant or promise to grant, directly or indirectly, gifts, prizes, bonuses, pecuniary advantages or benefits in kind to patients.

Although companies are under an obligation to provide Infarmed with a summary description of all advertising materials, no prior-approval requirement exists. In addition, companies must notify Infarmed in advance of the sponsorship of any congress, symposium or event of an educational or promotional nature.

The regime applicable to advertising and promotion of medical devices is very similar to that applicable to medicines. There is, however, no prohibition on granting gifts or benefits to the public. The advertising of medical devices, the use of which requires the intervention of healthcare professionals, such as implantable medical devices, cannot be promoted to the public.

Medical device companies are also required to notify Infarmed in advance of the sponsorship of any congress, symposium or event of an educational or promotional nature.
x Distributors and wholesalers

Wholesale distribution of medicines is subject to prior authorisation from Infarmed. Until 2019, the only exception to this regarded holders of manufacturing authorisations in relation to the products covered by those authorisations (similarly to what happens under the Directive). Further to the amendments introduced in the Medicines Act by DL 112/2019,17 MA holders or their local representatives are also exempted from this obligation in relation to the products covered by those authorisations, as long as such activity is pursued by a duly authorised wholesaler. In such cases, MA holders are nevertheless required to register their wholesale activity before Infarmed.

In fact, the legal regime applicable to wholesale activity in the Portuguese territory suffered several amendments in 2019 with the entry into force of the above-mentioned Decree-Law. A distinction is now drawn between wholesalers and logistics operators and, more importantly, supply obligations falling upon wholesalers have been reinforced with a view to ensuring patient access to medicines.

It is now clearly stated in the Medicines Act that the wholesale activity’s main function is to guarantee adequate and continuous supply of the Portuguese territory. Wholesalers continue to be under a legal obligation to have medicines permanently available in sufficient quantity and variety to ensure the appropriate and continued supply of medicinal products with a view to guaranteeing the satisfaction of patients’ needs. However, it is now clearly stated in the Medicines Act that wholesalers can only export or sell within the European Union, once they have ensured that they have fully satisfied national demand. These amendments do not arise from the Directive, the current setting in Portugal, in this regard, thus deviating from the regime provided for therein. Finally, the minimum quantities of products that wholesalers must keep at all times to ensure satisfaction of patient demand are set out in a regulation issued by Infarmed.

The granting of the wholesale distribution authorisation is dependent on the applicant having adequate equipment and premises, located in Portugal, to ensure proper conservation and distribution of medicines and a technical director, who must ensure, effectively and permanently, the quality of the activities carried out in the distribution premises. The technical director must be a pharmacist registered with the Portuguese Order of Pharmacists and personally fulfil his or her responsibilities in the wholesale premises. Technical directors may cumulate functions within the same wholesale premises, up to a limit of five wholesale distribution authorisations. In 2015, a new regulation on good distribution practices applicable to the wholesale distribution of medicines18 was approved, closely following Commission Guideline 2013/C 343/01.19

As of 2019, and as per the amendments made by DL 112/2019, the wholesale authorisation details the wholesale activities for which it is granted, the premises where the activity is conducted, and may be pursued by either a wholesaler or a logistics operator with premises in Portugal. Logistics operators – a notion that was created by DL 112/2019 – are entities responsible for performing logistics services and pursuing wholesale activities on behalf of the MA holder or the manufacturer.

In addition, wholesalers are under a legal obligation to have medicines permanently available in sufficient quantity and variety to ensure the appropriate and continued supply

of medicinal products with a view to guaranteeing the satisfaction of patients’ needs. The minimum quantities of products that wholesalers must keep at all times to comply with this public service obligation were set out in a regulation issued by Infarmed.

Finally, Infarmed has the power to prevent the exportation of medicines – be it inside or outside the European Union – on the grounds of protection of public health or to ensure patient access to a given medicinal product.

The regime governing the brokering of medicinal products under the Medicines Act follows closely that of Directive 2011/62/EU,20 thus engagement in the activity of brokering does not require prior authorisation from Infarmed; neither is it dependent on the existence of premises or a permanent address in Portugal. Persons brokering medicines with a permanent address in Portugal must register their activity with Infarmed.

The engagement in the activity of wholesale distribution of medical devices, although not subject to express authorisation from Infarmed, must be notified in advance to that authority, and is only permitted if (as is the case for medicines) the applicant has adequate premises and equipment with capacity to ensure good storage, conservation and distribution of medical devices and a responsible technical director is appointed to the wholesale premises to ensure the quality of the activities performed. In contrast to the regime applicable to medicines, the technical director does not have to be a pharmacist but must have an adequate technical qualification to ensure the quality of the distribution activity, as well as adequate knowledge of the legislation and regulations applicable to medical devices. Also, differently from the regime applicable to medicines, the wholesale premises do not have to be located in Portugal. Nonetheless, should the premises be located abroad, the applicant must comply with the Portuguese legal provisions applicable to the wholesale distribution of medical devices. In 2016, good distribution practices applicable to the wholesale distribution of medical devices were approved (although initially legally set out in 2009).21 This regime is extremely demanding and, in many aspects, follows the good distribution practices for medicines.

xi Classification of products
The criteria laid down in the Medicines Act for classifying a medicine for medical prescription are very similar to those set out in the Directive.

The classification has related consequences for the regime applicable to advertising, pricing, reimbursement and point of sale or dispensing. Only non-prescription products may be promoted to the general public, which is the same under the Directive. In addition, while there is no price control for non-prescription drugs (unless these are reimbursed – the general rule, however, is that non-prescription products are not subject to reimbursement), prescription products have their maximum sale prices approved, regardless of whether they are reimbursed or not. Finally, whereas the dispensing of prescription drugs is restricted to pharmacies – unless subject to restricted medical prescription, in which case they can only be dispensed or administered in hospitals – over-the-counter products (OTCs) may be sold at points of sale duly authorised by Infarmed.

xii Imports and exports
In line with the regime laid down in the Directive, the importation of medicines is subject to prior authorisation from Infarmed, with requirements very similar to those applicable to the manufacture of medicines (see Section II.viii). The importation of active substances is also subject to registration with Infarmed. The export of medicinal products does not require any authorisation from Infarmed, nor does it require registration with Infarmed.

As regards medical devices, there are no additional requirements related to imports and exports other than those applicable to the manufacture, placing on the market and wholesale distribution, analysed above.

xiii Controlled substances
The manufacture, use, marketing, distribution, importation, exportation and possession of narcotics and psychotropic substances are subject to a specific regime. Narcotics and psychotropic substances are divided into several categories, each identifying the relevant substances. Infarmed is the entity responsible for authorising engagement in these activities in relation to certain categories of substances. Specific requirements also exist for prescribing, dispensing and keeping records when such substances are included in medicinal products.

Further to constituting a misdemeanour punishable with a fine, engagement in any of the above-mentioned activities without the relevant authorisation may be considered a criminal offence.

In addition, the use of cannabis-based medicines, preparations and substances for medicinal purposes, was authorised under Law 33/2018.22 ‘Cannabis-based medicines, preparations and substances’ are defined as the leaves, flowers and fruits of the cannabis plant, as well as oil and other standard extracts or preparations obtained from the plant.

Physicians are only allowed to prescribe cannabis-based products if conventional treatments with authorised medicines are not having the expected effects or they are generating relevant adverse effects; also, cannabis-based products can only be prescribed for use in indications authorised by Infarmed.

Law 33/2018 further indicates that these products must be prescribed by a physician, pursuant to a special medical prescription, which must be approved by the Ministry of Health. The prescription must mention the names of the physician and the patient, and it must identify the cannabis-based medicine, preparation or substance, as well as the relevant quantity, dosage and form of administration.

Since they are considered medicinal products, they will, generally, require a marketing authorisation from Infarmed before being placed on the market.

Law 33/2018 is regulated by DL 8/2019,23 which establishes the terms under which the authorisations for the activities of farming, manufacturing, wholesaling, importing, exporting and transfer of cannabis-based medicines, preparations and substances are granted. This legal decree further establishes that the placing on the market of cannabis-based preparations and substances depends on a marketing placing authorisation granted by Infarmed.

---

22 Law No. 33/2018 of 18 July 2019.
Cannabis-based products can only be sold in pharmacies. The buyer is required to provide identification, or evidence of being the legal guardian of the patient, together with the prescription. Each prescription can only be used once (i.e., the law does not provide for a renewable prescription, or for a prescription that can be used several times).

MO 44-A/2019\(^{24}\) establishes the pricing regime of these medicines, preparations and substances.

\textbf{xiv Enforcement}

Infarmed is entrusted with the supervision and enforcement of regulatory provisions applicable to medicines and medical devices.

A breach of these provisions is considered a misdemeanour punishable with a fine calculated according to the infringer’s annual turnover, or a fine of a predetermined fixed amount (whichever is lower). In addition to this penalty, a breach of the provisions of the Medicines Act, including advertising, may also give rise to ancillary sanctions to be applied by Infarmed, such as a prohibition on exercising the activity, exclusion from participation in public tenders and the suspension of any authorisations and permits – all up to a maximum of two years.

Should the infringement of promotion rules be at stake, both regarding medicines and medical devices, Infarmed may order that the condemnatory decision be published in the media as well as the suspension of advertising of the product concerned for a period of up to two years. Medicinal products may further be delisted as a result of infringement of promotion rules.

\textbf{III PRICING AND REIMBURSEMENT}

On 1 June 2015, Decree-Law No. 97/2015 was published, creating the System of Assessment of Health Technologies (SiNATS). In creating SiNATS, this single Decree-Law consolidated the provisions applicable to pricing, reimbursement and prior evaluation procedures, and introduced three main changes:

\begin{itemize}
  \item[a] clear reinforcement of the powers of public authorities – with the state being granted the capacity to unilaterally and in an almost unlimited manner amend and terminate contractual agreements executed with the pharmaceutical industry;
  \item[b] an unprecedented concentration of powers within Infarmed; and
  \item[c] flexibility on applicable rules, considering that several matters are referred to governmental and Infarmed regulations, thus facilitating the swift change of provisions.
\end{itemize}

Several decrees have been approved since the entry into force of SiNATS, establishing the regime regarding specific matters, such as the procedure for reimbursement and prior evaluation,\(^{25}\) and the rules and procedures applicable to the setting and revision of prices of medicines subject to medical prescription and reimbursed OTCs, as well as corresponding marketing margins.\(^{26}\)

\begin{flushright}
\textsuperscript{24} Ministerial Order No. 44-A/2019 of 31 January 2019.
\textsuperscript{25} Decree No. 195-A/2015 of 30 July 2015 as amended.
\textsuperscript{26} Decree No. 195-C/2015 of 30 July 2015 as amended.
\end{flushright}
Notwithstanding the importance of SiNATS, the essential features of the previous regimes remain untouched. For example, the rules on pricing and reimbursement of medicines continue to differ, essentially depending on the classification of the product for dispensing purposes.

Medicines subject to medical prescription but not a restricted medical prescription, and generally sold in street pharmacies, have to undergo a price approval procedure before Infarmed prior to being launched on the market. In this context, a maximum sale price is approved, which, in the case of branded products, is determined by reference to the price applied in three reference countries. This price is subject to annual revision in accordance with the same criteria.

Approval of reimbursement is within the competence of the Minister of Health and will only be granted should the therapeutic added value and economic advantage of the product be demonstrated.

Another striking feature of SiNATS lies in the increased importance of the execution of agreements between Infarmed and the marketing authorisation holders, although the execution of such agreements is still not legally mandatory – save in the case of hospital products. These agreements typically set a maximum sale value for the product, which, once exceeded, will determine a payback by the marketing authorisation holder to the National Health Service equivalent to the amount of public expenditure in excess of the limit. Other types of agreements are now expressly provided for under SiNATS, such as risk-sharing arrangements. SiNATS also approved specific rules for the reimbursement of similar biological medicines conditioning the approval thereto to its price not exceeding 80 per cent of the price of the reference biological medicine.

A ‘reference price’ system exists in the context of reimbursement. Until a generic is launched on the market, the percentage of state reimbursement, ranging from 15 per cent to 90 per cent, save in exceptional circumstances provided for in specific regulations, applies to the sale price of the product. The placing on the market of a generic, however, gives rise to the creation of a ‘homogenous group’, composed of branded or innovative medicines and generics with the same active substance, dosage, method of administration and pharmaceutical form, and to the approval of the corresponding reference price – equivalent to the average of the retail sale price of the five lowest-priced products included in the group. Following approval of the reference price, the maximum amount of state reimbursement for products included in the relevant group will be determined by applying the applicable reimbursement percentage to the price.

Similarly, before they can be sold to National Health Service hospitals, medicines subject to medical prescription have to undergo an evaluation procedure, in the context of which the applicable maximum sale prices are approved by the Ministry of Health, or Infarmed, should this competence be delegated. Until the approval of SiNATS, this regime only existed for medicines subject to restricted medical prescription. Note, however, that if the medicine is already subject to reimbursement, it is exempt from this procedure – unless otherwise decided by the Ministry of Health, or Infarmed, should this competence be delegated.

As with reimbursement, the therapeutic added value and economic advantage of the product under evaluation must be demonstrated within this procedure for a favourable decision to be issued. That decision further implies the execution of an agreement between Infarmed and the marketing authorisation holder. Just as we have seen in the context of
reimbursement, these agreements also usually establish a maximum sale value for the product and, if this amount is exceeded, the difference should be refunded by the marketing authorisation holder.

The relevance given to the economic advantage factor was further highlighted with the entry into force of MO 391/2019, regarding Methodologic Guidelines for Studies on Economic Evaluation of Health Technologies. Said MO, together with the Guidelines published by Infarmed, should be taken into account by pharmaceutical companies in the context of reimbursement procedures, as well as evaluation procedures applicable to products to be sold to National Health Service hospitals.

Prior to the approval of SiNATS in 2015, the applicable rule regarding medical devices was that the relevant sales price was either free or arose from public procurement procedures, whenever applicable, with the exception of test strips, needles, syringes and lancets destined for persons with diabetes that were subject to a price control and reimbursement regime.

Since then, reimbursement regimes have been set for pressurised inhalers, medical devices for ostomates and medical devices for patients with urinary incontinence and urinary retention.

As a result of SiNATS, the medical devices sector may evolve from a state of relative commercial freedom, in which only the prices of these products were controlled, to one of high regulation. In fact, SiNATS sets out the possibility of administratively determining the sale prices of medical devices and of approving their reimbursement, as well as requiring these products to undergo a prior evaluation procedure, similar to the existing procedure for medicines being considered for use or purchase by National Health Service hospitals. In practice, this general legal framework has rarely been enforced and the medical devices sector continues to be poorly regulated. In September 2017, significant changes were made to SiNATS. Homogeneous groups were created for similar biological medicinal products and a maximum price was enacted for the sale of these products to National Health Service hospitals.

Infarmed’s powers regarding reimbursement have been strengthened. Not only can it modify the terms of reimbursement, but it can also now promote, on its own initiative and at any time, the evaluation or re-evaluation of reimbursement when public health reasons require it.

The rule that medicines covered by the prior evaluation procedure can only be purchased by National Health Service hospitals on an exceptional basis (namely when the patient suffers from a life-threatening disease or risks severe complications and there is no therapeutic alternative), following a specific request from the hospital concerned and prior authorisation from Infarmed, was reiterated and reinforced. This matter was further developed in a regulation approved by Infarmed regarding early access programmes. Subject to this regulation, and in line with what is set out in the law, prior to obtaining a favourable decision

29 Ministerial Order No. 246/2015 of 14 August 2015.
33 Infarmed Resolution No. 80/CD/2017 of 24 October 2017.
within the context of a prior evaluation procedure, medicines should be supplied to National Health Service hospitals free of charge. Supply free of charge is subject to a maximum period, determined by reference to the legal deadline for the procedure.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Final decisions from Infarmed in the context of regulatory, pricing and reimbursement matters are subject to judicial review by administrative courts. The decisions are immediately effective, with the initiation of legal action per se not suspending the effects thereto. Matters of a technical nature are not reviewed by administrative courts, except in cases of manifest error, and administrative courts do not issue technical judgments.

In addition, decisions issued by Infarmed within the context of misdemeanour proceedings initiated for a breach of regulatory provisions are subject to appeal before the judicial courts.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The Medicines Act transposed into Portuguese law the provisions of the Directive on the promotion of medicinal products, including interactions with healthcare professionals. The rule is, therefore, that pharmaceutical companies cannot offer or promise to offer, directly or indirectly, gifts, pecuniary advantages or benefits in kind to healthcare professionals, unless they are inexpensive and relevant to the practice of medicine or pharmacy. For several years there was no legal indication as to what should be considered inexpensive. This state of affairs changed in 2013 when for the first time a decree was published that set the inexpensive limit – as had been foreseen in the Pharmaceutical Industry Association Code of Ethics. Since then, this amount has been increased and is currently set at €60.34

In addition, transparency obligations were enacted in 2013, requiring pharmaceutical companies to notify Infarmed of any payment or offer in excess of €60 made to any individual or legal entity, such as healthcare professionals, medical or scientific associations, patient associations and healthcare institutions. The recipient is also required to validate this notification and the absence of a validation, or a rejection, will be taken to indicate that the notification is correct. This information is publicly available on Infarmed’s website.

Similar rules exist in the context of medical devices. The principle that no offer can be made to healthcare professionals unless of insignificant value and relevant to the healthcare professional’s practice dates back to 2009 and, as from 2017, is subject to the exact same limit as that provided in relation to the promotion of medicinal products: €60.35 Also in 2017, the transparency obligations that apply in the medicines sector were implemented for medical devices. Currently, pharmaceutical companies and medical device companies are subject to the exact same transparency rules.

In early 2014, a specific conflict-of-interest regime for the health sector was approved. The regime prevents, among other things, members of commissions, working groups, juries and National Health Service consultants whose role involves the market access of products (e.g., involvement in pricing and reimbursement procedures, in pharmacoeconomic assessments, in the approval of therapeutic guidelines and purchase procedures) from

34 Order No. 1542/2017 of 31 January 2017.
35 id.
performing functions, either regularly or occasionally, for payment by pharmaceutical companies. A breach of these rules constitutes a misdemeanour punishable with a fine. In addition, in the event of such a breach, the opinions issued or decisions adopted by the commissions, working groups, juries and consultants do not produce any legal effects and any decisions adopted by decision-making bodies based on the same are considered null and void.

In addition, as from 2017, National Health Service establishments and services are prohibited from receiving direct or indirect financial benefits or benefits in kind from pharmaceutical and medical device companies, unless it can be demonstrated that receiving these benefits does not compromise the establishment or service’s exemption or impartiality, and prior authorisation from the Ministry of Health is obtained. Furthermore, educational or scientific events with promotional purposes or sponsored by pharmaceutical or medical device companies cannot take place in National Health Service establishments and services.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

With the exception of damages arising from harm suffered by subjects in clinical studies (see Section II.iii), there is no specific compensation or liability regime applicable to damages arising from harm caused by the use of medicines or medical devices. Product liability claims are therefore subject to the general legal regime concerning liability for defective products.

VII TRANSACTIONAL AND COMPETITION ISSUES

The Portuguese Competition Law prohibits agreements, concerted practices and decisions by associations of undertakings, as well as abuses of a dominant position, capable of preventing, distorting or restricting competition in the Portuguese market. Competition rules apply to pharmaceutical companies, despite these companies being subject to strict regulation in matters such as market access, distribution and pricing.

On June 2017, the Lisbon Court of Appeal confirmed the decision by the Portuguese Competition Authority (PCA) fining the National Association of Pharmacies (ANF) and three undertakings of the same group for an abuse of dominant position in the form of a margin squeeze in the market for the sale of studies based on pharmacies’ commercial data; however, the Court of Appeal reduced the amounts of the fines significantly.

The case dates from 2015, when the PCA concluded an investigation into the market for the sale of pharmacies’ commercial data, a market in which the ANF group is dominant. The PCA decided that, between 2010 and 2013, the prices charged by the ANF group for the sale of pharmacies’ commercial data (the upstream market), when compared to the prices charged by the same group for the sale of market studies based on those data (the downstream market), did not allow an equally efficient competitor active in the downstream market to achieve an adequate margin to cover its production costs. The PCA found that this behaviour had affected not only ANF’s competitors, which were unable to enter or compete in the downstream market, but also consumers purchasing such studies, namely pharmaceutical laboratories.

37 Law No. 19/2012 of 8 May 2012.
When the decision was first challenged, the Competition, Regulation and Supervision Court (TCRS) upheld the PCA decision but reduced the fines to a total of €6.89 million on the understanding that only the turnover related to the markets in which the abuse of dominance took place should be considered for the purpose of calculating fines. On 14 June 2017, the Lisbon Court of Appeal rendered a final judgment in this case, confirming the existence of an abuse, but dismissing the finding that the holding company (Farminveste SGPS) was also liable for the infringement. Since that company had the highest turnover, the fine initially imposed by the PCA was substantially reduced, to a mere €815,000 (a reduction of 92 per cent of the fine imposed by the PCA).

In September 2017, the TCRS confirmed a PCA decision to close an investigation into pharmaceutical companies that had unilaterally decided to refuse to supply a new wholesaler. The TCRS decision established that:

- a distinction could be established between the relevant market for the medicine and the relevant market for the wholesale distribution of the medicine;
- if a company holds a dominant position, a refusal to deal may be justified by objective reasons related to legitimate commercial interests of the supplier;
- a refusal to supply a (potentially) new counterparty to ensure the stability of the existing distribution network may be treated differently from a termination of an existing commercial relationship;
- a refusal to deal may also be considered a discrimination; and
- the effects of the refusal to deal on consumer welfare may be disregarded as long as the wholesale distribution market remains competitive.

During 2019 the PCA continued to engage in a nationwide awareness campaign on the need to fight bid rigging, with a focus on awarding authorities. In 2019, a limited number of first phase merger approvals were decided. One second phase hospital merger clearance was also granted on the grounds of the failing firm defence. In May 2019, the PCA carried out dawn raids in eight locations of nine healthcare providers in Lisbon, Porto and Algarve, following suspicions of anticompetitive practices harmful to consumers’ freedom of choice. No further details have been given on the nature of the infringement.

VIII CURRENT DEVELOPMENTS

Medicines’ shortage in the Portuguese territory has been a critical concern in 2019, leading to significant changes having been enacted in the Medicines Act with regard to supply obligations of all intervenients in the supply chain: MA holders, wholesalers and pharmacies. Guaranteeing patients’ access to medicines in the Portuguese territory is, as from the amendments made by DL 112/2019 to the Medicines Act, a public service essential duty which cannot be limited by any of the intervenients in the supply chain. It is in this context that all intervenients in the supply chain must abide by the principle of continuous service to the community, which entails the obligation to, among others, endeavour, before any player of the supply chain, to ensure satisfaction of a prescription or a supply request. In addition, abusive practices, including discriminatory practices and refusals to supply, that affect the transparency and balance between the several players, impacting, directly or indirectly, the public service duty, are forbidden.

As noted above, wholesalers supply obligations were reinforced, as well as those falling upon MA holders. MA holders have, among other things, an obligation to supply medicinal
products to the other players in the medicines market in a continuous manner and in the necessary quantities to permanently satisfy patients’ needs in the national territory at all times. MA holders are further obliged to monitor, on a regular basis, market needs and the supplies they make, maintaining a permanent dialogue with the other players of the supply chain – an obligation that is independent from and complementary to the supply obligation.

At this stage, the impact of said changes in the distribution systems put in place by pharmaceutical companies is still unclear, with no guidance having been issued by the Portuguese agency, Infarmed. The upcoming year should bring some clarity on this matter, be it with guidance, be it as a result of actions being conducted by the Agency in enforcement of these new rules. Achieving a balance between limited production, ensuring satisfaction of patients’ needs and free movement will certainly be a challenge.

At a different level, public policy continues to be driven by a desire to contain public expenditure on pharmaceuticals. The National Strategy for Medicines and Health Products, approved by the government in October 2016 for the period 2016–2020, is consistent with this purpose. The stated priorities for this period include the systematic re-evaluation of reimbursed medicines, the issuance of therapeutic recommendations, the introduction of changes to the price-referencing system when generics or biosimilars exist, and an increase in the quota of generics and biosimilars. In line with what already exists in the pharmaceutical sector, the proposed State Budget for 2020 foresees the creation of an extraordinary contribution to be applied to entities supplying the National Health Service with medical devices and in vitro medical devices – a contribution that, in practice, equates to a levy upon the sales.

On the other hand, the debt to pharmaceutical companies has reached an historic peak, leading the Portuguese government to announce, in December 2019, a supplement of €800 million for 2020 for the National Health Service and €550 million to reduce the hospital debt value of 2019. The terms under which these reinforcements will take place remain unclear.

Finally, the approval in 2018 of the use of cannabis for medicinal purposes has the potential to be a game changer in certain therapeutic areas, with the recent approval of the placement in the market of products of this nature.
Chapter 23

RUSSIA

Evgeny Alexandrov and Ilya Goryachev

I INTRODUCTION

The Russian life sciences framework is primarily shaped by the Federal Law of 12 April 2010 No. 61-FZ on turnover of medicines (the Pharmaceutical Law) and the Federal Law of 21 November 2011 No. 323-FZ on the principles of healthcare of citizens in the Russian Federation (the Healthcare Law). The Ministry of Healthcare of the Russian Federation (MoH) is the primary regulatory body and its subsidiary, the Federal Service for Surveillance in Healthcare (Roszdravnadzor), is the enforcement authority.

More detailed aspects of life sciences regulation are provided in the by-laws of the government and the MoH (including the good practices).

Aspects of the life sciences industry related to intellectual propery (IP) are codified in the Russian Civil Code.

General issues on state procurement contracts are subject to regulation by the Civil Code, while the detailed regulation on state tenders and procurement contracts (including aspects related to the supply of pharmaceuticals) are provided for in the Federal Law of 5 April 2013 No. 44-FZ on the contractual system for the supply of goods, work and services for meeting state and municipal needs.

Advertising and competition issues are governed by the Federal Law of 13 March 2006 No. 38-FZ on advertising (the Advertising Law) and the Federal Law of 26 July 2006 No. 135-FZ on the protection of competition (the Competition Law), of which the Federal Antimonopoly Service is the regulator.


In addition, because of ongoing regional integration procedures between Russia and neighbouring states within the framework of the Eurasian Economic Union (EAEU), the legislative base for the unified regional drugs market becomes effective.²

---

1 Evgeny Alexandrov is a partner and Ilya Goryachev is a senior lawyer at Gorodissky & Partners Law Firm.
2 On 23 December 2014, the Member States of the EAEU (Belarus, Kazakhstan and Russia) signed the Agreement on unified principles and rules of turnover of medicines within the EAEU (Armenia and Kyrgyzstan have also acceded to this Agreement). Various instruments, aimed at implementing the unified regional market, became effective as of 6 May 2017.
II THE REGULATORY REGIME

i Classification

The Pharmaceutical Law defines medicines as substances or their combinations that have the following classification features:

a capable of contact with the human or animal body, or penetrating into the organs and tissues of the human or animal body;

b applied for the prevention, diagnosis (except for substances that do not make contact with the human or animal body) and treatment of disease, rehabilitation, or preservation, prevention or interruption of pregnancy; and

c obtained from the blood, blood plasma, organs or tissues of a human being or animal, from plants, minerals using synthetic methods or using biological techniques.\(^3\)

Medicines fall into two categories:

a pharmaceutical substances – active ingredients of biological, biotechnological, mineral or chemical origin, with pharmaceutical activity, intended for the manufacturing and production of pharmaceutical medicines and determining their effectiveness; or

b pharmaceutical medicines – pharmaceutical products in dosage form, used for the prevention, diagnosis or treatment of disease, rehabilitation, or preservation, prevention or interruption of pregnancy.

Further classifications defined by the Pharmaceutical Law are: referential (original), generic, biosimilar and interchangeable medicines; biological, immunobiological, biotechnological, gene therapy medicines; botanical and homeopathic medicines, narcotic and psychoactive medicines, radiopharmaceutical drugs; and adulterated and counterfeit medicines.

Medical devices have the following classification features:\(^4\)

a they are instruments, apparatus, tools, equipment, materials and other products, applied for medical purposes, separately or in combination, as well as with other accessories, that are necessary for application, including special software;

b they are intended by the manufacturer for prevention, diagnosis, treatment and medical rehabilitation, health monitoring, medical research, recovery, substitution, change of anatomical structure or physiological functions of the body, or prevention or interruption of pregnancy; and

c their function is achieved not by pharmacological, immunobiological, genetic or metabolic influence.

The new Federal Law No. 180-FZ on biomedical cell products (adopted on 23 June 2016) has been in effect since 1 January 2017. This law regulates development, trials and other aspects of commercialisation of biomedical cell products for treating diseases, as well as citing various types of such products and the biological material necessary for the production of such products.

Occasionally, problems arise because of the distinction between medicines or medical devices and food products (including biological food additives) and cosmetics. In the event of a dispute, it should be borne in mind that all these products have different regulatory

\(^3\) Article 2 of the Pharmaceutical Law.

\(^4\) Article 38 of the Healthcare Law.
regimes, and it is necessary that they be governed by the criteria stipulated in the related legislation. Apart from the specific regulatory issues, there may be different consequences in terms of import duties (e.g., some products may attract a higher rate of state customs duty), advertising requirements and terms of sale. Judicial practice has seen the customs authority, for example, refusing to classify silicone gel as a medical device (classified by the company as a type of bandage), claiming that the gel was cosmetic and therefore subject to the increased rate of import duty; however, in subsequent litigation, the company managed to prove that this gel was, in fact, a medical device, used during the treatment of burns and scars in specialised institutions, which was also confirmed by the related marketing authorisation (MA) from the competent state authority, and by expert opinions. Cosmetic products, pursuant to the effective legislation, are used for rendering a more pleasant appearance to the skin. In this case, the courts agreed with the applicant and revoked the customs authority’s classification decision.5

ii  Non-clinical studies

Pre-clinical trials are held for the use of chemical, physical, biological, microbiological, pharmacological, toxicological and other experimental research on the substance, drug and physical effect, means, methods and technologies of preventive measures, diagnostics and treatment by applying scientific methods of evaluation for the purpose of researching a specific effect and or proof of safety for health.

Pre-clinical trials are governed by good laboratory practice,6 the specific focus of which is, among other things, requirements for research laboratories and related documents.

Use of the information in the results of pre-clinical trials for commercial purposes is not allowed within the first six years without the consent of the owner of the information. However, in the case of generic medicines, the applicant is allowed to use a review of scientific publications on the results of pre-clinical trials of the original product.7

iii  Clinical trials

A clinical trial is defined as the study of diagnostic, therapeutic, prophylactic and pharmacological features of the drug during its use on human beings and animals, including the processes of absorption, distribution, excretion and changes by scientific methods to obtain evidence for the safety, quality and efficacy of the drug, data on adverse reactions in the human or animal body and the effect of its interactions with other drugs and food or feed.8 The Pharmaceutical Law also encompasses multi-institutional, international multi-institutional and post-registration clinical trials.

Clinical trials are undertaken upon filing an application for drug registration and approval from the quality and ethics committee.9 Compliance with the rules of clinical practice as approved by the MoH is obligatory.10

---

5 Meda Pharmaceuticals Switzerland GmbH v. the Russian Federal Customs Service (Resolution of the Federal Commercial Court of the Moscow Region of 22 February 2013, Case No. 40-72336/12-145-16).
6 Order of the Russian MoH of 1 April 2016 No. 199n.
7 Section 10, Article 18 of the Pharmaceutical Law.
8 Section 41, Article 4 of the Pharmaceutical Law.
9 Article 39 of the Pharmaceutical Law.
10 Order of the Russian MoH of 1 April 2016, No. 200n.
Use of the information in the results of pre-clinical trials for commercial purposes is not allowed within the first six years without the consent of the owner of the information.

For generic drugs, full-scale clinical trials may not be undertaken – in this case the applicant is allowed to submit bioequivalence trial results.

The management of a clinical trial may be exercised by the sponsor itself, educational facilities or research institutions, but clinical trials as such should be undertaken in medical institutions duly accredited by the MoH in accordance with the requirements as approved by the Russian government. Relations between the clinical trial authorisation (CTA) holder and the accredited medical institution are regulated by a private contract between them. This contract should contain certain essential features: the terms of the trial; an indication of the total costs, including remunerations to the researcher (co-researcher); and a description of the form of report for submission to the MoH.

The chief officer of the medical institution appoints the researcher (co-researcher), who selects patients for the clinical trials. Patients should participate in the trials voluntarily.

The Pharmaceutical Law provides the outline of the requirements that are set out for patients. Requirements are also set out regarding the information that should be included on the written consent form completed by the patient, namely:

1. details of the drug, its safety and risks;
2. the terms of participation;
3. what the patient should do in the event of side effects;
4. insurance conditions; and
5. confidentiality guarantees.

Informed consent is obligatory, which is confirmed by the patient’s signature (or the signature of his or her duly authorised representative) on an information list for the patient. Patients have the right to terminate their participation in a trial at any time.

Minors may act as patients only with the written consent of their parents and on condition that the trial is specifically focused on the aspects of using the drug on minors.

People with mental afflictions may participate in clinical trials for drugs intended for the treatment of mental afflictions on the condition that their representatives give their written consent.

Certain sections of the population cannot participate in clinical trials, such as:

1. law enforcement officers;
2. military officers (except for trials of drugs developed specifically for use in warfare, emergency situations or other similar circumstances);
3. pregnant women as well as breastfeeding women (except for trials of drugs intended only for such women in compliance with risks-mitigating requirements);
4. orphaned children; and
5. imprisoned people.

---

11 Regulation of the Russian Government of 3 September 2010, No. 683.
12 Article 43 of the Pharmaceutical Law.
The CTA holder is obliged to insure the patients against death (cover of 2 million roubles) or disability (cover ranges from 300,000 to 1.5 million roubles, depending on the degree of impairment to health) as result of the clinical trial. A patient cannot participate in a trial should the CTA holder fail to obtain insurance for that person.\(^{13}\)

Clinical trials results must be recorded and safety reporting is obligatory. Should the trial be terminated, the CTA holder must inform the MoH of the reasons for the termination.

iv Named-patient and compassionate use procedures

In Russia, the general rule is that an MA is required for administering medicine, although the following exceptions exist when an MA is not required:

\(a\) drugs produced by pharmacies according to the prescriptions and requirements of medicinal institutions;

\(b\) drugs purchased by individuals abroad and intended for personal use;

\(c\) drugs imported to Russia for providing medical help owing to the life-saving necessity of the patient based on the regulator’s decision;

\(d\) drugs imported to Russia based on the regulator’s permission for holding clinical trials or for holding examinations for state registration;

\(e\) pharmaceutical substances;

\(f\) radiopharmaceutical drugs produced directly by medical institutions as per the established regulations; or

\(g\) drugs manufactured for export.\(^{14}\)

v Pre-market clearance

Marketing of a drug is allowed only once the MA is approved (except for those circumstances described in Section II.iv). The stages of the pre-marketing procedure are as follows:

\(a\) Development stage: the search for new pharmaceutically active ingredients, their subsequent examination, pre-clinical trials and development of manufacturing technologies. It is not possible to determine the specific timing of this stage, as it depends on the activity of the sponsor.

\(b\) State registration: the application for CTAs (if necessary) and examination of the quality, efficacy and safety of the drug. The general timing for original drugs is approximately 160 business days (excluding the time for clinical trials) and 80 days for medicines under the fast-track examination procedure. The following stages may be discerned:

- the applicant files an application with the MoH and the registration dossier is prepared;
- the registration dossier is reviewed by the specialised institution by the MoH, considering whether the CTA may be issued – an ethics committee also participates at this point;
- based on the results of this examination and ethics committee review, a decision on the issuance of the CTA by the MoH;
- the CTA holder launches clinical trials (by entering into an agreement with the accredited medical institution, arranging insurance for the patients, etc.);
- the results of the clinical trials are submitted to the MoH;

\(^{13}\) Article 44 of the Pharmaceutical Law.

\(^{14}\) Article 13 of the Pharmaceutical Law.
• the examination of the drug’s quality, efficacy and safety, as well as a risk-benefit analysis is undertaken by the specialised institution approved by the MoH; and
• based on the results of the examination, the MoH issues the MA, requests a re-examination or refuses to issue the MA.

Similar stages exist for the registration of medical devices, depending on their class.15

**Special procedures**

An expedited (fast-track) procedure is applicable to the following types of drugs:

- orphan medicines;
- the first three medicinal products for registration in Russia as generic products; and
- medicines for use exclusively by minors.

The fast-track procedure does not apply to:

- biosimilar medicines;
- original medicines (except for orphan medicines);
- generic medicines, except for:
  - the first three medicinal products for registration in Russia as generic products; and
  - medicines for use exclusively by minors;
- new combinations of previously registered medicines; and
- medicines, registered previously, but manufactured in other pharmaceutical dosage forms in accordance with the list of pharmaceutical dosage forms and in the new dosage.

For generic drugs, reference to a review of scientific publications on the results of pre-clinical trials of the original product (instead of pre-clinical trials of a generic drug) and bioequivalence trials (instead of clinical trials) is allowed.16

All the aforementioned tests (quality, safety, etc.) are undertaken during the expedited procedure, except for clinical trials, and the requirements during the examinations are the same as in the general procedure.

**Fees**

The specific fees depending on the type of the CTA or depending on the medicine at issue, as well as depending on the registration forum (Russia or EAEU) are provided in the Russian Tax Code.17 The following are examples of applied fees: 110,000 roubles for Russian examination to issue the CTA; and 325,000 roubles for risk-benefit examination to issue the MA.

For medical devices, the fees for examination, depending on the class, may range from 45,000 to 115,000 roubles. The fee to issue an MA is 7,000 roubles.18

---

16 Articles 18 and 26 of the Pharmaceutical Law.
17 Article 333.32.1 of the Russian Tax Code.
18 Article 333.32.2 of the Russian Tax Code.
vi Regulatory incentives

**Patent protection**

Pharmaceutical products may be protected by a substance patent, a process patent or a use patent.\(^{19}\) Patent protection is effective for 20 years starting from the priority date. Regular renewals are required to keep the patent in force.

The patentee has the exclusive right to import the patented product into Russia, manufacture, use, offer for sale, sell or otherwise commercialise the product; this matches with the patentee’s right to forbid other persons from infringing that exclusive right.

The list of activities that fall under the scope of a patent is non-exhaustive. The following types of activities are specifically mentioned:

- **(a)** importation into Russia, manufacturing, working, offering for sale, sale or other commercialisation or storage of the product according to the purpose for which the subject of the patent is used;
- **(b)** the same actions in (a) in respect of a product, manufactured directly from the patented process;
- **(c)** the same actions in (b) in respect of:
  - a device, if such a device automatically functions using the patented process; and
  - a product working in accordance with the purposes indicated in the manufacturer’s claims; and
- **(d)** implementation of a process in which the invention is used, including by means of using the process.

Research on a product or process in which the patent is used, or experimentation on it, is not a patent infringement, but if the defendant’s activities extend beyond the scope of research or experimentation (e.g., the defendant starts commercialisation), its activities may be considered an infringement.

In judicial practice, there are examples where courts ruled that submission of a drug for an MA before the expiry of a patent does not as such constitute infringement of a patent, but further commercialisation of a drug before the patent expires is viewed as an infringement.\(^{20}\) Nevertheless, if the generic MA or maximum sale price registration is filed some time prior to expiry of the patent, the patentee may argue that there is a threat of patent infringement, and an example of this has been seen in judicial practice, where the court recognised the activities of early filing of an MA and subsequent maximum sale price registration as constituting a threat of infringement.\(^{21}\)

If the court adjudicates that the commercialisation of a specific drug is a breach of the patent legislation, the MoH is obliged to revoke the MA.\(^{22}\)

---

\(^{19}\) Article 1350 of the Russian Civil Code.


\(^{22}\) Article 32 of the Pharmaceutical Law.
**Extension of patent protection**

Extension of a pharmaceutical patent is possible for no more than five years if more than five years elapse between the filing date and the date when the MA is issued.

**Data exclusivity**

It is not permitted to use (without consent), for commercial purposes, the information in the results of pre-clinical trials and clinical trials, submitted by an applicant for the original product within six years of the registration of the original medicine in Russia.

It is permitted to file for the MA four years after registration of the original product (three years for biosimilars). Non-compliance with the term results in the MoH dismissing a generic drug application.

**vii Post-approval controls**

The MoH and Roszdravnadzor are competent for monitoring the safety of drugs. There are specific rules on monitoring safety, as well as guidelines introduced by the Roszdravnadzor with regard to in-house monitoring of drugs safety.

As part of pharmacovigilance, the MA holder and other entities involved in product commercialisation are obliged to report any side effects not listed in the instructions for use of the drug, serious adverse reactions, unexpected adverse reactions in the application of drugs, and the peculiarities of drug interactions with other drugs that have been identified in clinical trials. The MoH is entitled to suspend commercialisation of a product in the event of any such report.

Furthermore, as of 1 January 2016, the MA holder is obliged to report regularly to the regulator with the results of pharmacovigilance.

The MA may be revoked in the following cases:

- if, as result of state safety monitoring, it is evident that a risk to health exists;
- a voluntary revocation application is filed;
- if an MA was issued for five years, but upon expiry of that term no confirmation of state registration exists;
- in the event that the registration dossier needs to be amended, but the MA holder fails to respond to the related request within 30 days;
- if an MA is issued for a trade name that has already been registered for another drug with a different combination of active ingredients;
- if one and the same drug has been registered under various trade names;
- if a court renders a decision on infringement of IP rights during commercialisation;
- if the drug is not commercialised within three years;
- when there has been a failure to comply with pharmacovigilance obligations; or

---

23 Article 1363 of the Russian Civil Code.
24 Article 18 of the Pharmaceutical Law.
26 Articles 5, 9 and 64 of the Pharmaceutical Law.
28 Article 18 of the Pharmaceutical Law.
29 Article 32 of the Pharmaceutical Law.
if there has been a refusal to amend an instruction for use if the risk of taking the drug exceeds the effect of using the drug.

Any amendments or changes regarding the MA holder should be notified to and approved by the MoH.

viii Manufacturing controls
The manufacturing of a drug is allowed once the appropriate licence is obtained by the manufacturer in Russia; licence control is exercised regularly.\textsuperscript{30}

The manufacturing procedure should comply with the rules of good manufacturing practice approved by the Ministry of Industry and Commerce,\textsuperscript{31} which set out specific technical requirements depending on the type of pharmaceutical product.

The manufacturer is obliged to develop internal regulations that include a list of the pharmaceutical substances and auxiliary ingredients, the data on the equipment used in manufacturing and a description of the technological process and control methods for each stage of manufacturing, as well as to appoint a responsible authorised person (meeting qualification requirements) that confirm compliance of the manufactured medicines with the MA and good manufacturing practice.

ix Advertising and promotion
Advertising and promotion of drugs (and the following points (c) to (j) also relating to medical equipment) is subject to general advertising and competition rules (such as restrictions on unfair advertising and unfair completion, including incorrect comparisons)\textsuperscript{32} and specific restrictions and prohibitions,\textsuperscript{33} under which it should not:

\begin{enumerate}
  \item be addressed to minors;
  \item cite specific cases of cure or improvement of health (not applied to advertising intended only for medical professionals in specialist publications or events);
  \item use expressions of gratitude by specific individuals (not applied to advertising intended only for medical professionals in specialist publications or events);
  \item invoke the results of obligatory clinical trials or examinations as evidence of any advantages of the drug;
  \item contain the assertion that consumers have certain diseases or health problems;
  \item give the impression that a healthy person should use the drug (not applied to advertising of preventive drugs);
  \item give the impression that by using the drug, it is not necessary to consult a doctor;
  \item guarantee favourable effects of the drug, its safety and effectiveness, and the absence of side effects;
  \item imply that the drug is a biologically active additive or food supplement or any other product that is not a medicine; and
  \item imply that safety or effectiveness of the drug is explained by its natural origin.
\end{enumerate}

\textsuperscript{30} Article 45 of the Pharmaceutical Law.
\textsuperscript{31} Order of the Russian Ministry of Industry and Commerce of 14 June 2013, No. 916.
\textsuperscript{32} Article 5 of the Advertising Law; Chapter 2.1 of the Competition Law.
\textsuperscript{33} Article 24 of the Advertising Law.
The description of the features and characteristics of the drug should not go beyond the scope of the instructions for use. A special notice is also required that instructs the user to read the instructions for use and of the need to consult a doctor (except for advertising aimed at medical professionals).

The advertising of prescription medicines or medical devices for use where special knowledge is required is allowed only if the advertising is aimed at professionals (i.e., only at the related conferences or in specialist publications). Promotional events at which drug samples that contain narcotic and psychotropic ingredients are distributed are forbidden.

Special rules on promotional communications between representatives of pharmaceutical companies and hospital or pharmacy employees are also established to prevent conflicts of interest (such as a restriction on the distribution of promotional merchandise among doctors).34

Recent years have seen the increasing role of self-regulation between advertisers in the life sciences industry. Namely, in 2018 the Recommendations on advertising on over-the-counter drugs have been signed by representatives of the industry under approval from the Federal Antimonopoly Service.35 The Recommendations clarify certain problematic issues on over-the-counter drugs' advertising and consolidate the previous enforcement experience.

x Distributors and wholesalers
The initial distribution of drugs and medical devices is exercised by the holders of the MA and the related licences (to manufacture drugs and medical devices). Wholesale and retail sales of drugs are subject to licensing (sales of medical devices are not licensed).36

In the sale of drugs, it is possible to apply for both wholesale and retail licences.

As part of the government incentive to have an increased level of localised manufacturing, restrictions on state procurement of foreign pharmaceuticals were imposed at the end of 2015.37

Furthermore, the wholesale and retail of medicines are subject to good distribution practices and good pharmacy practices, and compliance with these practices is subject to state control.38

xi Classification of products
A distinction is made between drugs that may not be sold to end consumers without a prescription from a doctor (prescription drugs) and drugs that may be sold over the counter. The MoH regulates the procedure of doctors issuing prescriptions.39 There is also a limit on the total number of medicines that may be covered by one prescription.40 Classification of a drug as a prescription drug affects its advertising in that it is only allowed if aimed at professionals.

34 Articles 74 and 75 of the Healthcare Law.
38 Article 5 of the Pharmaceutical Law.
39 Order of the Russian MoH of 14 January 2019, No. 4n.
40 Regulation of the Russian MoH of 12 February 2007, No. 110.
xii Imports and exports

The import of drugs into Russia is regulated in detail by the government within the framework provided by the Pharmaceutical Law.41 The precondition of importation is that there should be a certificate from the manufacturer confirming the compliance of the drugs being imported with the requirements of the pharmacopoeia monograph or — in its absence — with the regulatory documents.

There are specific categories of entities that may import drugs (such as sponsors, wholesale companies and medical institutions). Importation for personal needs by individuals is also allowed.

As a general rule, there should be a Russian MA for imported drugs, but exceptions are made for clinical trials and their import by individuals for personal use, or cases when there is a decision by the regulator to allow use of a specific medicine for a specific individual. A permit to import, issued by the MoH, is generally required.

The export of drugs from Russia may be exercised without restriction, although a special procedure is provided for drugs being exported for use in humanitarian aid or emergency situations.43

xiii Controlled substances

Narcotics and psychotropic drugs are subject to detailed control over commercialisation (manufacturing and storage) and use. Every aspect of their commercialisation is subject to specific requirements as set out in the Pharmaceutical Law. The list of substances to which this applies is provided by the government.44

xiv Enforcement

While the MoH is the main regulatory authority, enforcement is mainly undertaken by Roszdravnadzor. Monitoring is exercised and compliance with licence requirements is observed. Penalties may range from administrative fines to criminal punishments. Revocation or suspension of product commercialisation may also take place as a sanction.

III PRICING AND REIMBURSEMENT

State regulation of prices for essential drugs is undertaken by the government and the list of drugs is approved annually. The prices for these listed drugs are subject to state registration.46

The executive authorities of the constituent parts of the Russian Federation are entitled to regulate flat wholesale and retail benefits with regard to the actual prices for end users.47

---

41 Regulation of the Russian Government of 29 September 2010, No. 771.
42 Article 47 of the Pharmaceutical Law.
43 Article 47 of the Pharmaceutical Law.
45 Article 60 of the Pharmaceutical Law.
46 Articles 61 and 62 of the Pharmaceutical Law.
47 Article 63 of the Pharmaceutical Law.
IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Decisions made by the regulatory authorities may be challenged in the commercial courts, and these cases are heard by judges specialising in administrative cases. The procedure is general, as it is used for other cases when state authority decisions are challenged; the time limit for filing an action is three months after the decision was issued.48

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The following restrictions and prohibitions are imposed on prescribers in their relations with medical representatives:49

a. gifts and money cannot be received from manufacturers, MA holders and other entities participating in the commercialisation drugs (except for remunerations as result of clinical trials or scientific and educational activities);

b. no undertakings to provide recommendations should be made;

c. samples of products cannot be accepted for patients’ use (except for use in clinical trials);

d. it is forbidden to provide incorrect or misleading information concerning alternatives to prescribed drugs;

e. it is forbidden to entertain medical and pharmaceutical representatives (except in connection with clinical trials or except for conferences undertaken by the administration of the hospital); and

f. doctors should not write prescriptions for drugs for patients on the advertising materials of specific drugs or on printed materials bearing the trade names of specific drugs.

With regard to payers, the main aspects are in the field of advertising and prohibition of passing-off, as well as the requirement for package marking.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

In the event that damage results from the use of drugs, the manufacturer is liable should either of two conditions be present:

a. the drug was used according to its purpose as provided in the instructions for use and the damage was caused because the drug was substandard; or

b. the damage was caused when the instructions for use contained incorrect information.

Wholesalers and retailers may be also held liable if damage resulted from a breach of the requirements for sale.50

In addition, commercialisation of substandard (off-grade), falsified or counterfeit medicines may give rise to criminal liability.51

---

48 Chapter 24 of the Russian Commercial Procedure Code.
49 Article 74 of the Healthcare Law.
50 Article 69 of the Pharmaceutical Law.
51 Article 238.1 of the Russian Criminal Code.
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law
Patent-related agreements are exempted from antitrust control, but this does not preclude risk estimation in the event of the patent-related agreements containing provisions going beyond the scope of the patent transaction.

Further, a patentee holding the dominant position who unduly refuses to enter into a supply agreement with another company, invoking its exclusive right to a patent or a trademark used with regard to the drug, risks facing liability.

ii Transactional issues
Corporate transactions, including mergers and acquisitions and strategic partnerships, are subject to general antitrust control based on the economic criteria.

VIII CURRENT DEVELOPMENTS
In 2018 the MOH initiated public discussion with regard to the introduction of a 'patent-linkage'-alike system for registration of medicines. The basic suggestion by the MOH is to introduce an obligation on the MA applicant to provide a written commitment that MA registration will not infringe third parties’ trademarks and patents. The MOH also suggests indication of patents that protect the medicine submitted for state registration. In the case of generic medicines – if the original medicine is under patent protection – the MOH suggests grant of the MA with delayed effect of term – that said the MA for a generic medicine will become effective upon expiry of the patent for the original medicine.

The initiative of the MOH also implies creation of the Unified register of pharmacologically active ingredients, protected with invention patents. It is suggested that the register will be maintained by the PTO and will help the MOH to determine the date of effect of the MA for the generic medicine.

Over recent years among the legislative trends are laws that amend the quality control system in drugs manufacturing. That said, on 29 November 2019 new legislative amendments came into force providing more detailed regulation over entry of medicines into circulation. Amendments have also been introduced with regard to the administrative procedures dealing with maximum sale price registrations applied to essential and indispensable drugs.

Practical developments on the launch of telemedicine services took place in 2019, including the launch of national online (electronic) prescriptions for drugs.

The procedure for building a unified pharmaceutical market in the EAEU continues to be of significant importance, and the adoption of new regulations is under way.

Among other current developments are preparations for the launch of mandatory marking of medicine packaging, starting from 1 July 2020, to monitor the life cycle of medicines on the market (the related test launch of obligatory marking of medicines already took place in 2018).

---

52 Section 4, Articles 10 and 11 of the Competition Law.
53 Resolution of the 9th Commercial Appellate Court of 6 October 2014 No. 09AP-34696/2014; Case No. A40-42997/2014.
54 Chapter 8 of the Competition Law.
Discussions are continuing regarding initiatives aimed at introducing antitrust control over certain aspects of using IP rights. The Federal Antimonopoly Service has continued to pay close attention to the advertising of pharmaceuticals. That is combined with the increasing trends on self-regulation in advertising, supported by the FAS, which may also affect consideration of life sciences advertising breaches to the extent of establishing more in-depth industry rules.
Chapter 24

SINGAPORE

Melanie Ho and Chang Man Phing

I INTRODUCTION

The life sciences industry in Singapore is regulated by the Health Sciences Authority (HSA),\(^2\) operating under the oversight of the Singapore Ministry of Health (MOH). Regulation of health products such as pharmaceuticals, cosmetics, medical devices fall under the purview of the HSA.

The regulatory framework for medicinal and other health-related products consists of the Health Products Act (Chapter 122D) (HPA), the Medicines Act (Chapter 176) (MA), the Medicines (Advertisement and Sale) Act (Chapter 177), the Poisons Act (Chapter 234) and the Sale of Drugs Act (Chapter 282), with subsidiary legislation and guidelines as promulgated by the HSA, the MOH and the Singapore Medical Council (SMC), which regulates registered medical practitioners.\(^3\) In particular, the SMC Ethical Code and Ethical Guidelines (ECEG 2016) set ethical benchmarks for medical practitioners.

Human biomedical research is regulated by the Human Biomedical Research Act (HBRA)\(^4\) and subsidiary legislation, namely, the Human Biomedical Research Regulations 2017, the Human Biomedical Research (Restricted Research) Regulations 2017, the Human Biomedical Research (Exemption) Regulations 2018, the Human Biomedical Research (Tissue Banking) Regulations 2019, the Human Biomedical Research (Requirements for Appropriate Consent – Exemptions) Regulations 2019, and the Human Biomedical Research (Tissue Banking and Notification – Exemption) Regulations 2019. The legislation is supplemented by the Ethics Guidelines for Human Biomedical Research (the Ethics Guidelines) of the Bioethics Advisory Committee (BAC).

Competition issues arising out of the pharmaceutical and medical sector are regulated under the Competition Act (Chapter 50B). Privacy issues arising out of clinical trials are regulated under the Personal Data Protection Act\(^5\) and the relevant subsidiary legislation of the MA and HPA.\(^6\)

---

1 Melanie Ho and Chang Man Phing are partners at WongPartnership LLP.  
2 A body established under the Health Sciences Authority Act (Chapter 122C).  
3 Act No. 29 of 2015.  
4 Act No. 26 of 2012.  
5 Health Products (Clinical Trials) Regulations 2016 and Medicines (Clinical Trials) Regulations 2016.
II THE REGULATORY REGIME

Control of all medicinal products, devices and substances falls under the purview of the HSA. The HPA governs the regulation of therapeutic products, medical devices and cosmetic products as part of the HSA’s continuing efforts to consolidate the regulation of health products into one Act. The MA regulates medicinal products (such as cell, tissue and gene therapy products and complementary health products,7 including traditional medicines, homeopathic medicines and quasi-medicinal products). The Poisons Act regulates specific substances (excluding use in medicines supplied by medical practitioners),8 whereas the Sale of Drugs Act regulates the sale of any substance or mixture of substances used as a medicine.

Separately, healthcare professionals are governed by their respective professional boards which fall under the auspices of the MOH. Each profession is self-regulated and the respective professional boards have issued their own guidelines and practice circulars to supplement the statutory framework.9 To ensure consistency across the regulation of all healthcare professionals, the MOH announced that a single Secretariat of Healthcare Professional Boards (SPB) will be established to oversee the secretariat and operational functions of 11 professional boards with effect from 1 January 2020.10 The SPB is intended to streamline the regulatory framework for all healthcare professionals to bring about ‘better efficiency and productivity across all the professional boards’.11

In January 2019, the SMC, in consultation with the MOH and the Ministry of Law, has appointed a committee comprising members from the medical and legal fraternities to review sentencing sanctions and principles in disciplinary proceedings involving medical professionals.12 In March 2019, another committee was set up by the MOH comprising medical and legal professionals to look into and provide appropriate recommendations on the taking of informed consent and the SMC’s disciplinary process.13 The outcomes of these reviews were published on 28 November 2019.14

---

8 The Schedule (Poisons List) to and Section 7 of the Poisons Act.
9 Examples of Professional Boards are the Singapore Medical Council (SMC), Singapore Dental Council (SDC), Singapore Nursing Board (SNB), Singapore Pharmacy Council (SPC), Traditional Chinese Medicine Practitioners Board (TCMPB), Optometrists and Opticians Board (OOB), Family Physicians Accreditation Board (FPAB), Specialists Accreditation Board (SAB), Dental Specialists Accreditation Board (DSAB), and Pharmacy Specialists Accreditation Board (PSAB).
13 MOH Press Release ‘MOH appoints members of Workgroup to review the taking of informed consent and SMC’s disciplinary process’ dated 14 March 2019.
Classification

As mentioned above, the regulatory regime classifies relevant products into the following categories: medicinal products used to treat or prevent disease, to diagnose disease, for contraception, to induce anaesthesia, etc.;\textsuperscript{15} medical devices used for the diagnosis, prevention, monitoring, treatment or alleviation of disease not through pharmacological, immunological or metabolic means;\textsuperscript{16} cosmetic products used on the external parts of the human body to clean, perfume, change appearance, etc.;\textsuperscript{17} therapeutic products used for a therapeutic, preventative, palliative or diagnostic purpose that is constituted by certain specified chemical and biological active ingredients, etc.;\textsuperscript{18} complementary health products, including Chinese proprietary medicines and traditional medicines.\textsuperscript{19}

Food and supplements of a food nature (including food-based complementary health products) fall under the purview of the Singapore Food Agency (SFA) and regulated under the Sale of Food Act (Chapter 283). If there is ambiguity in classifying a product as a food or health product, clarification should be sought from either the HSA or the SFA, depending on whether the product appears to be part of a daily diet, taken as supplement to a diet, or taken for medicinal purposes.\textsuperscript{20}

For devices used primarily for aesthetic purposes (e.g., lasers for skin tightening and dermabrasion), the Aesthetics Practice Oversight Committee (APOC) has revised its Guidelines of Aesthetic Practices (the APOC Guidelines),\textsuperscript{21} which doctors have to abide by to carry out any of the procedures listed therein. The list of invasive treatments that non-specialists can perform has been reduced under Table 1 of the APOC Guidelines, compared to its predecessors in 2008. Additionally, the list of invasive surgeries, previously under List A, is now reflected in Table 2, with a clear list of specialists who can perform the procedure. List B procedures under the 2008 Guidelines are now disallowed unless performed in the context of a formal and approved clinical trial.\textsuperscript{22} Doctors intending to perform procedures or use devices outside Table 1 or 2 have to apply to the APOC to include the procedure or device under Table 1 or 2 before doing so.\textsuperscript{23}

\begin{itemize}
\item[15] Medicines Act, Section 3.
\item[16] Paragraph 1 of the First Schedule to the HPA.
\item[17] Paragraph 2 of the First Schedule to the HPA.
\item[18] Paragraph 3 of the First Schedule to the HPA.
\item[21] Aesthetic Practice Oversight Committee, Guidelines on Aesthetic Practices for Doctors (updated October 2016). The new Guidelines do not have retrospective effect. Incidents that occurred before 1 August 2016 will have to be referred to the 2008 Guidelines on Aesthetic Practices.
\item[22] The MOH’s letter to all licensees and managers of medical and dental clinics entitled ‘Revised Regime of Non-List A Aesthetic Procedures’ dated 1 March 2015.
\end{itemize}
ii Non-clinical studies

In vitro human biomedical research

The HBRA, which regulates the conduct of human biomedical research, first came into force on 1 July 2016 (the first phase) and was enforced in stages. On 1 January 2017, provisions prohibiting the commercial trading of, and the advertising of commercial trading of, human tissue came into force (the second phase). Notably, commercial trading of human tissue was outlawed and offenders may be fined up to S$100,000 or imprisoned for up to 10 years, or both.24 In the third phase, which commenced on 1 November 2017, provisions on the regulation of human biomedical research took effect.25 These include the taking of consent, and the constitution of institutional review boards (IRBs)26 in relevant research institutions as part of the system of ‘self-accountability’ for reviewing research proposals.

The next phase (the fourth phase) came into force in 2019. Under this phase, provisions on the regulation of human tissue research are now effective.27 Subsidiary legislation regulating tissue banking includes the Human Biomedical Research (Tissue Banking) Regulations 2019 and the Human Biomedical Research (Tissue Banking and Notification – Exemption) Regulations 2019. The legislative framework serves to regulate, among other things, the duties of tissue banks, such as to notify the Director of Medical Services of its activities,28 to maintain a record containing a detailed description of the condition of each tissue under the tissue bank’s supervision and control,29 to establish a system to ensure the quality and safety of any tissue under the tissue bank’s supervision and control,30 and restrictions on disclosure of information on tissue donors.31

Other provisions of the HBRA relate to codes of practice and ethics, and enforcement powers with respect to activities that contravene the HBRA or any relevant codes of practice or ethics32 or are contrary to public interest.33

Subsidiary legislation regulating human biomedical research includes the Human Biomedical Research Regulations 2017, the Human Biomedical Research (Restricted Research) Regulations 2017 and the Human Biomedical Research (Requirements for Appropriate

24 Section 32 of HBRA. Section 32 of the HBRA does not apply to the trading of human organs and blood, which is separately prohibited under Section 14 of the Human Organ Transplant Act (Chapter 131A). See also Public Prosecutor v. Tang Wee Sung [2008] SGDC 262.
25 Sections 6–31, 65 and 68, and the Third, Fourth and Fifth Schedules to the HBRA.
26 Institutional review boards (IRBs) are made up of no fewer than five individuals meeting the qualifications under Regulations 11 and 12 of the Human Biomedical Research Regulations 2017. The appointed IRB is to review the researchers and research proposals to ensure they comply with the HBRA 2015 and its subsidiary legislation. See also https://www.moh.gov.sg/docs/librariesprovider5/legislation/hbra-faqs-17-apr-2018.pdf.
27 Human Biomedical Research Act 2015 (Commencement) Notification 2019 provides that Sections 34–36, 37–39 and 64 of the HBRA came into operation on 1 November 2019.
28 Sections 34, 35(1) and 36 of the HBRA; Regulations 4-14 of the Human Biomedical Research (Tissue Banking) Regulations 2019.
29 Section 35(2) of the HBRA; Regulation 22 of the Human Biomedical Research (Tissue Banking) Regulations 2019.
30 Section 35(2) of the HBRA; Regulation 26 of the Human Biomedical Research (Tissue Banking) Regulations 2019.
31 Section 39 of the HBRA; Regulation 16 of the Human Biomedical Research (Tissue Banking) Regulations 2019.
32 Section 42(1)(b) of HBRA.
33 Section 42(1)(d) of HBRA.
Consent – Exemption) Regulations 2019. Read with the HBRA, this legislation cumulatively regulates the conduct of human biomedical research, and subjects certain types of research to stricter controls, such as research involving human eggs or embryos, human-animal combination embryos, and the introduction of human stem cells (pluripotent or not) into animals. Ethically unacceptable human biomedical research, such as the implantation of human-animal embryos into both human beings and animals, is also prohibited under the legislation.

The BAC (appointed by the Singapore Cabinet) released its Ethics Guidelines for Human Biomedical Research in June 2015. These Ethics Guidelines do not have statutory force, but operate alongside the more recent HBRA subsidiary legislation to provide guidance and emphasise the fundamental principles of solidarity, respect for persons, justice, proportionality, sustainability, beneficence and research integrity.

For the creation of human embryos under the Human Cloning and Other Prohibited Practices Act (Chapter 131B), the development of a human embryo created other than via fertilisation of a human egg by human sperm, for a period of more than 14 days, is prohibited.

Written approval from the Director of Medical Services must be obtained for all research involving human embryos, human oocytes and human-animal combination gametes or embryos.

Animal models

Any research facility that uses animals for scientific purposes must obtain a licence from the Animal & Veterinary Services (AVS). Further, the research facility must comply with the National Advisory Committee for Laboratory Animal Research Guidelines on the Care and Use of Animals for Scientific Purposes, and allow AVS to carry out inspection of the research facilities. The facility must also establish an Institutional Animal Care and Use Committee to oversee and evaluate its animal care and use programmes.

Singapore adheres to the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data scheme. Acceptance of this harmonising scheme amounts to an endorsement that Singapore-generated research data complies with the OECD’s Principles of Good Laboratory Practice. Such data can be accepted automatically by other OECD countries, facilitating the sharing of research.

34 Fourth Schedule to the HBRA.
35 Third Schedule to the HBRA.
36 BACs Ethics Guidelines (June 2015) at Paragraphs 2.3–2.17.
37 Section 7 of Human Cloning and Other Prohibited Practices Act.
38 Section 31 read with the Fourth Schedule to the HBRA and Regulations 3 and 4 of the Human Biomedical Research (Restricted Research) Regulations 2017.
39 Human oocytes include those obtained from excised ovarian tissue.
40 Human-animal combination gametes or embryos are those containing both human and animal genetic or non-genetic material and includes embryos created by the fertilisation of human and animal gametes.
41 Rule 7(1) of Animal & Birds (Care and Use of Animals for Scientific Purposes) Rules.
iii Clinical trials

**Therapeutic and medicinal products**

The Health Products (Clinical Trials) Regulations 2016 introduced a new assessment regime for clinical trials. A clinical trial of a therapeutic product may either require a clinical trial authorisation (CTA) or a clinical trial notification (CTN), depending on the risk classification of the therapeutic product. A high-risk therapeutic product is a product that is locally unregistered or its use is unapproved, and therefore requires a CTA. Low-risk therapeutic products only require a CTN, as the products have already been reviewed by the HSA for product registration. A CTN can be obtained in a shorter time than a CTA because low-risk therapeutic products undergo a simplified regulatory screening and verification process. For the clinical trial of medicinal products, a Clinical Trial Certificate (CTC) in accordance with the Medicines Act is still necessary.

Under the CTC and CTA/CTN regimes for medicinal products and therapeutic products respectively, a sponsor is mandatory. Insurance must be maintained to provide for compensation in the event of injury or loss.

**Medical devices**

A CTC or a CTA/CTN is not necessary for studies assessing the safety, performance or effectiveness of a medical device. Prior approval by each institution’s IRB is, however, still required. The Health Products (Medical Device) Regulations (HP(MD)R) also regulate the use of medical devices in clinical trials.

**Ethical considerations**

The ECEG 2016 stipulates that a doctor must not offer patients remedies that are not generally accepted by the profession, except in the context of a formal and approved clinical trial. The term ‘remedy’ encompasses a broad range of treatments, including the use of...
medical devices.\textsuperscript{50} Under the ECEG 2016, doctors may offer innovative therapy\textsuperscript{54} to patients in desperate or dire situations, and where conventional therapy is unhelpful.\textsuperscript{52} Patients' informed consent must be obtained; failing to do so can result in the doctor being struck off the Register of Medical Practitioners.\textsuperscript{53} The ECEG 2016 further mandates that any medical research must be approved by an ethics committee and conform to the Singapore Guidelines for Good Clinical Practice.\textsuperscript{54}

Additionally, the HSA's Guideline on Alternative Measures for Investigational Product Management for Investigator-Initiated Clinical Trials helps to overcome difficulties faced in managing investigational products without contravening the principles of the aforementioned Guidelines for Good Clinical Practice.\textsuperscript{55}

\textbf{iv} Named-patient and compassionate-use procedures

The Health Products (Therapeutic Products) Regulations (HP(TP)R) allow imports of therapeutic products for use on a named-patient exemption basis. Under this exemption,\textsuperscript{56} the importer’s and wholesaler’s licences are not required for the import of an unregistered therapeutic product that is required by a healthcare institution or a pharmacy holding the relevant licences or a qualified practitioner.\textsuperscript{57} However, prior approval from the HSA must be sought.\textsuperscript{58} For a company acting on behalf of a hospital or clinic to import therapeutic products on this exemption basis, the importer’s and wholesaler’s licences must still be obtained.\textsuperscript{59}

The HSA’s Guidance on the Requirements for Exemption from Product Registration for Import of an Unregistered Medical Device for Supply on a Named-Patient Basis further allows licensed qualified practitioners to seek approval for the supply of unregistered medical devices in an emergency, or in circumstances in which conventional therapies have failed. These applications are made to the HSA and the HSA’s approval is conditional upon, inter alia, the requirement to report adverse events arising from the use of such medical devices.\textsuperscript{60}

The Human Biomedical Research (Requirements for Appropriate Consent – Exemption) Regulations 2019 has reduced the elements of ‘appropriate consent’ required

\begin{itemize}
  \item \textsuperscript{50} Pang Ah San v. Singapore Medical Council [2014] 1 SLR 1094 (SGHC) at [26].
  \item \textsuperscript{51} Innovative therapy is defined as a completely novel or significantly modified standard therapy with little or nothing in the way of studies or evidence of efficacy, effects or side effects. See also SMC Handbook on Medical Ethics 2016 at B6.1.
  \item \textsuperscript{52} SMC Handbook on Medical Ethics 2016 at B6.1.
  \item \textsuperscript{54} ECEG 2016 at Guideline B8.
  \item \textsuperscript{55} Clinical Trials Guidance: Alternative Measures for Investigational Product Management for Clinical Trials of Locally Registered Therapeutic Products or Medicinal Products (May 2017) – Paragraph 1.2.
  \item \textsuperscript{56} Regulation 51 of the Health Products (Therapeutic Products) Regulations 2016.
  \item \textsuperscript{57} A registered medical practitioner under the Medical Registration Act (Chapter 174) and a registered dentist under the Dental Registration Act (Chapter 76).
  \item \textsuperscript{58} Regulation 51(3) of the Health Product (Therapeutic Products) Regulations 2016; Therapeutic Products Guidance – Import and Supply of an Unregistered Therapeutic Product for Patients’ Use (November 2016) at Paragraph 2.2.
  \item \textsuperscript{59} Therapeutic Products Guidance – Import and Supply of an Unregistered Therapeutic Product for Patients’ Use (November 2016) at Paragraph 2.2.
  \item \textsuperscript{60} Medical Device Guidance – Guidance on the Requirements for Exemption from Product Registration for Import of an Unregistered Medical Device for Supply on a Named-Patient Basis (June 2010) at Paragraph 1.2.
\end{itemize}
when the tissue donor's tissue is being removed primarily for a therapeutic or diagnostic purpose (i.e., consent taking in the presence of a prescribed witness under Section 6(d) of the HBRA), but this exemption does not extend to tissue use for restricted biomedical research.  

v Pre-market clearance

Therapeutic products

Therapeutic products are divided into two broad categories for registration in Singapore: a new drug application (NDA) and a generic drug application (GDA). Pursuant to the Guidance on Therapeutic Product Registration in Singapore, companies are subject to screening and regulatory evaluation before obtaining a licence for a therapeutic product.

Depending on whether the NDA or GDA has been previously evaluated and approved, as well as the subcategory of the NDA or GDA, the screening and evaluation fees may be abridged.

Applicants seeking approval for an NDA that has been approved by at least one drug regulatory agency at the time of submission may also apply for priority review, which will be granted if the drug is intended for treatment of a serious life-threatening condition and can potentially address local unmet medical needs, or there is currently a local public health concern.

Medical devices

The HPA and HP(MD)R require medical devices, other than those exempted in the aforesaid regulations, to be registered with the HSA prior to being placed on the Singapore market. There are four risk classes for the classification of general medical devices.

Several notable amendments to the HP(MD)R came into force in 2018. Product registration is no longer required for Class A medical devices (low-risk) that are manufactured, imported or obtained from a validly licensed manufacturer, importer or supplier. An abridged evaluation process for registration has been provided for the other three classes, to allow faster market access. New categories of exceptions for the manufacture of medical devices without a licence have been introduced, namely for clinical labs already licensed under the PHMCA.

---

61 Regulations 2 and 3 of the Human Biomedical Research (Requirements for Appropriate Consent – Exemption) Regulations 2019.
62 Whether it is (1) the first strength of a 'new' chemical or biological entity; (2) the first strength of a new drug product containing a new combination or proportion of a registered chemical in a new dosage form, presentation or format for use by a new route of administration or for new indications, dosage recommendations or patient populations; or (3) subsequent strengths of a new drug product. See Paragraph 5.2 of Guidance on Therapeutic Product Registration in Singapore (January 2019).
63 ‘Local unmet needs’ is defined by the absence of a treatment option, or the lack of safe and effective alternative treatment, such that the drug would be a significant improvement compared to available marketed products, as demonstrated by (1) evidence of increased effectiveness in treatment, prevention or diagnosis; or (2) elimination or a substantial reduction of a treatment-limiting drug reaction. See Therapeutic Products Guidance – Guidance on Therapeutic Product Registration in Singapore (January 2019) at Paragraph 14.2.1.
64 Third Schedule to the Health Products (Medical Devices) Regulations 2010; Medical Device Guidance – Guidance on Medical Device Product Registration (June 2018) at Paragraph 2.
65 Regulation 10b of the Health Products (Medical Devices) Regulations 2010.
66 Regulation 26 of the Health Products (Medical Devices) Regulations 2010.
67 Regulation 3B of the Health Products (Medical Devices) Regulations 2010.
and where the supply of medical devices is intended for charitable purposes. The category of implantable medical devices has been expanded to include orthopaedic, neurological, breast, intraocular and cardiovascular implants. In another amendment, wellness devices have been expressly excluded from the HP(MD)R.

All medical devices must adhere to the Essential Principles for Safety and Performance for Medical Devices in the First Schedule to the HP(MD)R prior to their placement on the Singapore market. Requirements under all applicable legislation for the supply and use of any medical devices must also be met. Additionally, for medical practitioners, the APOC Guidelines set out the minimum level of competence required for the operation of certain medical devices in aesthetic procedures.

The Association of Southeast Asian Nations (ASEAN) has developed a standardised framework for regulating medical devices – the ASEAN Agreement on Medical Device Directive (AMDD). Under the AMDD, only registered medical devices that conform to its standards are allowed in the Member States’ markets. The standardisation of regulation allows for the efficient trading of medical devices among ASEAN states, though it should be noted that the AMDD has yet to be fully implemented as Member States are still aligning the AMDD with their local legislation. Additionally, the ASEAN Product Working Group for Traditional Medicines and Health Supplements was established in 2004 with the aim of harmonising technical requirements, exploring possible mutual recognition arrangements and eliminating technical barriers to trade for traditional medicine and health supplements without compromising the health and safety of the users. Once these harmonisation efforts come to fruition, life sciences companies will enjoy easier access to the entire ASEAN market.

**Cosmetic products**

With the implementation of the ASEAN Cosmetic Directive, manufacturer and import licences are no longer required. Instead, the HSA must be notified before the supply or sale of the cosmetic product. Acknowledgement of a product notification does not constitute an agreement that the product has met all regulatory requirements. The onus is on the company responsible for placing the product on the market to ensure that it meets the requirements of the ASEAN Cosmetic Directive. Only a Singapore-registered company can file a product notification, subject to payment of varying fees based on the risk level of the cosmetic products.
Traditional medicines, homeopathic medicines and health supplements

Traditional medicines (e.g., traditional Malay and Indian medicines), homeopathic medicines and health supplements are not subject to pre-marketing approval or licensing for their import, manufacture or sale in Singapore. Dealers and sellers of this category of medicines are responsible for ensuring their safety and quality.79

Chinese proprietary medicine

Under the Medicines Act, Chinese proprietary medicine dealers must obtain approval from the HSA prior to the import, export, sale or supply of Chinese proprietary medicine.80

Biosimilar medicinal products

To be registered as a biosimilar medicinal product, the product must fall under the definition of a ‘biosimilar product’ in the HSA’s Guidance on Registration of Biosimilar Products in Singapore.81 Typically, a biosimilar product is eligible for registration through an abridged evaluation route.

vi Regulatory incentives

The Patents Act (Chapter 221) allows for a one-off patent extension of up to five years for pharmaceutical products in a limited exception.82

The HP(TP)R83 and MA84 provide for a data exclusivity regime over a five-year period. The data provided by the company to the HSA is protected by the HSA, which is obliged to take reasonable steps to ensure that the data submitted remains confidential and is not used when evaluating the grant of any other application.

Under the Inland Revenue Authority of Singapore’s Productivity and Innovation Credit Scheme (the PIC Scheme), businesses may receive a tax deduction of up to 400 per cent or allowances of up to S$400,000 (the cap) of their expenditure per year in research and development (R&D) from the years of assessment 2011 to 2018.85 R&D expenditure86 exceeding the cap will enjoy a tax deduction of 150 per cent if the R&D is done in Singapore. Any other R&D expenditure, including expenditure of R&D carried out overseas, will enjoy a tax deduction of 100 per cent. Accordingly, businesses engaged in R&D of new drugs may enjoy substantial tax benefits under the PIC Scheme.87

80 Section 5 of Medicines Act.
81 Guidance on Registration of Biosimilar Products (November 2016).
82 Section 36A of the Patents Act.
83 Regulation 26(1) of the Health Product (Therapeutic Products) Regulations.
84 Section 19A of the Medicines Act.
85 See https://www.iras.gov.sg/irashome/Schemes/Businesses/Productivity-and-Innovation-Credit-Scheme/.
86 R&D expenditure also encompasses staff costs and consumables. See Part 4 of IRAS Research and Development (R&D) Claim Form.
87 See https://www.iras.gov.sg/irashome/Schemes/Businesses/Productivity-and-Innovation-Credit-Scheme/ Six-Qualifying-Activities-under-PIC/ under ‘Research and Development (R&D) Activities’.
vii Post-approval controls

**Therapeutic products**

The product licence holder must put in place a system to ensure responsibility and liability for its products on the market and be able to take appropriate action, if necessary. For therapeutic products, the duty to maintain records and report defects and adverse effects is now required by legislation. Every manufacturer, importer, supplier or registrant of a therapeutic product must report the defect to the HSA as soon as it is identified.88

Under the HPA89 and MA90 the HSA has the power to suspend, revoke or vary licences. A licence may be revoked at the request of the licence holder, or if the HSA is satisfied that there is an infringement of a patent, or if there was fraud or misrepresentation in the application process.

**Medical devices**

Registrants of medical devices are required to notify the HSA of any changes to particulars provided in relation to the registration of the medical devices, or changes that may affect the safety, quality or efficacy of a registered medical device.91 In addition, registrants must report any defects or adverse effects that occur in connection with the medical device.

The HSA may also suspend or cancel the registration of a health product (including medical devices) if there is suspicion of fraud or misrepresentation in the first instance or safety concerns in the use of the health product.92

**Cosmetic products**

The manufacturer, importer, supplier or registrant of a health product or any cosmetic product has a duty to inform the HSA in the event of any defect or adverse effect arising from the use of the health product. Further, persons or companies supplying a product to the market must retain a product information file, which includes key information about the product’s composition and safety assessments.93

As with other health products, the HSA has the power to suspend, cancel or reclassify the registration of cosmetic products, as set out above.94

viii Manufacturing controls

A valid licence from the HSA is required for the manufacturing of health products and medicinal products under the HPA and MA respectively.95 For therapeutic products, under the HP(TP)R, a manufacturer’s licence will only be granted when the manufacturing facilities have been audited and found to comply with the Pharmaceutical Inspection Convention

---

88 If the defect leads to a serious threat to personal or public health, it must be reported within 48 hours. All other product defects must be reported within 15 days. See Regulation 34 of the Health Product (Therapeutic Products) Regulations 2016.
89 Section 27 of the Health Product Act.
90 Section 16 of the Medicines Act.
91 Regulation 49 of the Health Products (Medical Devices) Regulations 2010.
94 Section 27 of the Health Products Act.
95 Section 12 of the Health Products Act and Section 6(2) of the Medicines Act.
or Cooperation Scheme Guide to Good Manufacturing Practice for Medicinal Products.\textsuperscript{96} For medical devices, an ISO 13485 certificate for finished medical device manufacturing is required to obtain a manufacturer’s licence. Additionally, a manufacturer of medical devices must comply with the requirements set out in the First Schedule to the Health Products (Medical Devices) Regulations 2010.\textsuperscript{97}

Cosmetic products manufactured in Singapore must comply with Appendix VI of the ASEAN Cosmetic Documents entitled ‘ASEAN Guidelines for Cosmetic Good Manufacturing Practice’.

\textbf{ix Advertising and promotion}

It is an offence under the HPA and MA to issue false or misleading advertisements relating to therapeutic products or medicinal products.\textsuperscript{98}

Unlike medicinal products, prior approval from the HSA is not required for advertisements relating to therapeutic products.\textsuperscript{99} Advertisement of therapeutic products is governed by the HPA and the Health Products (Advertisement of Therapeutic Products) Regulations (HP(ATP)R). The onus is on the advertiser to ensure compliance with rules under the HP(ATP)R, with the HSA undertaking a monitoring role to ensure due compliance. Advertisements for both medicinal products and therapeutic products must not claim to prevent, alleviate or cure certain diseases or conditions specified in the First Schedule to the MA and the Second Schedule to the HP(ATP)R respectively.\textsuperscript{100}

Advertisements and promotions of medical devices also do not require prior approval from the HSA, but such advertisements must not be false or misleading, and must be capable of verification by objective evidence, pursuant to the HP(MD)R.\textsuperscript{101}

With regard to cosmetic products, advertisements cannot include claims that they have therapeutic benefits or can be used for therapeutic purposes,\textsuperscript{102} nor can they create an erroneous impression regarding the formulation, composition, quality or safety of the product.\textsuperscript{103}

The ECEG 2016 also prohibits doctors from associating themselves with ‘parties that do not provide legitimate medical or medical support services in a way which could mislead

\begin{itemize}
  \item \textsuperscript{96} Regulation 4 of the Health Product (Therapeutic Product) Regulations 2016. Guidance on Licensing for Manufacturers, Importers and Wholesalers of Medical Devices (August 2018) at Paragraph 5.2.
  \item \textsuperscript{97} Regulation 33 of the Health Products (Medical Devices) Regulations 2010.
  \item \textsuperscript{98} Section 50 of the Medicines Act.
  \item \textsuperscript{99} Explanatory Guidance to the Health Products (Advertisement of Therapeutic Products) Regulations 2016 (November 2016) at Paragraph 2.2.
  \item \textsuperscript{100} Section 51 read with the First Schedule to the Medicines Act for medicinal products, Regulation 6 read with the Second Schedule to the Health Products (Advertisement of Therapeutic Products) Regulations 2016. The list of diseases and conditions in both Schedules are the same.
  \item \textsuperscript{101} Regulation 19 of the Health Products (Medical Device) Regulations 2010.
  \item \textsuperscript{102} Regulation 9(a) of the Health Products (Cosmetic Products – ASEAN Cosmetics Directive) Regulations 2007.
  \item \textsuperscript{103} Regulation 9(b) of the Health Products (Cosmetic Products – ASEAN Cosmetics Directive) Regulations 2007.
\end{itemize}
the public into believing that any of the services are medically endorsed’. Doctors are only allowed to promote food, vitamins, tonics and health and nutrition supplements if there is sufficient scientific basis or if they are generally accepted by the medical profession.

x Distributors and wholesalers

Any person (except for licensed manufacturers) must apply for the relevant wholesaler’s licence for the resale of registered therapeutic products or medical devices or wholesale dealer’s licence for medicinal products. A licensee for a therapeutic product must appoint a responsible person to ensure compliance with the HSA’s good distribution practice (GDP). The licence for medicinal products will only be granted if the company has been audited and found to comply with the HSA’s GDP.

With regard to medical devices, a wholesaler must possess either a GDP for medical devices certificate or ISO 13485 certificate with the scope for storage and distribution. A licensed local manufacturer does not require a wholesaler’s licence to supply, by wholesale, any medical devices it manufactures.

In respect of cosmetic devices, the company responsible for supplying the cosmetic product in the market must notify the HSA before doing so.

xi Classification of products

The classification of therapeutic products is carried out by the Therapeutic Products Branch, a department of the HSA. Therapeutic products are classified under three forensic classes: prescription-only medicines, pharmacy-only medicines and general sales list medicines.

Therapeutic products may be reclassified if the product has been deemed sufficiently safe for use with reduced, or without, medical supervision. The reclassification may be effected by an application by the party who registered the therapeutic product or through legislative mechanisms.

Introduced in 2018, the collaborative prescribing service will allow collaborative prescribing practitioners (e.g., accredited pharmacists and nurses) to prescribe and dispense pharmacy-only and prescription-only medicines without having a medical practitioner sign them off. This will save both time and costs for patients and also ease the patient load on the already stretched healthcare system.
xii Imports and exports

Under the HPA, a person must now obtain an importer's licence to import therapeutic products or medical devices, and a wholesaler's licence to export them. Importers and exporters of therapeutic products must also appoint a person to be responsible for ensuring compliance with the HSA's GDP standards. This requirement of a responsible person does not extend to importers and exporters of medical devices, although they must possess either a GDP for medical devices certificate or ISO 13485 certificate with the scope for storage and distribution. Companies applying for an importer's or wholesaler's licence for therapeutic products for patients' use or restricted activities between 1 November 2016 and 31 October 2019 are eligible for a fee waiver to facilitate the adoption of this new regulatory regime.

Imports and exports of medicinal products remain under the purview of the MA, and importers of such products require either a product licence or an import licence, while exporters require a product licence.

xiii Controlled substances

As a party to both the 1961 United Nations Single Convention on Narcotic Drugs and 1971 United Nations Convention on Psychotropic Drugs, Singapore conforms to the international control measures provided in both conventions. The Misuse of Drugs Act makes it an offence to import, export or traffic controlled drugs, or to import, export or supply controlled equipment, materials or substances if one knows or has reason to believe that they are to be used in or for the manufacture of a controlled drug.

---

112 Section 13 of the Health Products Act. However, a holder of a manufacturer's licence for therapeutic products may import health products without an importer's licence if the health product is required for the purpose of carrying out the manufacture of a therapeutic product. See Regulation 54 of the Health Products (Therapeutic Products) Regulations 2016.

113 Section 14 read with Section 2 of the Health Products Act. However, a holder of an importer's licence may export therapeutic products without a wholesaler's licence if the imported therapeutic products were imported solely for the purpose of export. See Regulation 53 of the Health Products (Therapeutic Products) Regulations 2016.

114 Regulation 39 of the Health Products (Therapeutic Products) Regulations 2016.

115 Guidance on Licensing for Manufacturers, Importers and Wholesalers of Medical Devices (August 2018) at Paragraph 5.2.


117 Part II of the Medicines Act.

118 These control measures are implemented via, inter alia, the Misuse of Drugs Act (Chapter 185), the Health Products (Therapeutic Products) Regulations 2016 and the Medicines (Export Licence for Psychotropic Substances) Regulations.
To import or export controlled drugs and psychotropic substances or medicinal products with psychotropic substances, an applicant must obtain an import or export licence from the HSA, and the purpose of the import or export will be assessed before the licence is processed and issued.

xiv Enforcement

The HSA has the right of entry into premises for the purpose of ascertaining whether there is, or has been, any contravention of the MA. Any duly authorised person has the power to inspect, take samples and seize goods and documents to ascertain whether any contravention of the MA has taken place.

Under the HPA, an enforcement officer may, at any time and without warrant, enter, inspect and search a premise if there is reason to suspect a contravention of the HPA. The enforcement officer may also seize items, require a person to furnish information or documents in his or her knowledge, or arrest, without warrant, a person who is believed to have committed an offence under the HPA.

With regard to private hospitals and medical clinics, the MOH’s Director of Medical Services or any authorised enforcement officer may, at any time and without warrant, enter, inspect and search any premises if there is reasonable cause to suspect a contravention of the Private Hospitals and Medical Clinics Act (Chapter 248), or to assess the quality and appropriateness of the services provided, and the practices carried out in those establishments, including clinical laboratories.

III PRICING AND REIMBURSEMENT

Apart from a national medical savings scheme (Medisave) and a health insurance scheme for Singapore citizens and permanent residents (Medishield Life), patients receive drug subsidies based on their paying status and the scheme under which the drug is covered (e.g., the Standard Drug List and Medication Assistance Fund). Subsidised drugs cover up to 90 per cent of the total volume of public medication prescriptions and are reviewed and

119 As defined in the First Schedule to the Misuse of Drugs Act.
120 Regulation 3 of the Medicines (Export Licence for Psychotropic Substances) Regulations. Note that the Regulations were amended in 2016 to include medicinal products containing psychotropic substances.
121 See www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Manufacturing_Importation_Distribution/Overview/Audit_and_Licensing_Of_Importers_Wholesale_Dealers_and_Exporters/Controlled_Drugs_Psychotropic_and_Restricted_Substances.html.
122 Section 49 of the Health Products Act.
123 Section 12 of the Private Hospitals and Medical Clinics Act (Chapter 248).
124 Medisave allows Singaporean Citizens or Permanent Residents to set aside part of their income for future medical expenses. See https://www.moh.gov.sg/content/moh_web/home/costs_and_financing/schemes_subsidies/medisave.html#1. MediShield Life is a basic health insurance plan, administered by the Central Provident Fund Board, which helps to pay for hospital bills and selected costly outpatient treatments such as dialysis and chemotherapy for cancer. See https://www.moh.gov.sg/content/moh_web/medishield-life/about-medishield-life/what-is-medishield-life.html.
125 See https://www.moh.gov.sg/cost-financing/healthcare-schemes-subsidies/drug-subsidies-schemes. However, note that some drugs are only subsidised for specific, appropriate clinical indications for which the drugs are assessed to be clinically effective and cost-effective.
updated regularly by the MOH. Subsidies are also provided for medical devices, such as implants. In 2014, the government launched the Pioneer Generation Package, which provides senior citizens who were born before 1950 and obtained citizenship before 1987 with additional discounts on subsidised medications, as well as subsidies on their Medishield Life premiums. In August 2018, the government launched the Merdeka Generation Package for Singaporeans born in the 1950s, to help them cope with healthcare and other expenses, covering areas such as outpatient subsidies, Medisave account top-ups, MediShield Life premium subsidies and payouts for long-term care.

Health technology assessments are carried out by the Healthcare Technology Assessment (HTA) Unit under the auspices of the MOH. As part of its health technology assessments, the HTA Unit carries out reviews and cost-effectiveness analyses, and develops clinical practice guidelines in Singapore.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Any person aggrieved by the HSA’s decision in relation to granting, renewing or revoking a licence, or the registration of a health product, may appeal to the Minister of Health, whose decision is final.

Notwithstanding the finality of the Minister’s decision, applicants may apply for a judicial review of the Minister’s decision in accordance with common law administrative law principles; for example, where the Minister’s decision has exceeded its jurisdiction or where the Minister reached his or her decision in breach of the rules of natural justice.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The Singapore Association of Pharmaceutical Industries’ Code of Marketing Practices guides the conduct of marketing and promotion of medicinal and therapeutic products in Singapore, and serves as the basis for regulation within the industry.

The ECEG 2016 also provides guidance to doctors in relation to issues of financial conflicts of interest. While the requirements on disclosure of interests and prohibitions on exerting undue influence on patients still apply, the ECEG 2016 has expanded the scope of conflicts of interest to include the material interests of individuals close to doctors. Further, the practice of asking for fee kickbacks or other compensation in exchange for referring patients to other medical service professionals or healthcare facilities is prohibited under

131 Section 28 of the Health Products Act.
133 Guideline H3(1)-(5) of the ECEG 2016.
the ECEG 2016. Additionally, if the factual circumstances reveal a corrupt intent and the breach is egregious, this may potentially be an offence of corruption under the Prevention of Corruption Act (Chapter 241).

At present, doctors can only charge patients for fees paid to third-party administrators (TPAs) and managed care companies if the sums paid reflect the actual work they do and are not contingent on the services provided by the doctor or the amount of fees collected from patients. The rationale is to ensure that the patient’s interests would take priority over the doctor’s personal financial interests. Examples of TPA services include intermediary processing and managing of insurance claims and employer medical benefits. Historically, a large number of healthcare institutions would charge a fixed percentage of the total amount of the fees billed to patients for TPA services. The sharing or splitting of fees with a TPA or managed care company, merely for the privilege of being referred a patient with no commensurate work being done to justify the fees, is now considered unethical. In practice, whether the fees paid to a TPA would constitute an infringement of the ECEG 2016 would very much depend on the basis for the fees and the specific circumstances in each case. As a breach of the ECEG 2016 may lead to disciplinary sanctions against a doctor, some doctors have chosen to terminate their contracts with TPAs to avoid the risk of being sanctioned.

To give more clarity on the implementation of the new rules, the SMC has in various advisories stated that TPAs can still be paid a fee but the quantum must be commensurate to and fairly reflect the complexity of the actual work executed by the said third party. There also needs to be transparency to the patients about the fees payable to the TPA. In addition, the Academy of Medicine, the College of Family Physicians and the Singapore Medical Association have also jointly issued recommendations that doctors can consider a cap for

134 Guideline H3(5) of the ECEG 2016.
135 See Public Prosecutor v. Khoo Yong Hak [1995] 1 SLR(R) 769 (SGHC) at [23] to [26]. Section 5 of the Prevention of Corruption Act (Chapter 241) makes it an offence to corruptly solicit, receive, give, promise or offer any gratification as an inducement to any person (or public servant) doing or forbearing to do anything in respect of any matter.
136 Guideline H3(7) of the ECEG 2016 states that doctors may only pay managed care companies, third-party administrators, insurance entities or patient referral services fees that reflect their actual work in handling and processing the patients, and cautions that such fees must not be so high as to constitute ‘fee splitting’ or ‘fee sharing’. Further, doctors are required to disclose any such fees to their patients. Although the ECEG 2016 came into force on 1 January 2017, Guideline H3(7) only came into force on 1 July 2017, giving doctors an additional six months to comply; see Paragraphs 9 and 10 of the Advisory on the Payment of Fees to Managed Care Companies, Third Party Administrators, Insurance Entities or Patient Referral Services by the Singapore Medical Council on 13 December 2016. This was reiterated in the Second Advisory on the Payment of Fees to Managed Care Companies, Third Party Administrators, Insurance Entities or Patient Referral Services by the Singapore Medical Council on 23 June 2017, Paragraph 4.
137 See Paragraph 11 of the Advisory on the Payment of Fees to Managed Care Companies, Third Party Administrators, Insurance Entities or Patient Referral Services (‘Third Parties’) by the Singapore Medical Council on 13 December 2016.
138 Advisory on the Payment of Fees to Managed Care Companies, Third Party Administrators, Insurance Entities or Patient Referral Services by the Singapore Medical Council on 13 December 2016, and the Second Advisory on the payment of fees to managed care companies, third-party administrators, insurance entities or patient referral services by the Singapore Medical Council on 23 June 2017.
139 Joint opinion on Transactions with Managed Care/Third Party Administrators (TPAs) on 14 December 2016, Joint Advisory on Fees paid to Managed Care and Third-Party Administrator
TPA fees, a fixed methodology that allows TPAs to achieve a reasonable and appropriate profit margin, or a fee schedule for different scenarios to cater for the different types and complexities of work done by TPAs.

In late 2018, the local media reported that public hospitals retained the practice of engaging foreign agents who received payment from the public hospitals for ‘administrative services’ (i.e., to facilitate and assist foreign patients seeking medical treatment in Singapore for a certain percentage of the patient’s hospital bill). The MOH requested that public hospitals terminate all contracts with such foreign agents. The MOH’s position was that the ‘priority of public healthcare institutions is to serve Singaporeans’ healthcare needs’, and they are ‘not allowed to actively market themselves to foreign patients’. In light of the MOH announcement, there have been reports that foreign agents are turning to private practitioners and private hospitals for such referral arrangements.

The ECEG 2016 further provides more detailed guidelines on the relationships between doctors and the medical industry. In particular, financial reimbursements for doctors appearing at educational events must be fair, reasonable and commensurate with the time and expertise they have provided, and doctors must personally pay for any unrelated activities, additional stay or the costs of any accompanying persons. They also cannot accept extravagant gifts, hospitality or other inducements from companies that could be seen to potentially affect their decisions about patient care.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The regulatory regime does not provide special liability or compensation schemes in relation to medical products. Accordingly, compensation for injuries arising from medicinal products and medical devices derive from common law or statute. Although rare, class actions are possible.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The Competition Commission of Singapore is the primary regulator in this space. In October 2013, the Commission indicated that it would be actively considering the issue of patent disputes and ‘pay-for-delay’ agreements.
ii Transactional issues

In terms of strategic collaborations, Singapore provides diverse partnership opportunities with its public sector research institutes, leading pharmaceutical and biotechnology companies based in Singapore, clinical research units in hospitals, and international research organisations. Companies can also collaborate with scientists in Singapore’s public sector institutes to work on developing new medical technology innovations and applications. In addition, the government provides funding in the life sciences industry: for example, S$4 billion was pledged to further health and biomedical sciences research under the Research, Innovation and Enterprise 2020 plan.146

VIII CURRENT DEVELOPMENTS

As Singapore continues to experience low fertility rates, the adoption of new methods of fertility assistance has come under active consideration. Thus, the BAC has formed a review group to look into the ethical, legal and social issues arising from mitochondrial genome replacement technology.147 The MOH is currently reviewing the use of pre-implantation genetic screening (PGS) and its ethical implications, having commenced a three-year pilot programme to assess its clinical effectiveness at improving in vitro fertilisation (IVF) cycle outcomes by screening for chromosomal abnormalities in embryos created through IVF.148 The pilot programme is scheduled to end in December 2019, when the MOH will evaluate the clinical outcomes to evaluate whether PGS should become a routine clinical service.149

A recent High Court judgment150 has prompted governmental reviews of the status of surrogacy in Singapore.151 While surrogacy is not available in Singapore, the authorities have been faced with issues in relation to the legal status of children birthed through gestational surrogacy overseas (e.g., parentage, citizenship, residential status of the child). The case raised interesting questions about allowing the adoption of such a child by the child’s biological father, who intended to raise the child within the context of a homosexual relationship. Governmental reviews may result in legislative changes to the terms of assisted reproduction services, currently governed by the PHMCA.152

To control rising healthcare costs, the MOH has published the Fee Benchmarks for Private Sector Surgeon Fees (as of 13 November 2018) covering 222 surgical procedures.153

147 See www.bioethics-singapore.org/index/activities/current-projects.html. Mitochondrial gene replacement allows the replacement of mutant mitochondrial genes in unfertilised oocytes or zygotes with normal donor mitochondria, preventing the passing of the condition from mother to child. See also www.straitstimes.com/singapore/three-parent-baby-to-avoid-diseases.
152 Regulation 18(1) read with Second Schedule to the Private Hospitals and Medical Clinics Regulations.
153 MOH, Fee Benchmarks for Private Sector Surgeon Fees (As of 13 November 2018).
While the benchmarks are not intended to be a fee cap, doctors who charge above the benchmarks are expected to explain to patients and other stakeholders why their charges exceed the benchmarks.

The current PHMCA is to be replaced with a new Healthcare Services Act (HCSA), which will broaden the scope of regulatory coverage from the present hospitals, medical clinics and other healthcare institutions, to include allied health and non-physician healthcare, traditional medicine and complementary and alternative medicine. A new risk-based regulatory approach is expected be adopted whereby licences, which were previously premise-based, are now to be issued based on the types of services provided, such as hospital services and long-term residential care services, among others. Better safeguards for patient safety and welfare will also be implemented. The MOH will be empowered to directly ‘step-in’ or appoint a ‘step-in’ operator to take over a residential healthcare entity licensee that is in serious financial trouble, not complying with the provisions of the HCSA, or is otherwise carrying on its operations in a manner that is detrimental to the interests of patients or customers.

The Bill for the HCSA was passed in Parliament on 6 January 2020, with implementation to be carried out in three phases from early 2021 to the end of 2022. The first phase will bring PHMCA laboratory licensees under the Bill’s regulatory regime, while the second phase will involve medical clinics and other ambulatory care services, as well as ambulance services. In the third phase, hospital and long-term care services, as well as other new licensable services will be regulated by the Bill.

When the HCSA was first proposed in 2017, it was intended to make it mandatory for licensed hospitals and medical clinics under the HCSA to contribute critical patient health information to the National Electronic Health Records (NEHR). The NEHR is a database owned by the MOH to collect summary patient health records across different healthcare providers. At present, contribution is voluntary with primarily public institutions contributing patient data. Patients who do not wish for their records to be accessed via the NEHR may opt out, but by default their specified health data would be contributed to the NEHR. However, mandatory contribution to the NEHR has been deferred due to various events.

Before the HCSA could be enacted in 2019 as originally intended, Singapore witnessed its worst cyberattack, which occurred within the database of Singapore’s largest group of healthcare institutions, consisting of four hospitals and other healthcare centres. The personal particulars of 1.5 million patients, and outpatient particulars of around 159,000 people, were stolen. A Committee of Inquiry was convened and it issued a report on its

---

154 MOH, Fee Benchmarks for Private Sector Surgeon Fees (As of 13 November 2018) at Paragraph 7(a)(ii).
155 Fee Benchmarks Advisory Committee Report (9 November 2018).
158 The draft Healthcare Services Bill was made available to the public at https://www.moh.gov.sg/docs/librariesprovider8/default-document-library/healthcare_services_(draft)_bill_2017122241b0a3bc9c8c4d65b2ac0bbf0aa81bf.pdf.
160 WongPartnership LLP represented MOH Holdings Private Limited in the inquiry.
findings in December 2018. In January 2019, the Personal Data Protection Commission imposed fines on both the company responsible for administering the electronic medical record system and the healthcare institution (fined S$750,000 and S$250,000 respectively). The latter is the same institution that manages the NEHR.

Soon after the above inquiry was concluded, the MOH disclosed in January 2019 that another major data breach of healthcare information had been detected. This time, involving the data of more than 14,000 people diagnosed with HIV. These incidents have heightened public scrutiny on the frameworks in place to safeguard confidential data, especially with the increased prevalence of data use across the healthcare sector.

As a result, plans for the mandatory contribution of patient medical data to the NEHR have been deferred. The NEHR is still undergoing a series of cybersecurity assessments to ensure that the system is sufficiently robust.

The recent data breaches have given rise to concerns about the adoption of telemedicine. Singapore has seen a growth in the telemedicine sector with reports that funding into Asian telemedicine start-ups have grown since 2010. To ensure that telemedicine and other similar new and innovative services can be developed in a safe and controlled environment, the MOH launched a new Licensing Experimentation and Adaptation Programme (LEAP) on 18 April 2018, with telemedicine as the first service to come under LEAP. Under LEAP, the MOH is working alongside telemedicine providers to develop more timely, fit-for-purpose and effective regulations, with an intended focus on 'tele-consultation and mobile medicine (house call) services that provide direct clinical care, such as triage, history taking, diagnosis and treatment under the HCSA'. With the experience gathered through the LEAP framework, the MOH will be revising the National Telemedicine Guidelines issued in 2015, with the revised edition expected to be published in 2020.

The Workgroup to Review the Taking of Informed Consent and SMC Disciplinary Process convened by the SMC in consultation with the MOH and the Ministry of Law issued its recommendations on 28 November 2019. Key recommendations include: first, a new test for informed consent in response to the Singapore Court of Appeal's recent adoption

---

of the Modified-Montgomery test in 2017, which introduced a patient-centric assessment of ‘material information’. The new formulation of the test proposed by the Workgroup wishes to ‘make it clear that [materiality of information to be given to patients] should be assessed by a [responsible body of doctors].’ Second, substantive reforms to the SMC’s disciplinary process have been mooted, including establishing a new Disciplinary Commission to separate the SMC’s investigation and adjudication functions, establishing an Inquiry Committee to filter out ‘frivolous, vexatious, misconceived’ or unsubstantiated complaints at an earlier stage, granting the Complaints Committee wider-ranging powers, and encouraging mediation in the disciplinary process. It remains to be seen if and how the Workgroup’s recommendations will translate into legislation.

I INTRODUCTION

The principal regulator of pharmaceuticals and medical devices is the Ministry of Food and Drug Safety (MFDS), which regulates the manufacture, importation, distribution, sale and advertisement of pharmaceuticals and medical devices. The principle legislation that governs business activities of pharmaceutical companies and pharmaceuticals is the Pharmaceutical Affairs Act (PAA). Medical device companies and medical devices are regulated under the Medical Device Act (MDA).

Other relevant legislation includes the National Health Insurance Act (NHIA), which governs the pricing and reimbursement of pharmaceuticals and medical devices. The relevant government authorities involved in pricing and reimbursement for pharmaceuticals and medical devices are the Ministry of Health and Welfare (MOHW), the National Health Insurance Review and Assessment Service (HIRA) and the National Health Insurance Service (NHIS). In addition, general antitrust and fair trade statutes apply to the marketing and advertising of pharmaceuticals and medical devices including the Monopoly Regulation and Fair Trade Law (FTL) and the Fair Labelling and Advertising Act, enforced by the Korea Fair Trade Commission (KFTC).

II THE REGULATORY REGIME

i Classification

Pharmaceutical products are defined, in essence, as: (1) products listed in the Korean Pharmacopoeia; (2) products used for the purposes of diagnosis, alleviation, treatment or prevention of disease excluding appliances, machinery and equipment; and (3) products other than appliances, machinery or equipment (Article 2(4) of the PAA). Medical devices are defined, in essence, as instruments, machines, devices, materials or any other similar product used to diagnose, cure, alleviate, correct or prevent a disease, injury or impairment (Article 2 of the MDA).

Other regulated products such as food, cosmetics, chemical and general consumer products are regulated under different and separate statutes (e.g., food is regulated under the Food Sanitation Act and attendant regulations). Given the strict regulatory environment for pharmaceuticals and medical devices, for borderline products, companies would need to

---

1 Yong Hoon Cho is an attorney and Myung Soon Chung is a foreign attorney at Kim & Chang.
ensure that their products do not fall within the definition of pharmaceuticals or medical devices in order to classify their products as products other than pharmaceuticals or medical devices.

ii Non-clinical studies

Non-clinical studies involving animals, plants, microorganisms, physical or chemical media or their composites must be conducted in compliance with the Good Laboratory Practice guidelines (GLP), as prescribed under the PAA and the MDA. The purpose of the GLP is to ensure transparency and ultimate reliability of study results through the systematic management of non-clinical studies.

If non-clinical studies involve vertebrates, such studies must also comply with the Laboratory Animal Act and be registered with the MFDS. As a general matter, any study using animals must also comply with relevant provisions under the Animal Protection Act.

iii Clinical trials

Clinical trials conducted in Korea must comply with the Good Clinical Practice guidelines (GCP), as prescribed under the PAA and the MDA. The GCP provides guidelines on conducting, performing, analysing, recording and reporting of clinical trials. The MFDS has also issued detailed regulations that supplement the GCP, including the Guidelines on Compensation for Clinical Trial Subjects, which requires sponsors to be insured for covering patient harm.

A clinical trial application (including the trial protocol) must be submitted to, and approved by, the MFDS before a clinical trial can commence. No such approval from the MFDS is required for clinical trials of approved pharmaceuticals and medical devices for approved indications. Under the GCP, the clinical trial protocol must be separately submitted to and approved by the institutional review board (IRB) of the institution where the clinical trial will be conducted. Written informed consent must be obtained from the trial subjects, and all adverse events that are serious and unexpected must be reported to the investigators, institutions, the IRBs, and the MFDS.

Foreign entities conducting clinical trials in Korea are not required to establish a business in Korea and can utilise contract research organisations to conduct clinical trials on their behalf.

iv Named-patient and compassionate use procedures

Under the PAA, named-patient and compassionate use of unapproved pharmaceuticals outside of clinical trials are permitted for treatment purposes where a patient has (1) a serious life-threatening disease, such as terminal cancer or acquired immunodeficiency syndrome (AIDS); (2) a serious or urgent life-threatening condition; or (3) no other alternative treatment methods in a condition that warrants urgent treatment.

Under the MDA, medical devices that are not approved may also be used for diagnosis and treatment in case of an outbreak of an infectious disease and during radiation emergencies.
Pre-market clearance

To be an official holder of a product registration (i.e., marketing authorisation) of either a pharmaceutical or medical device, an entity must be located in Korea. Therefore, a foreign entity must establish a branch or subsidiary in Korea, or designate a third-party domestic entity to obtain the product registration. Such entity must also hold a manufacturer or importer business licence, which is issued by the MFDS.

Pharmaceuticals

A company seeking to manufacture or import a pharmaceutical in Korea for sale must be licensed as a pharmaceutical manufacturer or importer, and obtain product registration (i.e., marketing authorisation) from the MFDS for each pharmaceutical. The product registration of patented pharmaceuticals must follow the new drug application (NDA) procedure. The NDA dossier consists of: (1) safety and efficacy data; (2) standards and testing methods; (3) good manufacturing practice (GMP) evaluation data; (4) a drug master file (DMF); and (5) a risk management plan (RMP). A recurring issue is whether a bridging study (that is, a testing of the drug on the Korean population to determine any impact that ethnic differences may have on its safety and efficacy) should be included in the clinical data package. Pre-meetings with MFDS personnel are available to give applicants a sense of what will be required in the application package and to expedite the application process. The processing periods for GMP and DMF evaluations are 90 and 120 business days, respectively. It is possible to facilitate the process by commencing DMF approval early, before initiation of the NDA procedure.

Applicants seeking product registration of generic pharmaceuticals can follow the abbreviated new drug application (ANDA) procedure. The basic ANDA dossier comprises: (1) safety and efficacy data; (2) standards and testing methods; (3) GMP evaluation data; and (4) a DMF. The ANDA procedure does not require submission of clinical trial data if there is sufficient data showing that the pharmaceutical is therapeutically interchangeable with the reference pharmaceutical.

For both ANDA and NDA procedures, the processing periods for GMP and DMF evaluations are 90 and 120 business days, respectively.

Medical devices

Medical devices are classified into four classes depending on the possible health risks posed by the devices (Class I posing the least, Class IV posing the greatest health risk). A company seeking to manufacture or import a medical device for sale must be licensed as a medical device manufacturer or importer and register each medical device (Class I) or obtain product registration (Class II, Class III and Class IV) from the MFDS for each medical device. Companies must obtain GMP certification from an MFDS-authorised evaluation body before submitting an application for product registration. The certification process includes an audit of the manufacturing site. Class II, III and IV medical devices are subject to this audit. An application for product registration must include GMP certification as well as safety and efficacy data.

There is no prescribed review period for the initial GMP review but GMP certification must be renewed every three years and the application for recertification must be made three months before expiry. The processing period for technical document evaluation is 65 days without clinical trial data and 80 days with clinical trial data.
vi Regulatory incentives
Before the Korea-US Free Trade Agreement (FTA), the Korean regulatory authorities issued product registrations for generic pharmaceuticals even where the original pharmaceutical was still protected by a patent. Now, as a result of the FTA, patentee or original pharmaceutical makers are entitled to certain period of market exclusivity for patents listed on the Green List (similar to the US Food and Drug Administration’s Orange Book) and can prevent generics from entering into the market prior to expiry of the patent. Once a patent is listed on the Green List, an ANDA applicant who submitted market approval of its generic drug must notify a patentee or a party who listed the patent on the Green List regarding the approval. The patent holder then can file a patent infringement litigation within 45 days from the date of receiving notification from the generic drug applicant and petition the MFDS to stay or prohibit the sales of the generic drugs. The MFDS can prohibit the sale up to nine months from the date on which the patentee receives the notification.

vii Post-approval controls
To ensure the effectiveness and safety of approved pharmaceuticals, post-marketing surveillance is required pursuant to the PAA for pharmaceuticals. Post-marketing surveillance consists of the following three systems: (1) re-examination system (companies conduct every four or six years from the date of product registration for new pharmaceuticals and some prescription-only pharmaceuticals); (2) re-evaluation system (MFDS selects pharmaceuticals subject to re-revaluation to monitor effectiveness and safety of pharmaceuticals); and (3) safety information management system (for serious adverse events, companies must notify the MFDS within 15 days of becoming aware of such adverse events).

Similarly for medical devices, post-marketing surveillance in the forms of the re-examination system, re-evaluation system and safety information management system must be implemented pursuant to the MDA.

Administrative sanctions are possible for failure to conduct the post-marketing surveillance activities outlined above, including but not limited to confiscation or destruction of the relevant products, suspension of business and cancellation of product registrations (the severity of sanctions may vary depending on the type and frequency of the violation).

viii Manufacturing controls
Under the GMP certification system, manufacturers and importers of pharmaceuticals and medical devices must also obtain GMP certification of the manufacturing facility where the product will be manufactured. For importers, the MFDS will review the manufacturing facilities located overseas.

ix Advertising and promotion
The PAA and MDA and their respective attendant regulations regulate the advertising of pharmaceuticals and medical devices. The PAA and attendant regulations prohibit advertising of prescription pharmaceuticals directly or indirectly through mass media with limited exceptions such as communicating expert content to medical professionals. The MDA and attendant regulations permit advertising of medical devices through mass media but require that such advertisements obtain prior review from the industry association, the Korea Medical Device Industry Association.
When advertising pharmaceuticals and medical devices, only on-label advertising (i.e., use of the product for approved indications) is permitted and the advertising restrictions prescribed under the PAA and the MDA including the prohibition against false, misleading or exaggerated advertising would apply.

Sales on the internet or by mail order are prohibited for pharmaceuticals. Medical devices, however, can be sold on the internet and by mail order, but this requires a separate business licence under a separate regulatory regime for online businesses including the Act on Consumer Protection in Electronic Commerce, etc.

Pharmaceutical companies and medical device companies must also comply with the general advertising requirements under the Fair Labelling and Advertising Act, enforced by the KFTC.

x Distributors and wholesalers
To sell and distribute pharmaceuticals in Korea, companies other than manufacturers and importers of the pharmaceuticals must obtain a pharmaceutical wholesaler licence from the MFDS and comply with good supply practice (GSP) requirements.

Similarly, medical device sellers and distributors, other than manufacturers or importers, must obtain a seller business licence from the MFDS and comply with GSP requirements.

xi Classification of products
There are two legal classifications of pharmaceuticals: prescription pharmaceuticals and non-prescription (or over-the-counter) pharmaceuticals. Both prescription and OTC pharmaceuticals can only be sold at pharmacies. However, certain OTC products designated by the MOHW may be sold outside of the pharmacy at convenience stores. Such OTC products include antipyretics, analgesics, cold medicine, digestive medicine and pain relief patches.

The PAA also regulates quasi-pharmaceuticals such as gauzes, hand sanitisers and sanitary napkins (Article 2(7) of the PAA). Quasi-pharmaceuticals are specifically prescribed through a Notification issued by the MFDS. There is no restriction on point of sale for quasi-pharmaceuticals.

For medical devices, there is no restriction on the point of sale but a medical device seller licence obtained from the MFDS is required to sell medical devices. Some medical devices such as thermometers and pregnancy tests can be sold without a medical device seller licence.

xii Imports and exports
Pharmaceuticals
Pharmaceutical importers must obtain a product registration for each pharmaceutical imported and obtain an importer business licence from the MFDS.

Korean authorities no longer require product registrations for pharmaceuticals manufactured for the sole purpose of export. However, where the importing country’s authorities require a certificate of pharmaceutical product certification (CoPP), companies may still file for a product registration – in such case, the documentation submission requirements on safety, efficacy or quality may be relaxed or waived. GMP certification, however, is required even for products that are manufactured for export purposes.
Medical devices
To import medical devices, companies must obtain an importer business licence, product registration for the relevant product and GMP certification for the overseas manufacturing facility where the imported product is manufactured.

Companies that manufacture medical devices for export must hold a manufacturer business licence and a product registration for a medical device to be exported. The submission requirements (e.g., the technical documentation requirement) may be relaxed or waived for medical devices that are manufactured exclusively for export purposes. GMP certification is not required for export.

Controlled substances
The Narcotics Control Act (NCA) regulates (1) narcotics; (2) psychotropic drugs; and (3) marijuana (collectively ‘controlled substances’). Under the NCA, anyone intending to import controlled substances must be licensed by the MFDS as a narcotics importer, and must further obtain from the MFDS: (1) a product registration for any pharmaceutical classified as a controlled substance; and (2) approval for each imported shipment.

Under the NCA, a violation of the applicable requirements under the NCA can result in criminal sanctions. Anyone who imports controlled substances without a narcotics importer licence may be subject to imprisonment of five years or more. The employer can be held criminally liable for up to 100 million won.

Enforcement
Government agencies would hold their own proceedings for the purpose of determining whether to impose administrative sanctions for violations of relevant regulations. They may also refer the matter to the public prosecutor's office for a criminal investigation, if the relevant statutes provide for criminal sanctions.

The health authorities may take various administrative actions (e.g., order to test, recall, dispose, make public notice of ceasing the use of relevant products, revocation of business or product licences, order to cease relevant operations), impose administrative fines and/or make a criminal referral. The authorities may also decide to impose an administrative fine in lieu of an order for suspension of sales, manufacturing or import, in order to alleviate the detrimental effects that a suspension may have on a business or public health.

Additionally, industry associations for pharmaceutical and medical device companies have promulgated various industry codes of conduct, most notably for interactions with healthcare professionals (HCPs).

III PRICING AND REIMBURSEMENT
The Korean government offers universal health coverage, which means all citizens are eligible for at least some form of a public healthcare subsidy. As of 2018, 97.2 per cent of Korean citizens were enrolled in national health insurance, and those who were not enrolled received subsidies in the form of medical benefit payments from the government. The national health insurance scheme in Korea is a single-payer system operated by the NHIS.

When a manufacturer or an importer applies for pricing and reimbursement of a pharmaceutical, HIRA determines the eligibility for reimbursement and the NHIS determines the maximum reimbursement price (MRP) through negotiations with the companies. The pricing and reimbursement of new pharmaceuticals is determined based on a
cost-effective analysis (pharmaco-economic evaluation), while the pricing of generics is based on a set formula. Therefore, generics are not subject to price negotiations with the NHIS. The MOHW notifies the MRP of generics after HIRA decides that a generic product will be reimbursed under the NHI. For a drug to be reimbursed under the NHI, the manufacturer or importer must apply for listing, which is a two-part process involving separate negotiation over the reimbursement scope and MRP. Once a drug is listed for reimbursement, the reimbursement rate (the portion reimbursed by the NHI) is determined. Overall, patients are responsible for 30 to 60 per cent of medical service fees and about 30 per cent of the cost of pharmaceuticals.

Medical devices can be differentiated between those not covered by health insurance (non-reimbursed) and those that are covered by health insurance (reimbursed). For non-reimbursed medical devices, the final seller (medical institutions such as hospitals) independently decides the price based on market dynamics. Meanwhile, for reimbursed medical devices, the price can be included in the HCPs’ service fees and reimbursed, or separately calculated per medical device. Where the price of a medical device is separately calculated and reimbursed, HIRA determines eligibility for reimbursement based, in essence, on cost-effectiveness, and the MRP. The co-pay amount for patients is similar to pharmaceuticals.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

In an administrative enforcement action, companies are provided an opportunity to present their defence arguments before the relevant administrative agency before an administrative decision is rendered. Companies may also challenge the administrative decision (administrative fine, corrective order, etc.) by filing a lawsuit with the administrative court under the Administrative Litigation Act, or by initiating an administrative appeal with the general court system under the Administrative Appeals Act. Companies charged with criminal violations of relevant statutes can avail themselves of the criminal trial process to proffer defences.

The procedure for administrative cases is nearly identical to that of civil cases: a complaint is filed and served upon the defendant, arguments are made thereafter in the answer, reply brief, and other rebuttal briefs, evidence is examined at hearings, and a judgment is rendered. A final decision on the matter can be, in general, expected six months to a year following the initial filing.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

There are numerous anti-bribery and anti-corruption statutes that govern the interactions between pharmaceutical and medical device companies and prescribers and payors.

Mainly, the PAA and the MDA prohibits the provision of economic benefits to HCPs and medical institutions for promotional purposes unless specifically prescribed as exceptions. A violation of the foregoing prohibition would expose companies to administrative as well as criminal sanctions. Economic benefits include cash, goods, advantages, services, entertainment, labour or any other forms of benefits. Exceptions are not open-ended exceptions; for example, meals can be provided during product detailing sessions but cannot exceed 100,000 won.

The FTL, enforced by the KFTC, also prohibits companies from engaging in unfair solicitation of customers. Essentially, companies are prohibited from providing economic
benefits that are improper or excessive in light of socially accepted norms in order to induce customers. Companies in violation of the FTL may be subject to a corrective order, administrative fine or criminal referral. The respective industry associations have also promulgated codes of conduct, which were reviewed and endorsed by the KFTC for compliance with the FTL prohibition against unfair solicitation of customers, and reviewed by the health authorities for compliance with the PAA and MDA. While a violation of the industry codes is not a per se violation of the PAA, MDA or the FTL, the companies in practice could bear the burden of proving their compliance with the relevant statutes if a violation of the industry codes is found.

The Criminal Code penalises official and commercial bribery. Official bribery pertains to bribing government officials whereas commercial bribery pertains to bribing a person entrusted with conducting commercial duties for an employer or a company. Individuals can be held criminally liable for official bribery and commercial bribery.

The Act on Prohibition of Improper Requests and Provision/Receipt of Money and Valuables (the Anti-Graft Act) applies to the provision and receipt of things of value to public officials, a group that is broadly defined. For the healthcare sector, the statute applies to a wide range of individuals including government officials employed with health authorities as well as HCPs and faculty or staff members of public and private universities. Unlike official bribery under the Criminal Code, no quid pro quo or connection with the recipient’s official duties is needed for there to be a violation under the Anti-Graft Act. Individuals can be held criminally liable and companies can be held vicariously liable under the Anti-Graft Act for their employees.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The health authorities have set up an Adverse Event Compensation Scheme (AECS) for adverse reactions to pharmaceuticals, to provide compensation to patients and their families for death, injury, funeral costs and treatment costs caused by adverse effects from pharmaceuticals. The AECS is funded by pharmaceutical companies and operated by the Korean Institute of Drug Safety & Risk Management. The patients need not establish a defect in the product to be eligible for compensation under the AECS.

The statutory ceiling amount that pharmaceutical companies need to contribute to the AECS is up to 0.1 per cent of the preceding year’s manufacture or import amount. Additional contributions may be required of up to 25 per cent of the amount paid out to patients under the AECS during the previous year due to a company’s pharmaceuticals (not to exceed 0.1 per cent of the preceding year’s manufacture of import amount).

Buyers or users of defective pharmaceuticals or medical devices can also seek compensation under the Civil Code or the Product Liability Act (PLA). The claimant must prove negligence or intentional conduct that caused damage to the claimant under the Civil Code. Under the PLA, however, the claimant is only required to prove causation between the damages suffered and the defect in the relevant product (the claimant need not prove the manufacturer’s negligence or intent).
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law
In 2010, KTFC initiated an industry-wide investigation into intellectual property (IP) rights abuse, which was focused on whether innovators abused their IP rights, which would ultimately lead to delay in generic entry. Based on the survey and subsequent investigation, the KFTC found that a multinational drug company (innovator) and a domestic company (generic company) entered into a pay-for-delay settlement agreement in resolving a patent dispute, and also found that non-compete provisions in exclusive distribution agreements were unlawful as they went beyond the patent term, extended beyond the competing products and included irrelevant products (later affirmed by the Supreme Court).

In 2017, the KFTC commenced another IP rights survey of the pharmaceutical industry spearheaded by the Knowledge Industry Anti-Monopoly Division, which was established to oversee certain knowledge-based industries including the pharmaceutical industry. As a follow-on to the survey, according to media reports, the KFTC raided several pharmaceutical companies likely probing into collusive conduct stemming from business relationships between originator companies and generic companies. There has been no reports the KFTC has concluded its investigation.

ii Transactional issues
Two main collaborations in the pharmaceutical and medical device industries posing potential concern are licensing and distribution arrangements. For licensing arrangements, the KFTC’s Guidelines for Fair Patent Licensing Agreements provide for potential issues with patent licensing agreements that may violate the FTL and attendant regulations that include but are not limited to licence terms that restrict the licensee's ability to license or use competing technology and products due to confidentiality concerns, adequate allocation of benefits derived from improving the licensed patent technology and territorial restrictions.

For distribution arrangements, the FTL as well as the Fair Distributorship Transactions Act provide provisions governing relationships with distributors. Areas most likely to raise concerns for pharmaceutical companies and medical device companies in their relationships with distributors are, among others, resale price maintenance, namely, requiring the distributor to resell the product to its customers at a set price, setting of forced sales targets, and refusing to transact or renew an existing transaction without justifiable reasons.

VIII CURRENT DEVELOPMENTS

i Innovation-promoting legislation
Recently, the Korean government has been trying to provide a more innovation-friendly regulatory framework to support the life science industries. As a part of this effort, the In Vitro Diagnostics Act (the IVD Act) and the Act on Promotion of Medical Device Industry and Support for Innovative Medical Device Products (the Innovative Device Act), which will become effect on 1 May 2020, were enacted. The IVD Act was enacted to address concerns that in vitro diagnostics (IVDs) should be regulated separately from other medical devices as they are used for diagnostics purposes only and do not come in direct contact with the human body. Once in effect, the IVD Act will, among other effects, expand the scope of IVDs that can be marketed in Korea without a product registration and change the labelling requirements for IVDs. The Innovative Device Act will introduce systems to
encourage research, development and commercialisation of innovative medical devices. As an example, a company that has obtained certification as an innovative medical device company under the Innovative Device Act can enjoy preferential status for participating in various government projects and tax incentives. A medical device can be certified as an innovative medical device under the Innovative Device Act, in which case a simplified review process for product registration can apply.

ii Digital health

Recently, digital health has gained much traction and interest among industry leaders, physicians, patients, and the healthcare industry generally. Korea is a very attractive market for digital health since Korea has advanced medical technology, sophisticated IT infrastructure, a large amount of medical data, and an ever-increasing elderly population that demands a better healthcare system. However, it is reported that the regulatory environment has not been so friendly to the development of Korea’s digital health industry. Prohibition of remote healthcare and direct-to-consumer genetic testing and other data-related regulations are a few examples of such hurdles. To address this problem, government agencies such as the MOHW and MFDS are attempting to revise and improve regulations regarding digital health, and are publishing or releasing guidelines, handbooks and authoritative interpretations to better explain vague policies.

Since January 2019, as part of this effort to improve the regulatory environment and to encourage development of new technology and industries, the Ministry of Science and ICT and the Ministry of Trade, Industry, and Energy have adopted a ‘Regulatory Sandbox’ system. If existing regulations are unclear, irrational or prohibitive, the Regulatory Sandbox system allows three mechanisms to address these issues. First, under the ‘Proven Exception’ provision, the Regulatory Sandbox system will relax a restrictive regulation under specific conditions of scope, scale and duration. Second, under the ‘Temporary Approval’, the system allows for a market-first, evaluation-later approach. Third, under the ‘Active Administrative Interpretation’, it allows a more relaxed interpretation of existing regulations.

One example of the application of these Regulatory Sandbox mechanisms to the digital health field is the online brokerage service for clinical trial participants, which is a service that connects (applies and registers) clinical trial participants to the organisation conducting the trial through a smart phone application. Previously, providing information about clinical trials for a prescription pharmaceutical online and connecting participants with the clinical trial sponsors was prohibited under the PAA, because it was interpreted as prohibited mass-media advertisement of prescription pharmaceuticals. Under the Active Administrative Interpretation, such online brokerage service is permitted upon the IRB’s discretionary approval to allow online brokerage services after considering the nature of the clinical trial.

After the Regulatory Sandbox took effect, companies have begun to offer services that were previously prohibited in Korea due to strict regulations.
I INTRODUCTION

The main regulatory aspects of the life sciences sector in Spain are laid down in the Consolidated Text of the Law on Guarantees and Rational Use of Medicines and Medical Devices, approved by Royal Legislative Decree 1/2015 of 24 July (Royal Legislative Decree 1/2015). The Law on Guarantees implemented the Directive 2001/83/EC into Spanish law and its Consolidated Text includes the main regulation regarding the whole life cycle of medicines and medical devices: investigation, authorisation procedure, manufacturing, distribution, rational use, price and reimbursement, vigilance, withdrawal from the market and liabilities. Most of these phases are further regulated by specific royal decrees providing for specific details and requirements.

Precise requirements applicable to the medical devices life cycle are governed by Royal Decree 1591/2009 of 16 October on medical devices (Royal Decree 1591/2009), by Royal Decree 1616/2009 of 26 October on active implantable devices and by Royal Decree 1662/2000 of 29 December on in vitro diagnosis devices, implementing in Spain the corresponding European directives.

The competencies regarding healthcare issues are ascribed to the Ministry of Health, Social Services and Equality (MoH). The Spanish Agency of Medicines and Medical Devices (AEMPS) is the competent authority within the MoH with regard to overseeing the technical and quality requirements of medicines and medical devices, including the marketing authorisation, while the General Directorate of Reimbursable Basic Services of the National Health System (DGCB) is mainly responsible for the economic features (price fixing and reimbursement). The healthcare authorities of the autonomous regions have also assumed certain competencies, principally related to distribution, dispensation, advertising and pharmacovigilance control of medicinal products.

II THE REGULATORY REGIME

i Classification

Pursuant to the Royal Legislative Decree 1/2015, a medicinal product is any substance or combination of substances presented for treating or preventing diseases in human beings or animals, and that may be administered with a view to restoring, correcting or modifying physiological functions or to making a medical diagnosis.
Medical devices are defined as any instrument, apparatus, appliance, computer programme, material or other article, whether used alone or in combination, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process or control of conception, and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means.

The distinction between medical devices and medicines is not always clear, but if a product could be included within the definition of a medicinal product, the Royal Legislative Decree 1/2015 shall be applicable, although the product could also be subject to other regulations. The AEMPS is also competent to determine whether a product can be considered a medicine, a medical device or any other product (e.g., personal care or cosmetic products). To assess these cases, which would be settled on grounds of the actual health or medical utility of the product, specific European guidelines are applicable.²

ii Non-clinical studies

Non-clinical studies shall be performed in facilities that have obtained a certificate of compliance with good laboratory practices (GLP). The AEMPS is the competent authority regarding the adoption of the applicable GLP, determined by specific guidelines. It would also perform the necessary inspection before issuance of the corresponding certificate of compliance.

Non-clinical studies on animals shall comply with the requirements of Royal Decree 53/2013, of 1 February, on the basic rules on the protection of animals used in investigations, regarding their treatment, transport, registry or housing and care during the study.

iii Clinical trials

All clinical trials performed in Spain are subject to Royal Decree 1090/2015 of 4 December on Clinical Trials and Ethic Committees on Medicines Research and the Spanish Clinical Trials Registry (Royal Decree 1090/2015), which implements Regulation (EU) 536/2014.³ The document 'Instructions of the Spanish Agency of Medicines and Medical Devices (AEMPS) to conduct clinical trials in Spain', of 10 December 2019, is of particular interest, providing for a practical approach on the current regulation.

Pursuant to Royal Decree 1090/2015, three requirements must be met to perform clinical trials in Spain:

a single, binding and favourable decision of an ethics committee;
b resolution of authorisation issued by the competent authority (AEMPS); and
c conformity of the site where the clinical trial is going to be performed, by means of a Clinical Trial Agreement.

To conduct a clinical trial in Spain, the sponsor or its legal representative shall be established in the European Union and shall subscribe an insurance or financial guarantee that covers the damages that could arise for the trial subject, as well as any liability that might be incurred.

by the sponsor, principal investigator and members of the investigator team, except for cases of ‘low-intervention clinical trial’. Sponsors shall also assure that all the subjects taking part in the clinical trial (or their legal representative, in the case of minors or mentally disabled people) have given their written, informed consent, which may be revoked at any time.

While performing a clinical trial in Spain, the sponsor and the investigator shall ensure that it complies with the protocol and with the principles of good clinical practice. They shall also take into account the quality standards and guidelines of the International Conference on Harmonisation on good clinical practice. The sponsor is responsible for the continuous assessment of the benefit-risk balance of the clinical trials and, thus, it must report to the AEMPS any information substantially affecting these aspects. Royal Decree 1090/2015 also imposes on the sponsor the obligation to report unexpected serious adverse reactions associated with investigational medicinal products of which it becomes aware, whether occurring in Spain or in other countries.

Royal Decree 1090/2015 also applies to clinical trials conducted by investigators without the engagement of pharmaceutical or medical devices industry (i.e., non-commercial clinical research), containing special regulations regarding insurance requirements and applicable fees.

iv  Named-patient and compassionate use procedures

Under exceptional circumstances, the AEMPS can authorise the use of investigational medicines before they have obtained a marketing authorisation or have been the subject of a marketing authorisation application, pursuant to the requirements in Royal Decree 1015/2009, of 19 June, on the availability of medicines in special situations (as set out in Royal Decree 1015/2009), providing that the patients receiving them:

a  do not have access to a satisfactory therapeutic alternative available in the market;
b  are not taking part in a clinical trial; and
c  have an urgent medical need and therefore cannot wait until the investigation is over or alternative medicines are authorised.

Under Royal Decree 1015/2009, the healthcare professional responsible for the treatment can also authorise the use of medicines for different uses than those included in its marketing authorisation, provided the patient has been duly informed and no therapeutic alternative is available.

v  Pre-market clearance

Medicines

For medicinal products to be distributed within Spain, a marketing authorisation must be obtained first and the products must be registered with the medicines registry hosted by the AEMPS.

The marketing authorisation can be obtained through a centralised procedure before the European Medicines Agency (only applicable to certain products) and permits marketing throughout the European Union. A marketing authorisation to place the product wholly within Spain can also be obtained. Royal Decree 1345/2007 of 11 October on the authorisation procedure, registration and dispensation conditions of industrial medicinal products for human use in Spain (Royal Decree 1345/2007) provides for the requirements to follow a national, decentralised or mutual recognition procedure before the AEMPS.
The authorisation procedure requires the submission of an application containing all the relevant aspects of the medicinal product, including: name, composition and therapeutic conditions, safety measures, pharmacovigilance system, pharmacological tests, and preclinical and clinical trial results. These results are not required if the application is made with the consent of a marketing authorisation holder (MAH) or if it is referred to an active ingredient that has a clearly established use within the European Union or to a generic medicinal product that has been authorised for a minimum of eight years within the European Union (simplified procedure). The AEMPS would assess the positive therapeutic effects of the medicinal product on the grounds of its safety, quality and efficacy, under a benefit-risk balance approach.

Royal Decree 1345/2007 also contains special requirements applicable to the marketing of certain medicinal products, including vaccines (each batch shall be authorised by the AEMPS prior to its release), herbal medicines (only registration is needed) and homeopathic products (which requires a simplified procedure of authorisation when certain conditions are met).

Medical devices

Medical devices can only be placed on the market or put into service when they comply with certain requirements ensuring their safety. Medical devices can be categorised as diagnostic in vitro and active implantable, and are subdivided into Classes I, IIa, IIb and III, depending on their risk. Pursuant to Royal Decree 1591/2009, anyone who wants to place medical devices of Classes IIa, IIb or III on the Spanish market for the first time shall report it to the AEMPS, which must keep an up-to-date register of all communications. Manufacturers of Class I or custom-made medical devices that are responsible for their first commercialisation shall be included in a register organised by the AEMPS.

Further to these requirements, with the exception of custom-made devices and devices intended for clinical investigation, medical devices need to obtain the CE mark, which can only be placed by the manufacturer when the devices fulfil the legal requirements, according to the evaluation accomplished by the competent notified bodies, which shall be authorised by the MoH.

vi  Regulatory incentives

Royal Legislative Decree 1/2015 includes the European criteria regarding the protection of innovation and investigation, while ensuring competition in the Spanish market. An applicant for a generic medical product can submit its application for marketing authorisation after at least eight years have expired since the medicine of reference obtained a marketing authorisation in any of the EU Member States. This allows the evaluation procedure to move forward, although the generic medicine cannot be effectively placed on the market until the period of data exclusivity protection has elapsed (10 years after approval of the medicine of reference or 11 years if new indications have been authorised for the medicine during the first eight years).

This protection regime is completed with the inclusion of the Bolar exception into Article 61.1(c) of Law 24/2015, of 24 July, on patents, which implies that the patent's scope of protection shall not be extended to studies and trials performed for the authorisation of a generic medicine in Spain or abroad, and the subsequent practical requirements, including the preparation, production and use of the active ingredients for those purposes.
Regulation (EC) 469/2009\(^4\) allows for an extension of the patent term for medicinal products by means of a supplementary protection certificate (SPC), which shall be granted by the Spanish Patent and Trademark Office. This SPC can be extended by up to six months if the application for a marketing authorisation is accompanied by studies conducted in compliance with an agreed paediatric investigation plan, pursuant to Regulation (EC) 1901/2006.\(^5\)

**vii Post-approval controls**

Pursuant to Royal Decree 1345/2007, the MAH shall observe the conditions of the marketing authorisation as well as any modification adopted after it has been granted, introducing any changes that may be required regarding the manufacturing or control system of the product. The MAH must also respect the principle of continuity in the provision of the service and keep the product dossier up to date. Furthermore, the MAH must (1) have comprehensive knowledge of the medicinal product, promoting its rational use; (2) participate with the control programmes, informing the AEMPS of the product’s withdrawal from the market; and (3) guarantee the collection of any medicinal waste from the product.

According to Royal Decree 577/2013, of 26 July, on pharmacovigilance of medicinal products, a MAH must maintain a pharmacovigilance system that allows it to control the safety of the marketed medicinal products and to identify any change regarding the risk–benefit ratio. This regulation also includes further obligations to report and record any suspected adverse reactions, periodic safety update reports or the qualified person responsible for pharmacovigilance.

Manufacturers and authorised representatives, distributors or importers of medical devices are also required to notify the AEMPS of any defective operation or alteration within the characteristics of the devices or their labelling, as well as any technical or health-related circumstances that have led to the adoption of any systematic measure on the devices, according to Royal Decree 1591/2009.

Marketing authorisations are granted for a period of five years, although they can be renewed after such period, prior to the re-evaluation of the risk–benefit ratio. This renewed authorisation shall be valid indefinitely, provided there are no pharmacovigilance reasons that justify the submission of another renewal procedure. The marketing authorisation can be revoked or suspended because of a lack of quality, safety or efficacy, according to Royal Decree 1345/2007. It can also expire if the MAH does not market the medicinal product within three years or, if it is not available for three years, once it has been duly placed on the market. Any amendment, transfer, suspension or revocation of the marketing authorisation shall be authorised by the AEMPS and included in the medicines registry in order to produce its effects.

---


Manufacturing controls

The manufacturing of medicines in Spain is subject to the granting of a manufacturing authorisation by the AEMPS, pursuant to Royal Decree 824/2010, of 25 July, on pharmaceutical laboratories, manufacturers of active substances and external trade of medicines and investigational medicines. To obtain the manufacturing authorisation, the applicant shall identify the specific medicines and pharmaceutical forms that it intends to manufacture. The applicant must be in possession of appropriate facilities and technical and safety measures to develop the activity, and it must designate, at the very least, a technical director and a responsible production manager. The applicant is also obliged to comply with the good manufacturing practices adopted by the AEMPS according to European requirements. The AEMPS must keep a registry of the authorised manufacturing laboratories, and every amendment, transmission or expiry of the authorisation has to be authorised and registered to be effective.

The MAH that provides its own facilities to store its medicinal products in Spain must obtain authorisation as an MAH laboratory from the AEMPS – a manufacturing authorisation would facilitate this.

Manufacturing of medical devices is subject to a prior activity licence for the facilities, issued by the competent authorities pursuant to the requirements of Royal Decree 1591/2009.

Advertising and promotion

Medicinal products

The main principles concerning the advertising of medicinal products in Spain are laid down in Royal Legislative Decree 1/2015 and in Royal Decree 1416/1994, of 25 July, on advertising of medicinal products for human use. The autonomous regions have also adopted guidance interpreting the principles in the legislation and regulations setting their own proceedings for compliance. In addition, self-regulation has an important role in advertising: Farmaindustria (a private association of pharmaceutical companies) has adopted the ‘Spanish Code of Good Practice for the Pharmaceutical Industry’ and the Personal Healthcare Association (ANEFP) has released a ‘Spanish code of good practices for the promotion and advertising of non-prescription medicinal products’. Both texts extend the legal obligations for advertising and make them more demanding, but the texts are only applicable to members of Farmaindustria or ANEFP, or those who choose to abide by them.

As a general principle, only medicines that have complied with all the steps needed to obtain a marketing authorisation in Spain can be advertised, provided that the advertising encourages rational use of the medicine by presenting it objectively, without being misleading and not exaggerating its properties.

Advertising to consumers is only allowed for medicines not included in the public reimbursement system, which are not prescription medicines and that do not contain narcotic or psychotropic substances. Advertising does not require prior authorisation, although it

---

6 By way of example, Madrid Circular 1/2000 on advertising aimed at persons qualified to prescribe and supply medicinal products; Madrid Circular 1/2002 on medical sales representative visits and other medicinal products advertising activities; and the Madrid Clarification Document on Valid Advertising Forms (as of September 2015) and Catalonian Guidance for the Advertising of Human-Use Medicinal Products, released on April 2016 (4th edition).

7 The latest revision was released in October 2016.
shall be subject to regulatory supervision and certain restrictions are applicable regarding its content (i.e., recommendations by healthcare professionals related to the virtues of the product are prohibited).

Advertising aimed at persons qualified to prescribe or supply medicinal products shall be in line with the technical and scientific information of the medicine duly authorised by the AEMPS, and must be objective, well-founded, thorough and not misleading. When performed in written form, the advertising is subject to prior communication with the healthcare authorities of the autonomous regions. The supply of samples is exceptionally allowed when geared towards persons qualified to prescribe medicinal products under certain circumstances. Royal Decree 1416/1994 also contains provisions for other means of publicity aimed at healthcare professionals, which is further explained in Section V.

**Medical devices**

The main aspects of regulation regarding advertising of medical devices are laid down under Royal Legislative Decree 1/2015 and Royal Decree 1591/2009; the Code of Conduct of the Spanish Federation of Healthcare Technology Companies (FENIN) shall also be taken into account for members of the federation.

Every advertising message included in the general media (newspapers, radio, television, web pages, etc.) that is directly targeted at the general public must first be authorised by the competent healthcare authorities of the autonomous region.

When aimed at consumers, it is forbidden to advertise medical devices financed through the National Healthcare System (NHS) or that are intended to be used exclusively by healthcare professionals.

**Distributors and wholesalers**

Royal Decree 782/2013, of 11 October, on distribution of medicinal products of human use, contains obligations, restrictions and requirements applicable to the distribution entities allowed in Spain.

This Decree applies to wholesalers, pharmaceutical companies that perform distribution functions by themselves, third parties that assume distribution activities on behalf of wholesalers, and medicines warehouses subject to custom vigilance. The Decree also regulates the brokering activities that relate to those who carry out the distribution obligation but have no physical contact with the medical products.

To supply pharmacies and hospitals, wholesale distributors and third parties acting on their behalf shall obtain an authorisation granted by the healthcare authorities of the autonomous region where the business is located. If the wholesale distributors and third parties carry out distribution activities in the territory of another autonomous region, these activities shall also be notified to the competent authorities of that region. The AEMPS directly authorises any medicines warehouse subject to customs vigilance, and brokers are only compelled to notify their activity to the AEMPS, which keeps an updated registry.

**Classification of products**

Pursuant to Royal Decree 1345/2007, medicinal products can be categorised as:

a) non-prescription medicines (over-the-counter); and

b) prescription medicines, which can also be classified as:

• medicines subject to renewable prescription;
• medicines subject to special prescription (i.e., containing narcotic or psychotropic substances); and
• medicines subject to restricted prescription (medicines for hospital use and medicines for hospital diagnosis to be prescribed by a specialist).

This classification has important legal consequences: non-prescription medicines can be purchased online, while prescription medicines are the only types of medicines that can be included in public funding procedures.

xii Imports and exports
Regarding medicinal products, only those duly authorised and registered in the AEMPS registry can be imported into Spain. Companies willing to import medicinal products shall obtain an authorisation as a manufacturing laboratory by the AEMPS, and are subject to all the obligations contained in Royal Decree 824/2010. Exportation is allowed to laboratories and distribution entities that fulfil the legal requirements, and shall be notified to the AEMPS.

Laboratories that intend to import medical devices shall also obtain an activity licence for the facilities. Medical devices due to be exported to third countries must have this fact included in the labelling.

xiii Controlled substances
The regulatory competence regarding the importation, exportation and commercial sale of certain narcotics and psychotropic substances is attributed to the AEMPS, which must authorise the manufacture of such substances when they are intended to be marketed in other countries. The importation and exportation of narcotics and psychotropic substances are also subject to prior authorisation by the AEMPS, which would assume the control of said activities, and the further distribution and dispensation of such substances. The AEMPS also assumes administrative management regarding the control of the aforementioned substances, such as the production and distribution of official receipt templates or the issuing of certificates and permits for carriage by travellers for the purpose of medical treatment.

xiv Enforcement
The AEMPS and the healthcare authorities of the autonomous regions, according to their respective competence, may perform inspections to verify the fulfilment of the obligation imposed under the applicable regulation, such as compliance with the quality standards on good clinical practice, the pharmacovigilance duties imposed on the MAH, or good manufacturing practices. Issues regarding distribution, prescription, dispensation and advertising are mainly attributed to the autonomous regions. The infringement of legal obligations can be sanctioned with economic fines ranging from €6,000 to €6 million, depending on the nature of the infringement. With regard to medicines, infringements can be also penalised by confiscation by the Public Treasury of the profits obtained as a consequence of the infringement, as established in Royal Legislative Decree 1/2015.

Farmaindustria, FENIN and ANEFP also regulate the special mechanism to ensure the compliance of the obligations stipulated by their codes of conduct, which are only applicable to their members and those who choose to abide by them.
III PRICING AND REIMBURSEMENT

Once a medicinal product or medical device has complied with the requirements to be legally marketed in Spain, the first step to determine its price is to decide whether or not it can be included in the NHS, and thus if its price can be reimbursed. Pursuant to Royal Legislative Decree 1/2015, competence on this matter is attributed to the DGCB of the MoH.

The decision regarding inclusion would be made on the basis of objective criteria, such as severity, nature of the pathologies that the product was approved for, special needs of certain social groups, therapeutic and social value, rationalisation of public expenditure, availability of other products or the level of innovation.

Once a product is included in the NHS, the Interministerial Commission for Pharmaceutical Prices (CIPM) would determine the laboratory selling price. By adding the commercial margins and VAT to this price, the public retail price for wholesalers and pharmacies is determined. For the products to be dispensed through public hospitals, the final price would be fixed by the tender entity by means of public bids. All these prices are subject to a second intervention through the prices of reference, which determine the maximum amount the NHS would allocate for each product.

If the products are not included in the NHS, the laboratories would notify the prices to the CIPM, which can either accept the prices or make objections.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Each Decree lays down specific ways of challenging the decisions adopted by the regulatory bodies relating to the fulfilment of the legal requirements applicable to the different phases of the legal life cycle of medicines and medical devices. In general terms, decisions not finalising an administrative procedure can be challenged before a higher administrative body within a month from the date the decision is notified. The decision settling this claim can be further appealed before a contentious-administrative court within two months of its notification.

A decision finalising an administrative procedure can either be challenged before the same administrative body that adopted it within one month of its notification or directly appealed before a contentious-administrative court.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Pursuant to the ‘independence guarantee’ contained in Royal Legislative Decree 1/2015, it is prohibited to directly or indirectly offer any incentive to healthcare professionals involved in the prescription, dispensation and administration of medicines, and in the prescription of medical devices, by those that have a direct or indirect interest in the manufacture and commercialisation of medicines. According to Royal Decree 1416/1994, the prohibition on gifts would not impede the pharmaceutical companies from offering reasonable hospitality within the scope of scientific meetings, provided that it is reasonable and secondary to the main purpose of the meeting, and does not extend to persons other than the healthcare professionals.

These obligations have been further restricted and thoroughly regulated under self-regulation good practices codes, adopted by Farmaindustria, ANEPF and FENIN, which are in line with the European Federation of Pharmaceutical Industries and Associations codes.
and cover any activity carried out, organised or sponsored by pharmaceutical companies and provide for guidance and clear examples of prohibited conduct, and the adequate way to proceed in the relationship between pharmaceutical companies and healthcare professionals.

To promote transparency, these organisations have included in their codes of good practice the obligation to disclose the transfers of value between pharmaceutical companies, and between healthcare professionals and healthcare organisations. Although these codes are only applicable to the companies that are members of Farmaindustria and FENIN, they are considered a very useful tool for interpreting the obligations contained under Royal Decree 1/2015.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS
Under Spanish law, there is no specific system that aims to compensate persons injured by medicines or medical devices and, therefore, this matter is subject to the general rules contained under the Civil Code, which comprises the general regulation on contractual and non-contractual liability, and under Royal Decree 1/2007, of 16 November, enacting the General Law on the Protection of Consumers and Users.

Accordingly, to obtain compensation regarding damages that are the result of medicines and medical devices from manufacturers or importers, the claimant shall prove the existence of a defect in the product in question, the damage suffered and the causal relationship between the defect in the product and the damaged caused.

The regulatory competence regarding the recall of defective medical devices and medicinal products is attributed to the AEMPS and the healthcare authorities of the autonomous regions.

VII TRANSACTIONAL AND COMPETITION ISSUES
i Competition law
Spanish competition law does not differ from European law in the life sciences sector. In fact, on 28 January 2019, the European Commission adopted the Report ‘European competition authorities working together for affordable and innovative medicines’ on competition enforcement in the pharmaceutical sector, which has been drafted in close cooperation with the national competition authorities of the 28 EU Member States. The Report covers the period 2009–2017 and describes how intervening against anticompetitive practices by companies and preventing harmful mergers complements the efforts by other stakeholders (e.g., in regulation) to improve access to affordable and innovative medicines for patients in Europe.

Regarding proceedings before the CNMC in this sector, in February 2019 the CNMC initiated a disciplinary proceeding on anticompetitive practices in the Spanish radiopharmaceutical market (S/0644/18 RADIOFARMACOS).

ii Transactional issues
The pharma sector in Spain experienced important transactions during 2019, especially regarding mergers and acquisitions between life sciences companies that have been developing activities relating to the manufacture of medicinal products, medical devices or wholesale distribution.
In addition, in the field of pre-commercial procurement, several projects have been developed between public and private entities in relation to healthcare protection regarding new technologies and devices, which can pave the way for further strategic collaboration in the pharmaceutical sector.

VIII CURRENT DEVELOPMENTS

One of the main developments during this year has been the implementation of a national system of verification and authentication to prevent the entry of falsified medicinal products into the legal supply chain, following EU requirements. To that end, Royal Decree 717/2019 of 5 December 2019 has included several modifications on Royal Decree 1345/2007, providing for a regulation regarding the safety features that shall be included in each pack of medicinal products, as well as the controlling activities that shall be performed before distributing medicinal products covered by the NHS.

The intention to restrain pharmaceutical expenditure and make it more sustainable has also led some of the measures adopted in Spain during the past year. In April 2019, the Ministry of Health approved an action plan to foster the use of biosimilar and generic medicinal products with the aim of lowering entry barriers and increasing competition in the pharmaceutical market.

Chapter 27

SWEDEN

Camilla Appelgren and Odd Swarting

I INTRODUCTION

Healthcare in Sweden is the shared responsibility of the state, regions (formerly county councils) and municipalities. The state is responsible for the overall health and medical care policy.

The Ministry of Health and Social Affairs acts to meet the objectives set by the Swedish parliament and the government. Several independent agencies answer to the Ministry of Health and Social Affairs. The following agencies support the Ministry’s activities on health and medical care: National Board of Health and Welfare, Medical Responsibility Board, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Medical Products Agency (MPA), Swedish Agency for Health and Care Services Analysis, Dental and Pharmaceutical Benefits Agency (TLV) and Health and Social Care Inspectorate. In addition, the Swedish eHealth Agency and the Public Health Agency of Sweden were implemented on 1 January 2014. Manufacturing of medicinal products and medical devices is one of the largest industries in Sweden and seen as a high priority by the Swedish government; Sweden is the EU’s innovation leader, according to the European Innovation Scoreboard 2019.

Being an EU Member State, Sweden’s legal framework on medicinal products and medical devices is to a large extent based on relevant EU directives and is subject to EU regulations. The national legislative basis for oversight and enforcement of medicinal products in Sweden is primarily stipulated in the Medicinal Products Act and the Medicinal Products Ordinance, and for medical devices in the Medical Devices Act and the Medical Devices Ordinance (until Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices will be fully applicable in May 2020 and May 2022, respectively, see below).

---

1 Camilla Appelgren is a partner at Mannheimer Swartling Advokatbyrå and Odd Swarting is a senior counsel at Cirio Advokatbyrå.
2 SFS 2015:315.
3 SFS 2015:458.
4 SFS 1993:584.
5 SFS 1993:876.
II THE REGULATORY REGIME

The Medicinal Product Act and the Medicinal Products Ordinance are based on Directive 2001/83/EC, and the Medical Devices Act and the Medical Devices Ordnance are based on Directives 90/385/EEC, 93/42 EEC and 98/79/EC. There are additional regulations and guidelines issued by the MPA.

Notably, on 5 April 2017, two new regulations on medical devices were adopted within the European Union; Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices. They entered into force on 26 May 2017, replacing the existing directives. However, the new rules will only apply after a transitional period of three years after entry into force for the regulation on medical devices (in May 2020), and five years after entry into force for the regulation on in vitro diagnostic medical devices (in May 2022).

i Classification

The definition of a medicinal product corresponds with the definition found in Directive 2001/83/EC. According to Chapter 2 Section 1 of the Medicinal Products Act, a medicinal product is:

a. any substance or combination of substances having properties for treating or preventing diseases in human beings; or
b. any substance that may be used in or administered to human beings or animals either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The two primary determining factors for classifying a medicinal product are the content of the product and the intended use of the product. Other factors that may affect the classification of the product are, for example, (1) the formulation of the product, (2) how the product is marketed, and (3) whether or not the product meets the requirements of medical devices, in which case the legislation on medical devices will apply.

A product that does not fall under the definition of a medicinal product according to the above definition and determining factors, can nevertheless, because of its characteristics, purpose and use, be covered by the Medicinal Products Act, in line with MPA Regulation LVFS 2011:15. For instance, a product can be classified as a medicinal product even without containing any active substances (e.g., products that would seem to fall within the scope of food, food supplements or cosmetics).

The definition of a medical device is broad and includes products ranging from plasters to advanced diagnostics scanners. The definition in Swedish legislation is based on the applicable EU directives, and the primary national definition is stipulated in Section 2 of the Medical Devices Act, which states that a medical device is a product that, according to the manufacturer, is intended for use, separately or in combination with other products, in human beings for the purpose of:

a. diagnosis, prevention, monitoring, treatment or alleviation of disease;
b. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
c. investigation, replacement or modification of the anatomy or of a physiological process; or
d. control of conception.
However, if the product achieves its principal intended action in or on the human body by pharmacological, immunological or metabolic means, it is not a medical device according to the Medical Devices Act.

The Medical Devices Act also stipulates certain requirements of medical devices. For instance, according to Section 5 of the act, a medical device must be suitable for its intended use. A device is suitable if it is delivered and installed in accordance with the manufacturer’s directions and if it achieves its purposes according to the manufacturer and caters for the requirements of protection of life, personal safety and the health of patients and users. These safety requirements derive from the EU legislation on medical devices.

In addition, the Product Safety Act\(^6\) applies to medical devices that are intended for consumers, or if it can be assumed that the device will be used by consumers, in areas of product safety that are not covered by the Medical Devices Act.

### ii Non-clinical studies

A candidate drug must be tested for efficacy and security in a non-clinical study before it is tested on human beings in a clinical trial. The scope and type of experiments and studies that have to be carried out in the non-clinical study are laid down, for example, in guidelines issued by the European Medicines Agency (EMA). The European Commission has also issued guidelines on non-clinical studies, which give detailed information regarding the types of non-clinical studies that need to be carried out prior to conducting a clinical study.

Non-clinical studies sometimes involve animal testing. The Swedish legislation governing animal protection in general and animal testing in particular is strict, and animal testing methods may only be used if the intended results of the research cannot be reached with any other method. All animal testing in Sweden must be in accordance with the Animal Protection Act\(^7\) and before any animal experiment begins, it must be approved by an ethics committee.

A non-clinical study must, throughout the entire process, meet the requirements of good laboratory practice (GLP). The Swedish requirements on GLP are in line with the standards set out in Directives 2004/9/EC and 2004/10/EC. The monitoring authority on GLP in Sweden is the MPA. The authority may, for example, conduct inspections to ensure that non-clinical studies are in compliance with applicable GLP standards.

### iii Clinical trials

According to the Medicinal Products Act, a clinical trial may be carried out to establish or confirm the safety and effectiveness of a medicinal product. The trial may be conducted either with or without a connection to regular medical treatment. It must be performed by a qualified medical doctor (or dentist or veterinary surgeon, as applicable) with sufficient knowledge and experience of managing clinical trials. As mentioned above, a non-clinical trial must have been carried out prior to conducting the clinical trial.

Before a clinical trial can be conducted, it must be approved by the MPA, in line with the Medical Products Act. For clinical trials involving human beings, there are also applicable rules set out in the Ethical Review Act\(^8\), including, inter alia, the requirement to

---

7 SFS 1988:534.
8 SFS 2003:460.
obtain approval by an ethics committee. Clinical trials also require explicit consent of the study subject, and the trial subject must have been duly informed about the study, the risks involved and about his or her right to withdraw from the trial at any time.

MPA Regulations LVFS 2011:19 and 2004:6 state that the principles of good clinical practice and the most recent edition of the World Medical Association's Declaration of Helsinki must be observed during a clinical trial. In clinical trials where a substance is tested in human beings for the first time, the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products should be observed, and any deviation should be justified in the application to perform the trial.

According to the Medical Devices Act, the government or the relevant competent authority may decide what types of medical devices shall be tested clinically and how the clinical trial shall be performed. The MPA has been given the authority to oversee clinical trials of medical devices. A clinical trial shall only be performed when the necessary information about a device’s performance, safety and use cannot be established or confirmed without testing in human beings.

Clinical trials in Sweden have to be registered with the European Clinical Trials Register. The personal data of patients collected during clinical trials must be processed in accordance with the EU General Data Protection Regulation9 and the Patient Data Act,10 which specifically govern the processing of sensitive, or 'special categories', of personal data, including, for example, personal information about health, biometric data, genetic data or a natural person's sex life.

iv  Named-patient and compassionate-use procedures

In some cases, certain medical needs are not met by approved medicinal products. In such cases, affected patients are, in addition to participation in clinical trials, able to obtain treatment through named-patient use licensing, a compassionate-use programme (CUP) or through a hospital exemption. The use of unauthorised medicinal products is primarily governed by the Medicinal Products Act, the Medicinal Ordinance and MPA Regulations HSLF-FS 2018:25 and LVFS 2011:3.

There are mainly three ways in which a patient can get access to an unauthorised medicinal product. First, the MPA can at short notice allow a prescription through a special permission (licence) on a named-patient basis, either for a specific person (individual licence) or to a group of patients being treated at a clinic or another equivalent institution (general licence). The named-patient permission is available for prescribers to facilitate necessary treatment when medical conditions cannot be treated with approved medicinal products. The prescriber may initiate the application process by writing a prescription and handing it in at a pharmacy with their justification for the prescription. If there are no approved treatment options available, the pharmacy shall then submit the application to the MPA for individual assessment. There are certain specific requirements for the reporting of adverse reactions applicable to named-patient sales.

Second, patients are able to access unapproved medicinal products through a CUP that is governed by Regulation (EC) No. 726/2004 on compassionate use of medicinal

---

10 SFS 2008:355.
products. The purpose of a CUP is to complement the named-patient licensing procedure. It is intended for patients with a chronic or seriously debilitating disease, or patients whose disease is considered life-threatening and cannot be treated satisfactorily with an authorised medicinal product. Certain requirements about satisfactory documentation of efficacy and safety apply, as well as specific obligations for the responsible physician to report adverse reactions. The permit holder must also submit annual safety reports to the MPA.

Third, access to an unauthorised medicinal product can be provided through a hospital exemption. This means that, under certain conditions, a healthcare provider can obtain a manufacturing permit from the MPA to use advanced therapy medicinal products that have not been evaluated or approved in the European Union. The product must be customised for a specific patient on a non-routine basis. A qualified person must be appointed to be responsible for the treatment and the treatment is subject to applicable rules on good manufacturing practice (GMP). The MPA may revoke the permit temporarily or permanently.

v Pre-market clearance

The MPA grants marketing authorisation for medicinal products in Sweden according to certain procedures. A marketing authorisation is mandatory for manufacturers or importers of medicinal products before they can engage in any sales activity. The MPA grants marketing authorisations under the mutual recognition procedure (MRP), the decentralised procedure (DCP) and the national procedure. The EMA also grants marketing authorisations under the centralised authorisation procedure; these authorisations apply directly in Sweden.

When an application is made for marketing authorisation under the MRP, reference is made to a national marketing authorisation in another EU Member State, which should then be recognised in Sweden unless the MPA finds reason to believe that the medicinal product may pose a serious risk to public health. Under the DCP, an application is made in several EEA Member States with a request that the medicinal products agency in one particular state shall serve as the reference Member State. The medicinal products agency in that reference Member State (e.g., the MPA in Sweden) shall manage the review of the application by preparing the necessary documentation for assessment by the other Member States affected by the application.

When medicinal products are to be granted marketing authorisation in Sweden through the national procedure, the applicant must be able to establish, inter alia, that the medicinal product meets the requirements set out in Chapter 4 of the Medicinal Products Act. To obtain marketing authorisation, the medicinal product must meet the requirements of quality, efficacy and safety and be effective for its intended purpose. An applicant must also show that the medicinal product is not disproportionately harmful in achieving its intended effect. The packaging of the medicinal product needs to meet certain standards too (e.g., the packaging must be functional), and all information about the medicinal product has to be accurate and comprehensible. The MPA may grant a marketing authorisation subject to certain conditions, which should be reviewed annually.

A marketing authorisation is valid for a period of five years, and may thereafter be renewed for another five-year period or without any time limit.

Medical devices are not subject to pre-market approval in Sweden or the European Union. However, all medical devices must meet the requirements of the applicable legislation and it is the responsibility of the manufacturer to ensure compliance. To confirm that a medical device conforms with the applicable legal requirements, it should be provided with a
CE mark prior to being placed on the market. The CE mark procedure is dependent on the classification of the medical device. High-risk medical devices must also be assessed by a third person, known as a 'notified body', prior to being placed on the market.

vi Regulatory incentives

Patent protection for an invention is typically valid for 20 years from the filing date of the patent application. However, patents for medicinal products can, according to Regulation (EC) No. 469/2009, have the term of protection extended for generally up to five years by a Supplementary Protection Certificate (SPC). The rationale of the supplementary protection springs from the fact that development and authorisation of medicinal products is complex and time-consuming, and that long periods typically pass between the filing date of the patent and when the product may first be placed on the market. The purpose of an SPC is thus to compensate the patent owner for the time when the patent rights cannot be commercialised.

The Swedish Patent and Registration Office handles applications and grants certificates for supplementary protection. An SPC protects the active substance that is covered by the patent and authorised for sale on the market. The supplementary protection will take effect once the original patent has. In some circumstances, the initial term of protection by the SPC (never longer than five years) may be extended by an additional six months if the patent owner has tested the suitability of the medicinal product in children.

A medicinal product for use in human beings can also be granted a one-year regulatory data exclusivity by the MPA if an application for marketing authorisation has been granted for a new indication for an already established substance and if substantial clinical assessments and studies of the new indication have been made. Data exclusivity protection means a prohibition for generic medicinal products to refer to documentation of the reference medicinal product.

vii Post-approval controls

The legal framework for supervision and control of medicinal products is harmonised with applicable EU legislation, including, inter alia, Directive 2010/84/EC and Regulation (EU) 1235/2010. According to the Medicinal Products Act, the MPA is responsible for the supervision of medicinal products in Sweden. The purpose of the supervision is to collect, record, store and scientifically evaluate data on suspected adverse reactions. The MPA regularly controls authorised medicinal products and evaluates whether the authorisations should remain in effect. The MPA may order a marketing authorisation holder to verify that the medicinal product still meets the requirements and, if considered necessary for safety reasons, it may withdraw the marketing authorisation.

Swedish law also requires marketing authorisation holders to maintain an internal system for surveillance of safety and to observe and adjust to developments in the pharmaceutical field, such as new scientific research or new recommendations from the MPA. The marketing authorisation holder shall register, keep, evaluate and report to the MPA any information on all suspected adverse reactions of its medicinal products. If the marketing authorisation holder detects circumstances that may render inaccurate the information and documentation upon which the authorisation is based, it must report this to the MPA. Furthermore, there is an obligation for the marketing authorisation holder to inform the MPA two months in advance if a product is permanently or temporarily taken off the market in Sweden, and
to state the reasons for this. For the purpose of its overall safety surveillance, marketing authorisation holders must keep a qualified person with sufficient knowledge and experience at its disposal.

viii  Manufacturing controls

Manufacturing of medicinal products shall take place in suitable premises and be carried out using appropriate equipment. All manufacturing must be in accordance with GMP and a qualified person with sufficient knowledge and influence shall be responsible for ensuring that the quality and safety standards and the requirements of the medicinal products are met.

According to the Medicinal Products Act and MPA Regulation LVFS 2004:7, professional manufacturing of medicinal products requires a manufacturing authorisation by the MPA. The MPA will regularly perform inspections of the facilities to ensure compliance with the relevant requirements for the manufacturing authorisation. A manufacturing authorisation is valid for the time specified in the permit and may be extended subject to continued compliance with the requirements.

A manufacturing authorisation can be revoked by the MPA if, for instance, if any of the required conditions mentioned above are no longer being met or if the manufacturer has not paid the applicable annual fees to the MPA.

As mentioned in Section II.v, it is the responsibility of the manufacturer of a medical device to ensure compliance with the requirements of the applicable legislation, including the Medical Devices Act and MPA Regulations LVFS 2003:11 and LVFS 2001:7. To facilitate inspections by the MPA, inter alia, Swedish manufacturers and authorised representatives that manufacture or provide certain medical devices are required to register with the MPA. However, registration does not result in approval of the medical device.

ix  Advertising and promotion

The Marketing Practices Act,\(^\text{11}\) which governs advertisements in general, is also applicable to the advertising of medicinal products. Its aim is to protect consumers from misleading advertisement and unethical marketing practice. The Radio and Television Act\(^\text{12}\) is also applicable.

The Medicinal Products Act and the MPA’s provision published in the MPA’s Code of Statutes\(^\text{13}\) contains specific rules on the advertising of medicinal products. The Medicinal Products Act stipulates that only medicinal products that have been granted marketing authorisation may be advertised in Sweden. The Act includes requirements that, for example, an advertisement has to be up to date, objective and balanced. It must also be accordance with best practice for the advertising of pharmaceuticals. Advertisements that are misleading, addressed to children or for prescription-only medicinal products are prohibited (with the exception of campaigns for vaccination against human infection diseases). The rules apply both to advertisements aimed at the general public and at healthcare professionals. The Medicinal Products Act stipulates that pharmaceutical companies shall have an in-house function with scientific competence who is responsible for surveillance of the provision of information about their medicinal products.

\(^{11}\) SFS 2008:486.
\(^{12}\) SFS 2010:696.
\(^{13}\) LVFS 2009:6.
The research-based pharmaceutical industry in Sweden has, through its trade organisation, the Swedish Association of the Pharmaceutical Industry (LIF), developed a system of self-regulation in the pharmaceutical sector. LIF has adopted ethical rules and a self-regulation system concerning, inter alia, the advertising of medicinal products to the public sector and healthcare professionals in ‘The Ethical Rules for the Pharmaceutical Industry’ (the LIF Ethical Rules), which came into force on 1 October 2007; the most recent revision is valid as of 1 January 2020.

Compliance with the LIF Ethical Rules is kept under constant scrutiny by the LIF Information Examiner Committee (IGN). The IGN is responsible for investigating cases and imposing sanctions, both on its own initiative and in response to complaints. IGN’s decisions may be appealed to the Information Practices Committee (NBL).

The LIF Ethical Rules have a very important role in the marketing and promotion of medicinal products. Even though enforcement of the rules is based on contractual obligations and are not legally binding, the Rules are widely respected and adhered to by the pharmaceutical industry. They are also often considered by the courts as an expression of fair and ethical marketing.

Distributors and wholesalers

Distribution, including the wholesale and retail of medicinal products, is governed primarily by the Act on Trading in Medicinal Products,14 the Ordinance on Trading in Medicinal Products15 and MPA Regulation LVFS 2014:8. In addition, there are guidelines issued by the MPA on the interpretation of these rules, as well as guidelines on good distribution practice (GDP) issued by the European Commission.

According to the Act on Trading in Medicinal Products, all distribution of medicinal products shall be conducted in such a way that the products do not harm human beings, property or the environment, and that the quality of the products is not impaired.

The wholesale of medicinal products includes all handling of a medicinal product from the moment it is released from the manufacturer until it reaches the retail level, and is defined in the Act on Trading in Medicinal Products as activities that include acquisition, possession, export, delivery and sale (but excluding retail sale). Retail sale is defined as the sale of medicinal products to consumers, regions (formerly county councils), municipalities, hospitals or other healthcare facilities and to entities authorised to prescribe medicinal products.

A permit from any country within the European Economic Area (EEA) is required to engage in distribution of medicinal products. In Sweden, the MPA may grant such permits.

Permits for the wholesale or retail of medicinal products may be granted only to applicants that are proven capable of meeting certain specific requirements in the Act on Trading in Medicinal Products, including requirements regarding, inter alia, the suitability of the facilities being used and the competence of personnel involved in conducting the distribution activities. Specifically, a wholesaler must also be able to ensure, inter alia, a reliable supply to pharmacies of the medicinal products covered by its permit, must document the handling of medicinal products in such a way as to ensure traceability, must maintain active surveillance to discover and report any suspected forfeited pharmaceuticals, and must adhere to accepted standards of GDP. Retailers must, inter alia, ensure availability of at least one pharmacist in the retail facility during opening hours if supplying medicinal

---

products to consumers (e.g., pharmacies) and have an obligation to supply all prescription pharmaceuticals as well as all medicinal products included in the Swedish pharmaceutical benefits system.

Distribution of medical devices is generally not subject to any specific rules and therefore no particular authorisation is required. However, the trading and importation of syringes and needles are governed by a specific act, an ordinance by the government and a regulation by the MPA.

xi Classification of products

Pursuant to Chapter 4 of the Medicinal Products Act, a medicinal product will, in connection with the granting of marketing authorisation, be classified either as a prescription-only or a non-prescription medical product. The MPA will decide the classification for the medicinal product depending on its intended use and characteristics. A prescription-only medical product may be classified into other categories, with limitations for how it can be prescribed and dispensed.

The MPA shall reconsider and, if necessary, change the classification of the medicinal product if new information or circumstances of significant importance for the classification of the medicinal product comes to its attention or if the marketing authorisation holder applies for a change of classification.

Classification of medical devices is governed by Directives 93/42/EEC and 98/79/EC, the Medical Devices Act, the Medical Devices Ordinance and MPA Regulations LVFS 2001:7 and LVFS 2003:11 (see also Section II regarding new EU regulations on medical devices). There are six groups of classification for general medical devices and four groups for in vitro diagnostic medical devices, which reflect the risks associated with the devices. Active medical devices for implantation are considered to be consistently associated with very high risks and these devices are therefore not divided into risk classes. The classification will also determine what type of procedures the manufacturer must apply to ensure that the products comply with legal requirements (see Section II.v).

xii Imports and exports

According to the Medicinal Products Act, medicinal products can only be imported into Sweden from a country outside the EEA by someone holding a manufacturing authorisation or a specific authorisation for importation. The latter may be granted by the MPA if: (1) the medicinal product is imported to ensure that the demand for that medicinal product is met; (2) the medicinal product is intended to be used for purposes other than healthcare; or (3) the medicinal product is an investigational medicinal product. The importer of a medicinal product from a third country is responsible for the release of that product within the EEA.

An importation authorisation holder must appoint a qualified person with sufficient competence and influence to be responsible for the control of the imported medicinal product.

Repackaging and relabelling of medicinal products is also subject to a manufacturing authorisation by the MPA; the new package and label must comply with the requirements set out in MPA Regulation LVFS 2005:11 (which has been supplemented and amended by MPA Regulation HSLF-FS 2018:62, which entered into force on 9 February 2019).

There are exceptions to the requirement for importation authorisation for products from outside the EEA. For example, natural persons may bring medicinal products to
Sweden if they have a medical purpose and will be used personally by the importer. Second, veterinarians may under certain circumstances bring smaller amounts of medicinal products for animals into Sweden without an importation authorisation.

No specific importation authorisation is required to import medical devices into the EEA. In general, the manufacturer is responsible for ensuring that medical devices released on the EEA market comply with applicable rules and regulations. If an importer of a medical device from outside the EEA releases a product on the EEA market in its own name, the same requirements apply to the importer as would have applied to the manufacturer. Furthermore, as stated in Section II.xi, specific requirements apply to the importation of syringes and needles.

It should also be noted that the requirements applicable to manufacturers according to the definition in the Product Safety Act also apply to importers.

xiii  Controlled substances

Controlled substances particularly include narcotic substances. Narcotic drugs are defined in the Penal Law on Narcotics\textsuperscript{16} as medicinal products and hazardous goods with addictive properties or euphoric effects, or goods that can be readily converted into products with those properties or effects, and (1) on these grounds are included in an international agreement to which Sweden is a part (including the 1961 UN Convention on Narcotic Drugs) or (2) the Swedish government has declared that the substance shall be considered a narcotic. The MPA has listed all substances classified as narcotics in Regulation LVFS 2011:10.

According to the Act on the Control of Narcotic Drugs\textsuperscript{17}, medicinal products classified as narcotics are under the supervision and control of the MPA. A general permit issued by the MPA is required to import, export, transport, produce, trade or possess narcotic medicinal products. Furthermore, certain narcotic substances require an additional permit for each individual occasion when the substance is brought into or out of Sweden. However, there are some exceptions; for instance, governmental or municipal institutions do not need a permit to possess narcotics if used for scientific research, studies or education.

Other categories of substances subject to special control include, for example, psychotropic substances, doping substances and certain hazardous goods.

xiv  Enforcement

The MPA is responsible for the supervision and enforcement of compliance with Swedish legislation and a number of EU Regulations and Directives on medicinal products and medical devices. The EMA is responsible for the supervision of compliance with certain requirements relating to centrally approved medicinal products.

The MPA is authorised to demand any information needed during its supervision, both oral and in writing. The MPA has authority to access areas, premises and other facilities used for the manufacturing or handling of medicinal products and medical devices, active substances, auxiliary substances and packaging materials for medicinal products, and to obtain samples of medicinal products and medical devices. It may also gain access to facilities where testing of medicinal products takes place. However, the MPA does not have the right to access private homes.

\textsuperscript{16} SFS 1968:64.
\textsuperscript{17} SFS 1992:860.
If the MPA finds it necessary, it may issue injunctions and prohibitions for compliance with the relevant legislation. An injunction or prohibition may be combined with a fine. A fine may also be imposed if the MPA is denied access or assistance when conducting its supervision.

The MPA may decide to recall medicinal products from the market and to temporarily or permanently revoke marketing authorisations.

Certain violations of regulatory requirements relating to medicinal products and medical devices may be considered criminal and be punished pursuant to the Medicinal Products Act and the Medical Devices Act; punishments range from fines to imprisonment for up to one year. Offences may also be punishable under the Swedish Penal Code.

Pursuant to the Marketing Practices Act, in the event of a breach of regulatory requirements, prohibitions and constraints can be imposed by a competent court. A prohibition for a company to continue with a measure contrary to the Marketing Practices Act may be combined with a fine. Disruption of marketing practices may also lead to fines and liability.

The LIF Ethical Rules, while not legally binding, impose sanctions such as fines on non-complying organisations that have not contractually adhered to the rules. The IGN and NBL are responsible for enforcement of the LIF Ethical Rules.

III PRICING AND REIMBURSEMENT

Non-prescription (over-the-counter) medicinal products are not subject to regulated pricing, and are paid for entirely by the end customer. The pricing of prescription medicinal products that are included in the reimbursement system are regulated, however, and the patient makes a co-payment. The prices for in-patient care medicinal products are negotiated in public procurement processes, and the patient only pays the patient fee that applies for the in-patient treatment concerned.

The Swedish reimbursement system subsidises the costs for certain medicinal products through a reimbursement scheme. The patient pays the full cost, up to a certain ceiling. The costs for medicinal products above that ceiling are then reduced step by step over a period of 12 months. The maximum amount a patient will pay during this period is 2,350 kronor (as of 1 January 2020).

The TLV, which is an expert state agency, decides to what extent a medicinal product shall be reimbursed, according to the Pharmaceutical Benefits Act. For a medicinal product to be covered by the reimbursement scheme, an application must be submitted to the TLV. In the application, the applicant must state the requested price of the product and enclose documentation that includes a health economic analysis. An application is granted if the TLV finds that the health economic analysis shows that the requested price is justified on the basis of the value the medicinal product brings in terms of improved health (i.e., it is cost-effective and brings a marginal benefit to the market). The price should be based on general principles, such as cost-effectiveness, and the principle of prioritising patients with the greatest needs. A decision on reimbursement is thus based on value, which is often described in Swedish terms as applying ‘value-based pricing of pharmaceuticals’. In fact, prices can be freely set under a value-based ceiling. There are few countries that apply the value-based pricing of

18 SFS 2002:160.
pharmaceuticals. Instead, most EU countries apply international reference pricing in some form. The TLV also decides and sets the retail margin, which is the fee paid by the state when pharmacies sell a prescription medicinal product.

Since 1 January 2016, all children under 18 have been offered free medicinal products and medical devices included in the reimbursement scheme. The purpose of this is to reduce the inequality of children's health between societal groups with different financial conditions.

Pharmacies in Sweden are required to offer the least expensive medicinal product when there are equivalent and substitutable medicinal products available on the market within the pharmaceutical benefits scheme. Even if the patient has a prescription for a specific medicinal product, and as long as the prescribing doctor has not opposed substitution for medical reasons in writing, the pharmacy must offer the product with the lowest price within the benefits scheme (see Section VIII below regarding an upcoming extension of the mandatory substitution to enter into force on 2 June 2020). If the patient refuses a substitute, he or she may choose to pay the difference between the prescribed product and the cheapest alternative.

Medical devices are subject to the same reimbursement rules as medicinal products, as long as the devices are prescribed by a physician and are to be used by patients. However, the rules regarding substitution of medicinal products do not apply to medical devices.

**IV ADMINISTRATIVE AND JUDICIAL REMEDIES**

Decisions made by the MPA, the TLV and other governmental authorities can be appealed to the Swedish administrative courts. The Administrative Procedures Act\(^\text{19}\) governs the procedure for appeals. Decisions and judgments from the administrative courts may, in most cases subject to granting of leave to appeal, be appealed to one of the administrative courts of appeal, whose decisions and judgments may further be appealed to the Supreme Administrative Court. Proceedings in the administrative court system are primarily conducted in writing, but oral hearings are possible if requested by a party or if the court finds it appropriate.

Appeals of decisions by authorities such as the MPA and the TLV are submitted directly to the authority. The main rule is that an appeal must be submitted so that it is received by the authority no later than three weeks after the date on which the appellant received the decision, or it may be inadmissible. The appeal will be forwarded by the authority to the relevant administrative court only if the authority does not adjust its original decision as claimed by the appellant. If all formal requirements of appeal are fulfilled, and an appeal is not dismissed on formal grounds, the administrative courts are authorised to assess an appealed decision in its entirety. The likely outcomes are, depending on the circumstances in each case, either rejection of the appeal, material change of the appealed decision or referral of the case back to the authority for reassessment in accordance with any statements of reason from the court.

**V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS**

There are no mandatory anti-corruption laws aimed particularly at the pharmaceutical and healthcare industries. Instead, Sweden's anti-corruption rules apply on a general level. Additionally, Sweden is a signatory to many international anti-corruption conventions,
including, but not limited to, the UN Convention against Corruption and the Council of Europe’s Civil Law Convention on Corruption. On a national level, anti-corruption rules exist in the form of anti-bribery rules in Chapter 10 of the Swedish Penal Code. The Swedish Anti-Corruption Institute has supplemented the anti-corruption legislation with a ‘Code on gifts, rewards and other benefits in trade and industry’ (the Business Code). This Business Code does not have status as law, but constitutes a clarification of the general anti-corruption legislation. The intention is that entities that follow the Business Code should be able to rely on their actions being lawful. For a fee, the Ethics Committee of the Anti-Corruption Institute may render an assessment of whether or not a contemplated action is compatible with the Business Code.

There are specific rules applicable to the pharmaceutical industry through the LIF Ethical Rules, which are based on the ethical rules of the European Federation of Pharmaceutical Industries and Associations (although, as stated in Section II.ix, these ethical rules are not mandatory, strictly speaking). The LIF Ethical Rules govern collaboration between the pharmaceutical industry on one hand and healthcare professionals, healthcare organisations, patient organisations and decision makers on the other. The LIF Ethical Rules also include provisions regarding disclosure of transfers of value by the pharmaceutical industry to, for example, healthcare professionals, healthcare organisations, pharmacies, veterinary surgeons and decision makers. Pharmaceutical companies that are active on the Swedish market shall publish the persons or organisations in Sweden that have received transfers of value during a given calendar year, or the aggregate value of the transfers. LIF publishes reported transfers of value on its website.

Furthermore, the Swedish Association of Local Authorities and Regions, LIF, Swedish Medtech and Swedish Labtech have agreed on common rules regarding cooperation and interaction between stakeholders in healthcare and the pharmaceutical industry. The current version of the agreement came into force on 1 January 2020.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

According to the Patient Injury Act,20 patients who suffer personal injury while in the healthcare system may be entitled to financial compensation. If a medicinal product causes the injury, the patient may claim damages, according to the Product Liability Act.21 The Act is applicable to damages caused by correctly prescribed medicinal products. Damages can also be claimed under the general Tort Liability Act.22

There are several insurances that can cover injuries caused to patients within the healthcare system. For healthcare providers in Sweden, it is mandatory to hold insurance that covers bodily injuries caused to patients receiving treatment.

Other insurances are voluntary, such as the medicinal products insurance provided by the Pharmaceutical Insurance Association. Any manufacturer of medicinal products that finds it reasonable or necessary can acquire a medicinal products insurance policy to cover damages caused by its products to patients receiving medicinal products in medical treatment.

22 SFS 1972:207.
or to study subjects participating in clinical trials. Almost all pharmaceutical companies have obtained medicinal products insurance, and for this reason, almost 99 per cent of all pharmaceuticals sold in Sweden are covered.

Pursuant to the Patient Safety Act, healthcare professionals must fulfil their work based on medical findings and established practices. Patients who are not satisfied with their treatment can file a claim with the Health and Social Care Inspectorate, which supervises healthcare professionals. If the Inspectorate finds a breach in a patient’s treatment, it can report the healthcare provider to the Medical Responsibility Board, which is a court-like agency that examines authorisation issues regarding healthcare professionals and has authority, for example, to withdraw licences to practise medicine.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Swedish competition law is based on EU competition rules and is mainly regulated by the Swedish Competition Act. The Act regulates, inter alia, the prohibition of agreements between undertakings that may harm competition, as well as the prohibition of abuse of a dominant position. There are no specific competition rules for the pharmaceutical sector; however, the Act comprises block exemptions that are of importance to the sector.

The supervising authority, the Swedish Competition Authority (SCA), has not issued any competition guidelines specific to the pharmaceutical sector.

Companies that breach competition law can be required by the SCA to terminate the infringement. In addition, the SCA can decide to supplement such a requirement with an administrative fine. Infringements of competition law are also pursued by the patent and market courts as well as the European Commission.

Relevant to the application of competition law to the pharmaceutical sector is the fact that from 2009, the Swedish pharmacy market was re-regulated and new legislation was adopted. Since then any appropriate market actor can own and run pharmacies, except for producers and prescribers of medicinal products. The state-owned company Apoteket AB, which since 1970 had the exclusive right to conduct retail trade in medicinal products to consumers, is now competing with private pharmacies and other market stakeholders with regard to certain over-the-counter products.

There are many elements in Swedish legislation that are relevant to competition. One is the mandatory substitution of equivalent medicinal products (see Section III).

The pharmaceutical sector has often been subject to the scrutiny of the SCA. During 2015 and 2016, the Authority investigated a possible abuse of a dominant position by some pharmaceutical distribution companies refusing to supply medicinal products to a company that had both a retail and a wholesale licence. The SCA stated that pharmaceutical distribution companies are only obliged by law to supply medicinal products to retailers (i.e., pharmacies) and not to wholesalers, and that the pharmaceutical companies had not committed any abuse by refusing to supply once it became clear that the company was not purchasing under its wholesale licence (which did not include an obligation to supply).

23 SFS 2010:659.
24 SFS 2008:579.
ii Transactional issues

A number of complex issues arise in connection with transactions. What are the risks or problems of particular importance for the transaction? The material agreements (supply, manufacturing, licensing and other collaboration agreements) are often specific to the industry and subject to local rules and regulations, and may thus be complex and require sophisticated assessment. As many companies in the life sciences sector often have important intellectual property rights, it is very important that these rights are considered in a transaction. It is also essential to ensure that all the permits, licences and certificates required for operations remain valid after a transaction. This may include manufacturing authorisations, licences for the wholesale of pharmaceuticals, and licences for the handling, importation or wholesale of substances such as narcotics and radioactive substances, as well as GMP certificates. It is vital that communications with the authorities are scrutinised.

VIII CURRENT DEVELOPMENTS

There is a continued focus from the Swedish government on the pricing and reimbursement of medicinal products. In 2016, the Swedish government established a public inquiry to carry out the first review of the financing of subsidised medicines since 1998 (‘Läkemedelsutredningen’). The inquiry has also reviewed the national systems for pricing and reimbursement of pharmaceuticals. The main goal of the investigation was to find a long-term sustainable system for financing, pricing and reimbursement of medicinal products. The full investigation was reported to the Swedish government in January 2019.

The Swedish government has previously assigned a special investigator to investigate the pharmacy market (‘Nya Apoteksmarknadsutredningen’), with the assistance of the relevant authorities. The main goal of the investigation was to improve safety and quality in the pharmacy market and the intention was to achieve a safer and more effective provision of medicinal products. The inquiry also assessed the potential regulation of pharmacies’ trade margin on medicinal products not included in the pharmaceutical benefits scheme. The assignment included, inter alia, analysing the development of the pharmacy market since deregulation, the authorisation requirements for outpatient pharmacy businesses, what changes may be needed to secure adequate availability of pharmacy services across the country, how the legislation governing dose-dispensing pharmacies could be improved and what changes to current legislation these issues may entail. A report relating to safety and quality in the pharmacy market was presented to the government on 9 March 2017. The part of the assignment concerning potential regulation of the trade margin for medicinal products not included in the pharmaceutical benefits scheme was reported to the government on 9 October 2017, and in summary the investigation has proposed that the trade margin should be regulated. The full investigation was reported to the government on 19 June 2018 and the government has since submitted legislative proposals to the Swedish parliament.

As of 2 June 2020, certain legislation amending the rules on substitution of pharmaceutical products in pharmacies will enter into effect. In summary, the new rules will extend the mandatory substitution of pharmaceuticals in pharmacies to also include substitution of prescription medicinal products not included in the benefits scheme. This means that pharmacies shall also substitute prescribed pharmaceuticals not included in the benefits scheme for the cheapest alternative within the benefits scheme.

In December 2017, the Swedish government assigned a special investigator to investigate how control methods could facilitate a more equal and need-based healthcare.
The main goal of the investigation was to provide proposals on effective ways to achieve the goals set out in the Health and Medical Services Act, with a focus on equal healthcare. The full investigation was reported to the government on 1 October 2019.

There have been several recent and ongoing Swedish government initiatives in the area of eHealth and healthcare information standardisation. For instance, the Swedish parliament passed the new National Medication List Act\(^\text{25}\) in June 2018 to implement a new national medication register. The Act will enter into effect on 1 June 2020 (in some parts on 1 June 2022). The intention with the national medication list is to improve patient safety by improving the transfer of information on prescribed medicines that has to be shared between healthcare stakeholders, pharmacies and patients. Currently, this information is divided between several different sources and the prerequisites for access to these sources vary. This means, in practice, that stakeholders in healthcare, pharmacies and even patients themselves sometimes do not have access to comprehensive information about a patient’s pharmaceutical treatments, which could put the patient’s safety at risk.

\(^{25}\) SFS 2018:1212.
I INTRODUCTION

Switzerland harbours many sectors of the life sciences industry. Swiss research, development and production are well known in all corners of the planet. Switzerland is home to world leaders and is the origin of many groundbreaking ideas turned into successful start-ups, some set to become top players within a generation.

The Federal Institutes of Technology in Zurich and Lausanne, and the internationally recognised university hospitals in Geneva, Lausanne, Zurich, Basel and Berne contribute to this greatly.

Medicines and medical devices are mainly governed by the Federal Act on Medicinal Products and Medical Devices (the Therapeutic Products Act; TPA), which has recently been revised with regard to the provisions on integrity and transparency (the amended provisions came into force on 1 January 2020). There are numerous ordinances further specifying the provisions of the TPA. Reimbursement and pricing of medicinal products are subject to the provisions of the Federal Act on Mandatory Healthcare Insurance (KVG) and its main ordinances (KVV and KLV). While the Federal Act on Research involving Human Beings (the Human Research Act; HRA) contains provisions regarding research on humans, the Federal Act on Human Genetic Testing stipulates the conditions under which human genetic testing may be performed.

The Swiss Agency for Therapeutic Products (Swissmedic) and cantonal authorities are mainly responsible for enforcing the TPA and its ordinances. The Federal Office of Public Health (FOPH), part of the Swiss Ministry of Home Affairs, is the competent authority with regard to the enforcement of the KVG and TPA (the latter only when integrity and transparency in the collaboration between industry and healthcare providers are concerned). The enforcement of the HRA is the responsibility of cantonal ethics committees and the FOPH. Finally, the cantonal authorities are responsible for enforcing the Federal Act on Human Genetic Testing.
II THE REGULATORY REGIME

While medicines are tightly regulated by the TPA (Chapters 2 and 4) and numerous ordinances and must obtain a marketing authorisation, medical devices are governed by the principle of self-regulation. Medicines follow a genuine Swiss legislation, whereas medical devices are regulated in close accordance with EU law.

i Classification

Medicines are products of chemical or biological origin that are intended to have or are presented as having a medicinal effect on the human or animal organism, in particular in the diagnosis, prevention or treatment of diseases, injuries and handicaps. Blood and blood products are also considered to be medicinal products.2

Medical devices are products including instruments, apparatus, in vitro diagnostics, software and other goods or substances that are intended to have or are presented as having a medical use and whose principal effect is not obtained with a medicine.3

Foodstuffs are defined by the Federal Act on Foodstuffs and Utility Articles as all substances or products that are intended or may reasonably be expected to be consumed by human beings in a processed, partly processed or unprocessed state; medicines are not foodstuffs.4 Health claims in connection with foodstuffs must comply with, among others, the provisions of the Ordinance on Information on Foodstuffs.

Cosmetics, when used as normally intended, come into contact with the body externally, and with teeth or mucous membranes externally, and belong to the category of ‘utility articles’.5 Health claims are prohibited for cosmetics.6

With regard to chemicals, substances are defined by the Federal Act on Protection against Dangerous Substances and Preparations as chemical elements and their compounds in the natural state or obtained by any production process, while preparations are defined as mixtures or solutions composed of two or more substances.7 According to the Ordinance on Protection against Dangerous Substances and Preparations, said ordinance does not apply to medicines and medical devices.8

ii Non-clinical studies

The documentation of analytical, chemical and pharmaceutical test results in non-clinical trials – which is necessary to obtain a marketing authorisation for a specific medicine with a specific indication – must prove that the test procedures correspond with the current state of science and are validated. Studies carried out on animals or, where appropriate, on qualified or validated alternative models must (1) be in accordance with the rules and recommendations governing the protection of the animals used and ensuring impeccable test results; and (2) have been planned and implemented in accordance with the current state

---

2 Article 4 Paragraph 1 lit. a TPA.
3 Article 4 Paragraph 1 lit. b TPA; see also Article 1 MepV.
4 Article 4 Paragraph 1 and Paragraph 3 lit. d Federal Act on Foodstuffs and Utility Articles (LMG).
5 Article 5 lit. b LMG.
6 Article 47 Paragraph 3 Ordinance on Foodstuffs and Utility Articles (LGV).
7 Article 4 Paragraph 1 lit. a and c Federal Act on Protection against Dangerous Substances and Preparations.
8 Article 1 Paragraph 5 lit. c (2) Ordinance on Protection against Dangerous Substances and Preparations.
of science. Further, the marketing authorisation application for a new chemical entity must contain information and documents on pharmacodynamics, pharmacokinetics, toxicology and ecotoxicity.\(^9\)

Non-clinical studies are subject to the Federal Act on Animal Protection, the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Ordinance on Good Laboratory Practice.

### iii Clinical trials

Clinical trials are mainly governed by Article 53 et seq. of the TPA, the HRA and the Ordinance on Clinical Trials in Human Research. Clinical trials of medicines and medical devices require prior authorisation from Swissmedic. However, clinical trials involving compliant medical devices applied in accordance with the intended use specified in the conformity assessment are exempted from mandatory authorisation.\(^10\)

In addition to Swissmedic’s authorisation, an authorisation from the responsible ethics committee is required.\(^11\)

The sponsor is defined as a person or institution headquartered or represented in Switzerland that takes responsibility for organising a clinical trial, and in particular for the initiation, management and financing of the trial in Switzerland. The investigator on the other hand is the person responsible in Switzerland for the conduct of a clinical trial and for the protection of the participants at the trial site; an investigator who takes responsibility for organising a clinical trial in Switzerland is also a sponsor.\(^12\)

Clinical trials must be conducted in accordance with the rules of Good Clinical Practice.\(^13\)

The main principles in connection with clinical trials include the informed consent of the persons concerned, the primacy of individual interests over the interests of science and society, the requirement of a scientifically relevant topic, the principle of non-discrimination, the right of persons concerned to receive information on their health, the prohibition of the commercialisation of the human body and parts thereof, as well as compliance with certain scientific requirements. Furthermore, the person carrying out the clinical trial is liable for all damages suffered in connection with the project and must ensure that this liability is appropriately covered through insurance or in some other manner. In addition, the trial must be registered in a public registry and is subject to various notification and reporting obligations (e.g., completion or discontinuation of trial, adverse events, and safety and protective measures).\(^14\)

---

\(^9\) Article 11 Paragraph 2 lit. a (1) and (2) TPA; Article 3 et seq. Ordinance on the Requirements Regarding the Marketing Authorisation of Medicinal Products (AMZV).

\(^10\) Article 54 Paragraph 1 and 2 lit. b TPA.

\(^11\) Article 45 Paragraph 1 HRA; Article 24 et seq. Ordinance on Clinical Trials in Human Research (KlinV).

\(^12\) Article 2 lit. c and d KlinV.

\(^13\) Article 5 Paragraph 1 and Annex 1 number 2 KlinV.

\(^14\) Article 4 et seq., Article 19 et seq., Article 46 and Article 56 HRA; Article 3 et seq., Article 10 et seq., Article 37 et seq. and Article 64 et seq. KlinV.
iv  **Named-patient and compassionate use procedures**

In Switzerland, there are two main possibilities to use non-authorised medicines. A medical professional may, under certain circumstances, import non-authorised medicines, which are either authorised or part of a clinical trial in a comparable jurisdiction, for the treatment of an individual patient.15

Furthermore, Switzerland defines and allows compassionate use, whereby it may temporarily authorise the sponsor of a clinical trial approved in Switzerland to use medicines used in clinical trials on certain persons or on a certain group of persons outside of the clinical trial.16

A treatment with a non-authorised medicine is reimbursed by the compulsory healthcare insurance scheme if the medicine is authorised for the relevant indication in a country with an authorisation system recognised by Swissmedic as equivalent, and if either (1) the use of the medicine is an indispensable condition for another treatment covered by compulsory health insurance and if that treatment is clearly in the foreground; or (2) the use of the medicine is expected to have a great therapeutic benefit against a disease that is fatal or that could result in serious and chronic health impairments, and if no other effective and approved treatment is available owing to a lack of therapeutic alternatives.17

The reimbursement requires prior approval by the healthcare insurance after consultation with the medical examiner, and the costs must be proportionate to the therapeutic benefit.18

v  **Pre-market clearance**

The commercial distribution of medicines requires a marketing authorisation by Swissmedic, whereas medical devices may, in principle, be put on the Swiss market without a marketing authorisation.19

A marketing authorisation for a medicine is granted by Swissmedic if it is of high quality, safe and effective, if the applicant is the holder of an authorisation to manufacture, import or conduct wholesale trade, and if the applicant has a registered address, registered office or a branch office in Switzerland.20

The marketing authorisation is issued for five years. Its renewal is generally unlimited in terms of time.21

A simplified procedure ensures fast access to certain categories of medicines:

a  medicines with known active pharmaceutical ingredients;

b  medicines whose active substances are used in a medicine that, at the time of submission of the application, has been authorised for at least 10 years in at least one EU or EFTA country and that is comparable in terms of indications, dosage and method of administration;

---

15  Article 49 Ordinance on the Authorisations of Medicinal Products (AMBV). See also Article 48 AMBV with regard to the import of non-authorised medicines by individuals for their private use.

16  Article 9b Paragraph 1 TPA; Article 52 et seq. AMBV.

17  Article 71c Paragraph 1 in conjunction with Article 71a Paragraph 1 lit. a and b KVV.

18  Article 71d Paragraph 1 and 2 KVV.

19  Article 9 Paragraph 1 and Article 45 TPA.

20  Article 10 Paragraph 1 TPA. See also Article 11 and Article 16 et seq. TPA.

21  Article 16 Paragraph 2 and Article 16b Paragraph 2 TPA.
non-prescription medicines with an indication that, at the time of submission of the application, has been proven to have been used medically for at least 30 years, of which at least 15 years have been in EU and EFTA countries;

medicines that, at the time of submission of the application, are proven to have been authorised as medicines for at least 15 years in a canton;

complementary medicines;

herbal medicines;

medicines prepared by a hospital pharmacy or in the hospital’s own radiopharmaceutical unit for the needs of the hospital;

medicines prepared by the army and used in the context of the coordinated army medical corps;

important medicines for rare diseases; and

veterinary medicines, which are intended exclusively for animals not kept for the production of foodstuffs.\(22\)

Complementary medicines without indication, the active substances of which are included in lists of special therapeutic directions, may be placed on the market solely on the basis of a notification to Swissmedic. The same holds true for other medicines or groups of medicines for which, because of their low risk potential, a simplified marketing authorisation procedure proves to be disproportionate.\(23\)

The fees as of 1 January 2019 are as follows:

authorisation of a medicine with a new active substance: 80,000 Swiss francs;

authorisation of a medicine with a known active substance: 50,000 Swiss francs;

authorisation of a herbal medicine with a new active substance: 30,000 Swiss francs;

authorisation of a medicine in the simplified procedure: 100 to 80,000 Swiss francs;

renewal of an existing authorisation and change into authorisation unlimited in time: 500 Swiss francs; and

authorisation of orphan drugs: fee is waived (grant of orphan drug status: 3,000 Swiss francs).\(24\)

Medical devices may be put on the market if they do not endanger the health of users, consumers, patients or third parties when used in accordance with their intended use. Claims for their performance or effectiveness must be provable. The person placing a medical device on the market must be able to prove that the device satisfies the fundamental requirements set forth by the applicable EU Directives and that it has been submitted to the prescribed procedures for assessing conformity. Only a small group of medical devices is subject to a mandatory notification obligation before putting them on the market for the first time.\(25\)

\(22\) Article 14 et seq. TPA.

\(23\) Article 15 TPA.

\(24\) Article 4 Paragraph 1, Article 9 lit. a and annexes 1 and 2 Ordinance of the Swiss Agency for Therapeutic Products on its fees.

\(25\) Article 45 et seq. TPA; Articles 4, 6 and 9 et seq. MepV.
vi  Regulatory incentives

Upon application, the Intellectual Property Institution grants a supplementary protection certificate for medicines, which is valid after expiry of the maximum term of the patent for a period equal to the period that elapses between the date of patent filing and the date of the first marketing authorisation, minus five years. It is valid for five years at the most.26

Document protection is granted for 10 years for medicines with a new active ingredient. Document protection is also granted for 10 years for a new indication in the case of a considerable therapeutic improvement and for three years for a new indication, application, dosage form, dose strength or dosage recommendation of a medicine with a known active ingredient. Document protection is also granted to paediatric medicines (10 years) and orphan drugs (15 years).27

Medicines for paediatric use benefit from a six-month extension of the supplementary protection certificate, subject to certain conditions.28

Patent-protected medicines may be manufactured and exported to developing countries to combat public health problems, subject to certain conditions (compulsory licences).29

vii  Post-approval controls

Any person manufacturing or distributing therapeutic products (i.e., medicines or medical devices) must establish a notification system. He or she must notify Swissmedic of any adverse event or reaction that (1) is or may be attributable to the therapeutic product itself, its use or labelling; or (2) may endanger or damage the health of the consumer, the patient or a third party. That person must also notify Swissmedic of any quality defects and any further findings and assessments that could influence the basis of evaluation. Such notifications must be made in accordance with the recognised rules of good vigilance practice.30

The marketing authorisation is transferable.31 The rules regarding amendments to approvals (known as variations) have been largely harmonised with EU law.32

Swissmedic may revoke the marketing authorisation if the medicine is not actually placed on the market within three years of granting the authorisation or if it is no longer actually on the market during a period of three successive years after it has been placed on the market. If the authorisation holder intends not to place a paediatric medicine on the market, such intention is published by Swissmedic together with the information that the authorisation documentation can be obtained free of charge from the marketing authorisation holder.33

viii  Manufacturing controls

Manufacturers of medicines require a licence from Swissmedic, whereas manufacturers of medical devices are not required to obtain such a licence.34

26 Article 140a et seq. Federal Act on Patents for Inventions (PatG).
27 Article 11a et seq. TPA; Article 30 Ordinance on Medicinal Products (VAM).
28 Article 140n et seq. PatG.
29 Article 40d PatG.
30 Article 59 TPA.
31 Article 10 VAM.
32 Article 21 et seq. VAM; Article 22a et seq. AMZV.
33 Article 16a TPA; Articles 11 and 13 VAM.
34 Article 5 Paragraph 1 lit. a TPA.
Manufacturing licences are issued if the necessary technical and operational conditions are fulfilled and if an appropriate system of quality assurance exists.\textsuperscript{35}

The licence is unlimited in time in principle and specifies in particular the qualified person, the authorised activities and the business locations.\textsuperscript{36}

The manufacture of medicines must conform to the recognised rules of good manufacturing practice.\textsuperscript{37}

ix Advertising and promotion

Whereas the TPA contains provisions regarding advertising of both medicines and medical devices, the ordinances applicable to advertising of medicines and medical devices differ. Advertising of medicines is subject to the Ordinance on Advertising of Medicinal Products (AWV), whereas advertising of medical devices is subject to Article 21 of the Ordinance on Medical Devices (MepV).

Advertising of medicines is defined in the AWV as all information, marketing and incentivising measures aimed at promoting the prescription, supply, sale, consumption or use of medicines. General information on health and diseases without any direct or indirect references to individual medicines is not, however, considered to be advertising. The packing material and the drug information do not fall within the provisions of the AWV either.\textsuperscript{38}

The provisions regarding advertising of medicines clearly distinguish between advertising directed at healthcare professionals (HCPs) and advertising directed at the general public. Generally speaking, it is permitted to advertise all types of medicines if the advertising is directed exclusively at HCPs. However, it is only permitted to advertise non-prescription medicines to the general public.\textsuperscript{39}

With regard to medical devices, Article 21 MepV states that advertising to the general public is prohibited for medical devices that are placed on the market for the exclusive use by professionals.

Advertising is deemed unlawful if it is misleading or contrary to public order and morality, if it may incite an excessive, abusive or inappropriate use of medicines or if it is for medicines that may not be placed on the market nationally or cantonally.\textsuperscript{40}

Furthermore, advertising directed at the general public is deemed unlawful for medicines that contain narcotic or psychotropic substances and for medicines that may not, on account of their composition and their intended use, be used without the intervention of a doctor for the necessary diagnosis, prescription or treatment, as well as for medicines that are frequently the object of abuse, or lead to an addiction or dependence.\textsuperscript{41}

The infringement of the regulations on the advertising of medicines may entail criminal sanctions.\textsuperscript{42}

In addition, Swissmedic may take all administrative measures necessary to enforce the TPA. In particular, it may seize, hold in official storage, destroy or prohibit the use of illegal

\textsuperscript{35} Article 6 Paragraph 1 TPA.
\textsuperscript{36} Article 40 and 42 AMBV.
\textsuperscript{37} Article 7 Paragraph 1 TPA; Article 4 Paragraph 2 and Annexes 1 and 2 AMBV.
\textsuperscript{38} Article 1 Paragraph 2 lit. a and c; Article 2 lit. a AWV.
\textsuperscript{39} Article 31 Paragraph 1 and Article 32 Paragraph 2 lit. a TPA; Article 3 et seq. and Article 14 et seq. AWV.
\textsuperscript{40} Article 32 Paragraph 1 TPA.
\textsuperscript{41} Article 32 Paragraph 2 TPA.
\textsuperscript{42} Article 87 Paragraph 1 lit. b and Paragraphs 2–6 TPA.
advertising media, and publish the prohibition at the expense of the responsible parties as well as temporarily or permanently prohibit the advertising of a specific medicine in the event of serious or repeated infringements of the provisions of the TPA, and publish the prohibition at the expense of the responsible parties.\textsuperscript{43}

\textbf{x} \hspace{1cm} \textbf{Distributors and wholesalers}

Any person engaged in the wholesale trade of medicines must possess a licence issued by Swissmedic, which is issued if the necessary technical and operational conditions are fulfilled and an appropriate system of quality assurance exists. The licence is also issued if the applicant already possesses a manufacturing or import licence for medicines.\textsuperscript{44}

Brokers and agents require a licence for the distribution of medicines as well.\textsuperscript{45}

The licence is unlimited in time in principle and specifies in particular the qualified person, the authorised activities and the business locations.\textsuperscript{46}

Furthermore, anyone who dispenses medicines requires a cantonal licence.\textsuperscript{47}

In principle, mail-order trade in medicines is prohibited. However, cantons may issue a licence under certain conditions.\textsuperscript{48}

\textbf{xi} \hspace{1cm} \textbf{Classification of products}

In connection with the marketing authorisation, Swissmedic classifies medicines into four categories (A, B, D and E) depending mainly on their safety and their undesirable effects. Generally speaking, categories A and B contain prescription-only medicines, whereas category D contains over-the-counter medicines in pharmacies and drug stores, and category E contains medicines sold without any restrictions.\textsuperscript{49}

Category A and B medicines may be dispensed by doctors or pharmacies. Category A medicines may, however, only be dispensed once.\textsuperscript{50} Certain category B medicines may, under certain conditions, be dispensed by pharmacists without a prescription.\textsuperscript{51}

Category D medicines may be dispensed by pharmacies and drug stores after professional advice, whereas category E medicines can be sold anywhere without restrictions.\textsuperscript{52}

The former category C (over-the-counter medicines that may be dispensed by pharmacies after professional advice by a healthcare professional) has been abolished, starting from 1 January 2019, and all the medicines that were in it are being reclassified into category D or B. However, until completion of said reclassification, category C will continue to exist until all reclassifications are legally binding, which may take several years if such reclassifications are appealed.\textsuperscript{53}

\begin{itemize}
  
  \item [43] Article 66 Paragraphs 1 and 2 TPA.
  
  \item [44] Article 28 TPA; Article 2 lit. l and Article 11 et seq. AMBV.
  
  \item [45] Article 4 Paragraph 1 lit. e TPA; Article 24 et seq. AMBV.
  
  \item [46] Articles 40 and 42 AMBV.
  
  \item [47] Article 30 Paragraph 1 TPA.
  
  \item [48] Article 27 TPA.
  
  \item [49] Article 23 et seq. TPA; Article 40 et seq. VAM.
  
  \item [50] Article 41 et seq. VAM.
  
  \item [51] Article 45 VAM.
  
  \item [52] Article 43 et seq. VAM.
  
  \item [53] Article 88 VAM.
\end{itemize}

© 2020 Law Business Research Ltd
xii Imports and exports

Any person who, in a professional capacity, imports or exports ready-to-use medicines intended for distribution or dispensing, requires a licence issued by Swissmedic. The same holds true for anyone who, in a professional capacity, trades medicines in foreign countries from Switzerland, without their entering into Switzerland.\(^5^4\)

The licence is unlimited in time in principle, and specifies in particular the qualified person, the authorised activities and the business locations.\(^5^5\)

xiii Controlled substances

Advertising directed at the general public is deemed unlawful for medicines that contain narcotic or psychotropic substances as referred to in the Narcotics Act.\(^5^6\)

The import of medicines is generally limited to medicines that have been authorised or that are not subject to authorisation.\(^5^7\) As a general rule, opium for smoking and the residues created in its production or use, diacetylmorphine and its salts, hallucinogens such as lysergide (LSD 25) and narcotics containing an effective concentration of cannabinoids may not be cultivated, imported, produced or placed on the market. However, the FOPH may issue exceptional licences, subject to certain conditions. For the import, production and placing on the market of one of the mentioned narcotics that is an active ingredient in an authorised medicine, a licence from Swissmedic is required.\(^5^8\)

The export of medicines and their foreign trade from Switzerland is generally prohibited if they are prohibited in the target country or if circumstances suggest that they could be intended for illegal purposes.\(^5^9\)

xiv Enforcement

As a general rule, both Swissmedic and cantonal authorities – in certain situations the FOPH – are responsible for market surveillance, for conducting inspections and for enforcing the TPA.\(^6^0\)

Swissmedic may take all administrative measures deemed necessary and institute criminal proceedings, which are conducted by Swissmedic and the FOPH, and which may involve further federal or cantonal authorities.\(^6^1\)

The Code Secretariat is the self-regulatory body that is responsible for the implementation of the Pharma Code and the Pharma Cooperation Code, which are relevant and often referred to self-governing codices by the pharmaceutical industry. Both codes contain provisions regarding procedures in case of a breach of a code.

---

\(^{54}\) Article 18 TPA; Article 11 et seq. and Article 21 et seq. AMBV.
\(^{55}\) Articles 40 and 42 AMBV.
\(^{56}\) Article 32 Paragraph 2 lit. b TPA.
\(^{57}\) Article 20 Paragraph 1 TPA.
\(^{58}\) Article 8 of the Narcotics Act.
\(^{59}\) Article 21 Paragraph 1 TPA.
\(^{60}\) Articles 58, 60, 82 et seq. and Article 90 TPA.
\(^{61}\) Articles 66 and 90 TPA.
III PRICING AND REIMBURSEMENT

Healthcare insurance is compulsory for all people residing in Switzerland. It is regulated mainly by the KVG. A medicine or a medical device is eligible for reimbursement by the compulsory healthcare insurance scheme, if an accordant application has been filed with the FOPH. The list of specialities covers ready-to-use medicines, whereas the list of means and objects (MiGeL) covers medical devices used by patients. The KVG stipulates that to be included on such a list a product must prove to be effective, appropriate and economical.  

Prices for medicines are determined by the FOPH. It determines the ex-factory price of a product by conducting, on the one hand, a therapeutic cross-comparison in which it considers the treatment costs of already-approved medicines for the same condition. On the other hand, it carries out an international price comparison, considering the price of the same medicine in nine reference countries (Austria, Germany, Denmark, Sweden, France, Finland, Netherlands, the United Kingdom and Belgium). The therapeutic cross-comparison and the international price comparison are weighed equally in setting the final price. An innovation premium may be granted if the product represents a significant therapeutic advance. The price of every medicine in the list of specialities is reviewed every three years.

The maximum prices contained in the MiGeL for medical devices indicate how much the compulsory healthcare insurance scheme will reimburse for a medical device that falls within a specific MiGeL position. Any costs beyond the maximum price must be borne by the patient.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Decrees by Swissmedic and the FOPH can be appealed to the Federal Administrative Court. The latter’s decisions can be appealed to the Federal Supreme Court.

Both Swissmedic and cantonal authorities may institute criminal proceedings. On the federal level, such proceedings are conducted by Swissmedic and the FOPH and may involve further authorities.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The TPA states that persons prescriing, dispensing, applying or purchasing prescription-only medicines and organisations employing such persons shall not claim, have promised or accept for themselves or for the benefit of any third party any undue advantage. Similarly, it is prohibited to offer, promise or grant any undue advantage to any such person or organisation for its benefit or for the benefit of any third party. Not considered undue advantages are: (1) advantages of modest value relevant to medical or pharmaceutical practice; (2) contributions for research, education and training, provided that certain criteria are met; (3) compensation for equivalent services, in particular in connection with orders and deliveries of therapeutic products; and (4) discounts or refunds granted on the purchase of therapeutic products.

---

62 Article 32 KVG.
63 Articles 65b and 65d KVV; Article 34a bis et seq. Ordinance on the Indemnification by Compulsory Healthcare Insurance (KLV).
64 Article 44 Paragraph 1 KVG; Article 24 Paragraph 2 KLV.
65 Article 84 Paragraph 1 TPA.
66 Articles 66 and 90 TPA.
provided that they do not influence the choice of treatment.\textsuperscript{67} Furthermore, all discounts and refunds granted on the purchase of therapeutic products must be shown in the supporting documents and invoices and in the accounts of both the selling and purchasing persons and organisations and must be disclosed to the FOPH on request.\textsuperscript{68}

HCPs who receive discounts or benefits from other HCPs or persons or companies supplying medicines or medical devices must pass these on to the healthcare insurer or the insured person, either wholly or the majority of it (subject to certain conditions).\textsuperscript{69}

The Pharma Code and the Pharma Cooperation Code contain provisions regarding the relationship between the pharmaceutical industry and prescribers as well. Further self-regulatory codes include the Guidelines of the Swiss Academy of Medical Sciences on Collaboration between Medical Professionals and the Industry and the code enacted by H+, the Swiss Hospital Association.

The Pharma Cooperation Code contains the obligation to publicly publish, on a yearly basis, all monetary and in-kind benefits that they have given to HCPs and healthcare organisations in the previous year.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The general liability regime, including both contractual and non-contractual liability (including product liability), applies in relation to persons injured by medicines or medical devices. Swiss law does not provide a specific liability system for such cases. However, in cases where injuries are suffered in connection with medical treatment at public hospitals, cantonal state liability rules are applicable.

In connection with medical research on humans, the person carrying out the clinical trial is liable for all damages suffered in connection with the project and must ensure that this liability is appropriately covered through insurance or in some other manner.

The Federal Act on the Medical Profession stipulates that persons who exercise a university medical profession in the private sector and under their own professional responsibility are obliged to take out adequate professional liability insurance.\textsuperscript{70}

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

There are no provisions in Swiss competition law specifically addressing the life sciences sector. However, within the scope of their responsibility to enforce general competition and antitrust provisions, the Swiss Competition Commission (COMCO) and the Swiss courts do monitor and pass decisions on competition law matters within the life sciences sector. In a recent and ongoing case, COMCO fined three pharmaceutical companies for alleged unlawful agreements affecting competition. The three companies had been issuing non-binding price recommendations for medicines. The case has been adjudicated by

\textsuperscript{67} Articles 55 and 86 Paragraph 1 lit. h TPA; Article 1 et seq. Ordinance on Integrity and Transparency in the Field of Therapeutic Products (VITH).

\textsuperscript{68} Articles 56 and 87 Paragraph 1 lit. h TPA; Article 10 VITH; see, however, the exception for low-risk therapeutic products in Article 56 Paragraph 3 and Article 10 Paragraph 2 VITH.

\textsuperscript{69} Article 56 Paragraph 3 and 3bis KVG; Article 76a et seq. KVV.

\textsuperscript{70} Article 40 lit. h of the Federal Act on the Medical Profession.
both the Federal Administrative Court and the Federal Supreme Court, with the former overturning COMCO’s fine, stating that unlawful agreements regarding prices require elements such as pressure, the promise of specific benefits and a lack of transparency, none of which were deemed to be present in the case at hand, and the latter then siding with COMCO, stating that the conditions for concerted behaviour had been met. The case has now been re-adjudicated by the Federal Administrative Court, which adhered to its original verdict. Interestingly, the Federal Administrative Court held that the sales market of a prescription drug cannot be compared with that of a regular consumption good, especially when considering factors such as advertising, competition and price freedom.72

**ii Transnational issues**

While the Swiss pharma industry is host to many mergers, acquisitions and other strategic transactions, none have given rise to further scrutiny from a competition law standpoint in recent years. Swiss regulatory framework and intellectual property legislation allow for considerable flexibility, further facilitating such transactions or collaborations.

**VIII CURRENT DEVELOPMENTS**

The revised provisions in the TPA on integrity and transparency in connection with therapeutic products that came into force on 1 January 2020 aim to prevent the corruption of HCPs by manufacturers of medicines and medical devices, to increase transparency on granted discounts as well as to better enforce the obligation of HCPs to pass on received discounts. It remains to be seen whether the new legislation will have the desired effects or whether HCPs will insist on no longer receiving discounts because such discounts increase their administrative work and do not benefit them.

The legislation on medical devices is currently being revised so as to harmonise it with the new EU regulation; the consultation process ended on 5 September 2019. The evaluation of the consultation was not yet available at the time of writing, but it is expected that the revised provisions will enter into force in the first half of 2020.

Governmental (FOPH) reimbursement and pricing of medicines and of medical devices – whereby the focus is on medicines – faces similar challenges compared with the challenges in many other jurisdictions. The revenue expectations of an innovative industry must match the coverage capabilities of the social security system (i.e., the mandatory healthcare insurance scheme in Switzerland). Multi-indication pricing, pricing of IP-protected technologies versus generic technologies, and pricing of new technologies that do not match existing categories of medicine, medical procedure or medical device are challenges on the operational level. First proposals for new KVG provisions addressing some of the current pricing issues were introduced to stakeholders by the FOPH in 2018. It will most likely be years before the two chambers of parliament adopt new KVG provisions regarding the life sciences sector (i.e., its pricing), if ever.

Meanwhile, the three-yearly price reviews of medicines by the FOPH pose several questions that have led to numerous appeals before the Swiss Administrative Court; indeed,

---


72 Decision of the Federal Administrative Court B-843/2015 of 19 December 2017, consid. 6.
some provisions of the KVV and KLV were altered as from 1 March 2017. In 2020 and 2021, the Federal Administrative Court is expected to render relevant decisions, decisively shaping the FOPH price-revision practice.
I INTRODUCTION

The Taiwanese government places great importance on the life sciences sector with the aim of developing it. Although there is an abundance of laws and regulations governing different aspects of this sector, the most important law is the Pharmaceutical Affairs Act (PAA). The government strictly scrutinises relevant industries and business operations and often takes a conservative stand on borderline cases to ensure the protection of the public. The Ministry of Health and Welfare (MoHW) is the competent central authority that governs all health-related matters, such as healthcare professionals and institutions, foods, cosmetics, medicines, medical devices and national health insurance (NHI). The Taiwan Food and Drug Administration (TFDA), one of the sub-agencies of the MoHW, is the entity responsible for the enforcement of laws and regulations related to foods, cosmetics, medicines and medical devices, and the issuance of all licences, permits and authorisations.

II THE REGULATORY REGIME

The PAA provides the basic structure for the regulation of medicines and medical devices, and the MoHW has promulgated more than 100 subordinate regulations, guidelines and standards to clarify the implementation of the PAA.

i Classification

Both medicines and medical devices are regulated by the PAA. The PAA provides definitions for medicines and medical devices (jointly, medicaments) to define the scope of its application. Under the PAA, ‘medicines’ are restricted to raw materials and preparations of any of the following:

a medicines used in diagnosing, curing, alleviating and preventing the diseases of human beings regardless of whether they are listed in the pharmacopoeia, listed by the PAA or recognised by the MoHW;

b other medicines capable of sufficiently affecting the body and physiological functions of human beings; and

c medicines used in preparing the above-mentioned medicines.

---

1 Katherine Juang is an associate partner, Jill Niu is a partner and Daisy Wang is a senior counsellor at Lee and Li, Attorneys-at-Law.
In general, the term ‘medical devices’ covers instruments, machines, and apparatuses and their accessories, fittings and parts, used in diagnosing, curing, alleviating and directly preventing diseases of human beings or that may affect the body or functions of human beings. Owing to the different characteristics of medicines and medical devices, the TFDA intends to establish a separate set of statutes for medical devices and proposed a draft Medical Devices Act in early 2015. The draft passed its third reading on 13 December 2019; however, it has not been announced by the President yet. In addition, it is provided in the draft that the enactment date thereof is pending the determination of the Cabinet. Thus, when the draft will become effective is still uncertain. Nonetheless, the TFDA has started to draft several sets of regulations under the new law.

Since the MoHW is the sole central authority with competence to enforce the relevant laws in the life sciences sector, the MoHW reviews all cases and determines the necessary classifications of medicines, medical devices, cosmetics and cosmeceutical products, foods and food additives. With respect to chemicals, they are subject to the governance by the Environmental Protection Administration, the MoHW, and the Industrial Development Bureau depending on whether the chemicals are manufactured for medical or industrial products. If a product might fall within multiple classifications, the most stringent one would apply. There are no borderline cases at the moment.

**ii Non-clinical studies**

There are three Taiwanese regulations related to non-clinical studies: the Good Laboratory Practice for Non-clinical Laboratory Studies (GLP), the Guideline for the Non-clinical Safety Studies for Medicinal Products (GSS), and the Good Operational Practice for Non-clinical Studies (GLP-V2) amended by the MoHW in March 2006 and June 2014 and promulgated by the MoHW in February 2019, respectively. As indicated in their respective prefaces, the GLP, the GSS and the GLP-V2 were drafted by the MoHW by referring to the Good Laboratory Practice for Non-clinical Laboratory Studies promulgated by the United States Food and Drug Administration and other relevant regulations or guidelines of the International Conference on Harmonisation, the OECD and other developed countries. Hence, these regulations are generally in line with, and cover all the provisions stipulated in, international practice, excluding toxicokinetics studies.

**iii Clinical trials**

For clinical trials conducted to obtain marketing approval for medicaments, the PAA and its subordinate Guidelines for Good Clinical Practice (GCP), promulgated by the MoHW, must be considered. For human trials initiated and conducted by teaching hospitals or healthcare institutions, for the purpose of improving medical care or preventing diseases, the Medical Care Act (MCA) and its subordinate Regulations on Human Trials (RHT) must be considered. While there have been no specific regulations governing other types of trials, the Human Subjects Research Act (HSRA) was enacted in December 2011 (with minor amendment in January 2019) to provide general regulations on research (including trials) involving human subjects. In light of this development, all clinical trials and human research should comply with the HSRA, unless conducting clinical trials for medicaments registration purposes, in which case the GCP prevails, or when conducting human trials, in which case the MCA prevails, as the GCP and the MCA are special laws of the HSRA.

In general, approval from an institutional review board or ethics committee and informed consent of the subjects are required prior to conducting any research involving
human subjects, unless exempted by the MoHW. As for clinical trials under the PAA and human trials under the MCA, approval from the MoHW or TFDA and the research institutional review board or ethics committee, and informed consent from subjects are mandatory requirements. It is required under the GCP that the sponsor should be responsible for compensation and insurance for injuries inflicted on the human subjects. Allocation of liability between institutions or investigators and sponsors is mostly determined in the terms of the clinical trial agreements. Since there are no special laws or regulations governing investigator-initiated studies, the GCP should be applicable; for example, an investigator should assume the sponsor’s responsibility as set out in the GCP and a clinical trial agreement must be executed to specify financial support from a pharmaceutical firm, if any.

iv  Named-patient and compassionate-use procedures
A teaching hospital may treat seriously ill patients with medicaments that have not been registered with or approved by the MoHW if the medicaments are part of a project-related importation programme according Article 48–2 of the PAA. In its application to the MoHW, the teaching hospital should submit an approval from the ethics committee, any medical literature regarding treatment, the patient’s consent and documents providing evidence that the medicaments have obtained marketing approval from the competent sanitation authority of the country where they are manufactured.

In addition, pursuant to the Rare Disease Prevention and Medicaments Act, government agencies, healthcare institutions, patients with rare diseases or their relatives, and relevant foundations or associations may also apply for project-related importation programmes for rare-disease medicaments that have not been registered with or approved by the MoHW. The documents required for submission to the MoHW are similar to those mentioned above.

After the project-related importation programme application has been approved by the MoHW, the imported medicaments should be labelled as samples and should not be available for sale. Therefore, teaching hospitals may not charge their patients for the costs of the medicaments.

v  Pre-market clearance
The Regulations for Registration of Medicines (RRM), the Regulations for Registration of Medical Devices (RMD), the Regulations for Registration of Botanical Medicines (RBM), the Regulations for Registration of Biosimilar Products (RRB), the Regulations for Registration of Biosimilar Monoclonal Antibody Products (RRMA), and the Regulations for Registration of Human Cell Therapy Products (RHCT) provide application procedures for the registration of, and obtaining marketing approval for, medicines, medical devices, botanical medicines, biosimilar products in general, and biosimilar monoclonal antibody products, respectively. In general, applicants registering new chemical entity (NCE) medicines have to submit relevant information and data relating to, inter alia: clinical trials, formulation basis, testing specifications, methods and certificates of analysis of raw materials and finished products, and manufacturing records.

The RRM has constantly been amended to simplify the procedures or to relax the application requirements for registering drugs, and was most recently amended in August 2019. One of the most important recent changes is that e-submission has been introduced in the application procedure.

As for medical devices, they are subdivided into the three classes under the RMD: Classes 1, 2 and 3. Registration of Class 1 medical devices merely involves simple paper
review, but registration of Classes 2 and 3 medical devices requires submission of detailed documents, particularly the free-sale certificate and clinical trials data. The Classification Guidelines for Medical Device Software were also promulgated in 2015 to cope with recent needs in the industry.

With respect to the RBM, RRB, RRMA and RHCT, the TFDA indicated in the foreword of the Regulation that it does not have much experience in reviewing applications for registering botanical medicines, biosimilar, biosimilar monoclonal antibody and human cell therapy products so the RBM, RRB, RRMA and RHCT will be subject to further amendments after the TFDA gathers more information from the relevant industries and becomes more experienced in this regard. Additionally, the TFDA has proposed a draft Cell and Genetic Therapy Product Control Act in early 2017, and the Executive Yuan (EY) has proposed a draft Regenerative Medicinal Products Control Act in October 2018; both drafts are still under discussion.

According to the suggested timeline published by the MoHW, it takes approximately one year to obtain NCE marketing approval, 200 days for other kinds of new medicines, 220 days for new medical devices and only 80 days for Class 1 medical devices. The applicant (the prospective marketing approval holder) must be a company duly registered under the laws of Taiwan and must hold a pharmaceutical company licence.

As regards special circumstances, there is no alternative mechanism to accelerate approval of products for urgent medical needs, although the MoHW did accelerate its review of H1N1 vaccines during the H1N1 pandemic in 2009. Article 48–2 of the PAA, mentioned in Section II.iv, also gives a legal basis for obtaining an accelerated approval for a project-related importation programme; however, this form of approval is given on a case-by-case basis and has a shorter duration than ordinary marketing approvals.

vi Regulatory incentives
Where previously brand-name pharmaceutical firms provided information about their NCE patents and, when granting marketing approval for NCEs, the MoHW would publish the relevant patent numbers or patent file numbers, this submission of patent information was only for the MoHW’s records and files, and was not linked to patent enforcement. However, a bill to amend the PAA passed three readings by the LY on 29 December 2017 (PAA 2017) to include a patent linkage mechanism similar to that used in the US system. The patent linkage-related provisions in the PAA 2017 became effective in August 2019. The Enforcement Rules of Patent Linkage were also promulgated by the TFDA at the same time. In short, according to the PAA 2017, the holder of a new drug authorisation (the NDA holder) should report its related patents within 45 days, and the applicant for the generic drug is obliged to declare to the TFDA and inform the NDA holder that the generic drug does not infringe any patents of the reference new drug. After being informed, the NDA holder, relevant patentees or exclusive licensees should initiate patent infringement litigation within 45 days if it disagrees with the declaration. The TFDA, after being notified of the aforementioned litigation, shall stay the issuance of the generic drug authorisation for 12 months. The applicant for the generic drug that first overcame the patent infringement issue will be granted with the drug authorisation by the TFDA and enjoy a 12-month market exclusivity. In addition, any agreement between the NDA holder, patentees, exclusive licensees and the applicant of the generic drug regarding the 12-month market exclusivity should be submitted to the TFDA and the Taiwan Fair Trade Commission (TFTC) for review. The patent linkage mechanism is applicable to both chemicals and biologics.
The PAA provides data exclusivity and study exemption clauses to balance the benefit of brand-name and generic firms. The relevant provisions were amended and effective in the PAA 2017; these provide a three-year data exclusivity with the effect that the TFDA will not issue any marketing approval for a generic within five years of the issuance of marketing approval to the innovator. The PAA 2017 introduces a two-year data exclusivity for a medicine with a new indication or a newly changed indication with the effect that the TFDA will not approve the new indication or a newly changed indication to a generic within three years of the issue of approval of that indication to the innovator.

It is provided in the Orphan Drug Act that the pharmaceutical firm that holds the first marketing approval for an orphan drug may enjoy 10 years’ exclusivity for that marketing approval, to encourage the development or introduction of orphan drugs in Taiwan.

In addition, patent term extension is available under the Patent Act; the patentee may apply for one, and only one, extension of the term of the invention patent, for up to five years, based on the regulatory approval.

vii Post-approval controls
The pharmaceutical firm must employ a full-time resident pharmacist as part of its management to ensure the control of such firm. A similar mechanism for medical devices is included in the draft Medical Devices Act mentioned in Section II.i, which is that a full-time resident engineer with a relevant medical device background must be employed. In addition, starting from January 2019, it is mandatory for a pharmaceutical dealer to meet the Good Distribution Practice (GDP) requirements to sell and distribute medicinal products in Taiwan.

The MoHW, as required under the PAA, has promulgated the Regulation of Medicaments under Monitoring to implement five-year post-approval surveillance to ensure the continuing safety of marketed medicaments and to compel the marketing approval holder to report an adverse event caused by medicaments. After the surveillance period, the PAA still requires healthcare institutions, pharmacies and pharmaceutical firms to report serious adverse events caused by medicaments to the MoHW. The Regulation Governing the Reporting of Severe Adverse Reactions to Medicines was promulgated to provide the relevant reporting procedures.

After marketing approval has been granted, any variations or amendments to the approved contents of the packages, leaflets or labels have to undergo review and further approval by the MoHW. Marketing approval is generally valid for five years (those for rare-disease medicaments are for 10 years); an application for marketing-approval renewal must be filed at least six months before expiry of the existing marketing approval. If the marketing approval holder is aware that it is unable to supply the product or there might be a shortage of the product, it should notify the TFDA at least six months before that situation occurs. If the shortage of supply is caused by force majeure, the holder should notify the TFDA within 30 days of the event. The TFDA may proceed with a project-related importation programme to address the needs of patients.

viii Manufacturing controls
Medicaments must be manufactured by medicament manufacturing factories. Medicament manufacturing factories must obtain a factory registration licence pursuant to the Factory Management Act and a medicament manufacture licence pursuant to the Standards for Medicament Factory Establishment. As specified in the Standards, if a factory passes the
MoHW’s inspection pursuant to the Good Manufacturing Practices for Medicaments (GMP), it may further obtain a certificate of GMP. A manufacturer may only commence manufacturing upon receipt of the medicament manufacture licence and if its factory passes the GMP inspection, unless exempted by the MoHW through public notice. In addition, the manufacturing of medicaments must comply with GMP standards. PIC/S GMP has been adopted by the TFDA since December 2007. For imported products, the foreign manufacturer must pass the Quality System Documentation examination.

Relocation, expansion, transfer of premises ownership and expansion of product lines all require approval from the competent local sanitation authority and renewal of a GMP licence upon passing the GMP inspection by the MoHW.

The competent authorities are entitled to conduct inspections pursuant to the PAA and the Regulations of Medicament Manufacturer Inspection. The TFDA generally conducts such inspections regularly to ensure the safety and efficacy of the pharmaceutical products manufactured locally. The sellers or manufacturers of certain categories of medicine to be announced by the TFDA should set up a system to track the source and sales flow of such medicines, and should docket the information in the corresponding system established by the TFDA.

ix Advertising and promotion
According to the PAA, medicaments can only be advertised with prior approval by the MoHW and an application for this approval must be filed by the pharmaceutical firm holding marketing approval for the medicaments. Following approval, the advertisement should be published or broadcast with the name of the holder and the approval number or numbers. During the approved term of publication or broadcast, the approved particulars of medicaments cannot be modified. Advertisements for prescription medicaments can only be published in medical academic journals. Direct-to-patient promotions and advertisements for prescription medicaments are prohibited.

The term ‘pharmaceutical advertisements’ is broadly defined under the PAA to cover any act effectively deemed as communicating the medical efficacy of medicaments with the aim of soliciting and promoting sales. It is also specified in the PAA that interviews, news reports or propaganda containing information implying or suggesting medical efficacy will be regarded as pharmaceutical advertisements. In this regard, the TFDA and the local competent sanitation authorities are usually strict. There have been cases in which pharmaceutical firms provided information leaflets to healthcare professionals for their reference, but those leaflets were disseminated by healthcare professionals to their patients; the MoHW viewed this as disguised promotion so the pharmaceutical firms were fined. The courts usually uphold such views. In addition, advertisement and promotion of ‘off-label use’ are prohibited.

x Distributors and wholesalers
Salespersons employed by pharmaceutical firms are only permitted to promote sales after their employment has been registered with the competent local sanitation authority. They can only sell medicaments manufactured or sold by their employers and can only sell those products to pharmacies, pharmaceutical firms, healthcare institutions and medical research institutions. Salespersons should not commit the acts of peddling, street vending, tampering with medicaments without authorisation and illegal advertising.

There are no specific regulations governing the licensing of distributors and wholesalers. However, in keeping with the PAA, marketing approval holders can only license sales of
their products to distributors or wholesalers who have a pharmaceutical dealer licence and are qualified to conduct the business of selling medicaments, and who have GDP certification. Salespersons hired by such distributors and wholesalers must also comply with the aforementioned regulations concerning salespersons.

xi  Classification of products
Medicaments are subdivided into prescription-only and over-the-counter. There are no specific procedures on classification. Pharmaceutical firms are required to provide their deemed classification when filing an application for marketing approval, and the MoHW will rule on the classification and state it on the marketing approval. Sales of prescribed medicaments can only be made by pharmaceutical firms and pharmacies, while sales of over-the-counter medicaments can be made by general retailers. The different limitations on promotions are outlined in Section II.ix, above.

xii  Imports and exports
Only pharmaceutical firms holding marketing approval for a medicament are eligible to import that product. Marketing approval holders are, however, permitted to license a third-party pharmaceutical firm to import a product as long as the licence is notified to the MoHW and the MoHW has acknowledged receipt.

For medicaments manufactured and sold under marketing approvals, and intended for sale abroad through export, if an import certificate from the importing country is required, the manufacturer must obtain an export certificate from the MoHW prior to exportation. In this regard, the MoHW may, upon consideration of insufficiency to meet domestic demands, restrict or limit exportation of medicaments.

xiii  Controlled substances
Addictive narcotic medicines and psychotropic medicines are defined as controlled medicines and are regulated by the Controlled Medicines Act. Controlled medicines are subdivided into four classes depending on addictive intensity, with Class 1 being the most addictive. Import, export, sales and manufacture of Class 1 and Class 2 controlled medicines can only be carried out by TFDA-established factories, while for Class 3 and Class 4 controlled medicines the same processes can be carried out by pharmaceutical firms after obtaining marketing approval pursuant to the RRM.

All controlled medicines can only be dispensed and supplied with a prescription from a physician. When supplying controlled medicines, the identification certificate, name, address and uniform serial number of the receiver and the quantity of the controlled medicines received must be listed in detail and be kept with the prescription for future inspection. This information, data and records should be kept for five years.

xiv  Enforcement
The MoHW may, from time to time, send officials to inspect the premises of pharmaceutical firms, healthcare institutions and pharmacies, and to sample-test medicaments. Pharmaceutical firms, healthcare institutions and pharmacies cannot refuse any inspection and sample test without just cause. Competent local sanitation authorities should also conduct annual inspections of pharmaceutical firms and pharmacies.
The MoHW or competent local sanitation authorities may impose administrative fines of between NT$20,000 and NT$50 million for violations of statutory requirements and may even impose consecutive fines for continuous violations. The cap of the administrative fines has increased from NT$25 million to NT$50 million in the PAA to halt the manufacture and import of counterfeit and inferior medicines. For serious violations or refusal to cooperate, authorities may publish the name of the violating pharmaceutical firms, reject renewal applications for medicaments, revoke marketing approvals and shut down business operations. If a violation involves a criminal offence, such as the manufacture, import or sale of counterfeit, prohibited or defective medicaments, authorities can forward the case to the judiciary.

III PRICING AND REIMBURSEMENT

The NHI was launched in March 1995 and is a compulsory social insurance programme. All Taiwanese citizens and foreign nationals living in Taiwan with an alien resident certificate are obliged by statute to enrol in the programme. The NHI has extensive coverage of medicaments, taking up approximately 90 per cent of the market. The insurer of the NHI is the National Health Insurance Administration (NHIA), a subordinate agency of the MoHW. The NHIA is responsible for collecting premiums from the insured. When the insured use medical services, they do not have to pay for medical expenses other than a co-payment and registration fee. Healthcare providers will apply for reimbursement from the NHIA. The National Health Insurance Act (the NHI Act) was extensively amended in January 2010 (and slightly amended in June 2011 and November 2017). Although pharmaceutical firms had no role in first-generation NHI, an article was added to the amended NHI Act enabling pharmaceutical firms to voice their opinions with regard to rules on the inclusion of medicaments on the NHI reimbursement list and determination of reimbursement price standards.

Medicaments included on the NHI reimbursement list and their reimbursement prices are determined by the NHIA pursuant to the Pharmaceutical Benefit Scheme for NHI (the PB Scheme; promulgated in 1999 and lastly amended in August 2019). In general, the reimbursement price of brand-name medicaments is determined by referring to the reimbursement prices of these products in 10 developed countries. The reimbursement price of generics is set to be approximately 80 to 85 per cent of the price of a brand-name product. As there are usually gaps between the higher reimbursement prices and the lower market prices (known as drug-price black holes), healthcare providers have been making profits from these gaps. Since 1999, the NHIA has launched a biannual market survey of actual sale prices and the volume of reimbursed medicaments (the PV Survey) and used the results as a benchmark to lower reimbursement prices to reflect actual market prices. As a result, pharmaceutical firms have to further lower their sales prices to sell medicaments to healthcare providers, which is more disadvantageous for brand-name pharmaceutical firms. A price-volume agreement (PVA) between the NHIA and marketing approval holder is available under the PB Scheme for newly added medicines and indications. In this respect, the NHIA amended the PB Scheme in September 2019 to include the managed-entry agreement (MEA) mechanism, which allows the NHIA and the marketing approval holder more room to negotiate the drug price and budget based on treatment outcome or financial impact. Currently, certain biologics products are under the MEA with the NHIA.
Additionally, the amended NHI Act includes a provision that the NHIA should adjust reimbursement prices based on prevailing market conditions; prices for patented medicines should be gradually lowered to reasonable prices within five years of the expiry of patent protection based on prevailing market conditions. Accordingly, the NHIA published the Adjustment Guidelines of NHI Reimbursement Prices (the Price Adjustment Guidelines) on 2 October 2013, which were slightly amended between February 2015 and February 2017. According to these guidelines, the following three categories of drugs will each have their own price adjustment formula:

a. Category 1: a new drug that is protected by patent (either compound or pharmaceutical composition) in Taiwan;

b. Category 2: a new drug that was protected by a patent in Taiwan, but that patent expired less than five years ago; and

c. Category 3: a drug that does not fall into Category 1 or 2 (a drug that has never been protected by patent in Taiwan, a new drug that was protected by a patent in Taiwan but that patent expired more than five years ago) or a new drug that was protected by a patent in Taiwan but that patent expired on or before 1 January 2013.

The price of Category 1 and Category 3 drugs should be adjusted biannually based on the PV Survey, while Category 2 drugs should be adjusted annually for five consecutive years after expiry of the patent concerned, based on a less favourable formula than that of Category 1 and Category 3 drugs. The NHIA has also implemented the Drug Expenditure Target (DET) from 1 January 2013 to date to improve the transparency and predictability of pricing and reimbursement in the market. Under the DET, the price of all categories of drugs will be adjusted annually. The price cuts were periodically made pursuant to the Price Adjustment Guidelines. Owing to the stringent view of the NHIA regarding whether a drug can be deemed to be protected by compound or pharmaceutical composition patents, the price cut decisions have been widely disputed by marketing approval holders. In February 2016, the NHIA amended the Price Adjustment Guidelines to relax the criteria of drugs under patent protection.

Owing to the comprehensive coverage of NHI medicaments in the market, pharmaceutical firms have a disadvantageous position when negotiating medicament supply agreements with healthcare providers. To ensure a fair business relationship between healthcare providers and pharmaceutical firms, according to the amended NHI Act, in March 2013 the MoHW and the TFTC, the authority competent to enforce the Fair Trade Act (which deals with antitrust and fair competition issues in Taiwan), jointly produced guidelines for definitive contract clauses to be used in agreements between healthcare providers and pharmaceutical firms, covering matters that must and must not be recorded in such agreements, and they also produced a template agreement. However, the TFTC does not interfere with the price determination and adjustment by the NHIA.

**IV ADMINISTRATIVE AND JUDICIAL REMEDIES**

If a pharmaceutical firm receives an administrative penalty imposed by the MoHW or local authority, it may file an opposition against the authority's decision within 15 days of receipt of the decision pursuant to the PAA. The authority is required to re-examine the matter and issue a new decision. The opposition is not a compulsory procedure, but most pharmaceutical firms will file an opposition before pursuing further administrative or judicial
remedies, which provides an opportunity to have a discussion with the authority. Regardless of whether an opposition is filed, the pharmaceutical firm may file an administrative petition with the supervising agency of the MoHW, the EY, within 30 days of receipt of a decision pursuant to the Administrative Petition Act.

If the petitioner is not satisfied with the EY’s decision, it may further initiate an administrative suit against both the penalty decision and the petition decision before the administrative courts within two months of receipt of the petition decision. There are two avenues for pursuing an administrative suit: the high administrative courts and the Supreme Administrative Court. The high administrative courts review both factual and legal issues, whereas the Supreme Administrative Court only reviews legal issues.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

There are no laws or regulations that directly regulate the relationships between pharmaceutical firms and physicians or healthcare professionals who make decisions relating to the utilisation or reimbursement of medicaments. The International Research-Based Pharmaceutical Manufacturers Association (IRPMA), an entity composed of international pharmaceutical firms operating in Taiwan, has issued the IRPMA Code of Practice (the IRPMA Code) to provide guidance to its members when interacting with healthcare professionals. The IRPMA Code suggests that: (1) all events and meetings held or sponsored by pharmaceutical firms should be purely for scientific or educational purposes; (2) interactions at such events and meetings should not in any way be conducted with the intention of affecting the independence and integrity of the healthcare professionals’ decisions relating to their prescriptions; and (3) any honorarium, hospitality, entertainment and gifts at such events and meetings should not be excessive. The IRPMA Code was amended in 2012 to ensure the honorarium standards therein comply with the Integrity and Ethics Directives for Civil Servants (see below), and the Code has been constantly updated since then; the most recent amendment was published in 2019. As for local pharmaceutical associations, neither the Taiwanese Generic Pharmaceutical Association nor the Chinese Pharmaceutical Manufacture and Development Association has published similar guidelines. However, the Taiwan Advanced Medical Technology Association (TAMTA), an entity composed of medical-device innovators, has published similar guidelines in its Code of Ethics.

Healthcare professionals employed by public hospitals in Taiwan are deemed to be civil servants and so are subject to the Civil Service Employment Act and the Integrity and Ethics Directives for Civil Servants. As provided in the Integrity and Ethics Directives, civil servants may not receive any unjustifiable gifts, cash or cash equivalents from private entities, and honorariums for attending a meeting or event are capped at NT$5,000 per hour; if a civil servant also receives an author’s remuneration for any such activity, the remuneration should not exceed NT$2,000 per 1,000 words. Healthcare professionals employed by public hospitals will be subject to a penalty pursuant to the Civil Service Act for violating the Integrity and Ethics Directives. The MoHW also promulgated in 2006 the Physician’s Code of Conduct: Guidelines Governing the Relationships between Physicians and Corporations to provide ethical standards for physicians employed by public hospitals or private entities. It is stipulated that physicians should maintain their independence and integrity relating to prescription decisions, should not be unduly affected by pharmaceutical firms, and should not receive cash or cash equivalents or other improper gifts from pharmaceutical firms. Physicians will be subject to a penalty pursuant to the Physician Act for violations of the
Physician’s Code of Conduct. Pharmaceutical firms should refrain from abetting or aiding healthcare professionals in violating the Integrity and Ethics Directives or the Physician’s Code. A draft amendment to the Physician’s Code was published by the TFDA in March 2015, which incorporates the contents of the IRPMA Code. This draft has provoked wide discussion and controversy within the industry and may still take some time to be finalised and promulgated.

Civil servants are narrowly defined in the Criminal Code. Only healthcare professionals employed by public hospitals responsible for procurement or listing of medicaments are deemed to be civil servants under the Criminal Code and will be subject to criminal liability for receiving bribes. Thus, the anti-bribery clause in the Criminal Code does not apply to most physicians.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

If a user of market-approved medicaments dies or becomes disabled or seriously ill (medicaments injury) because of an adverse reaction to the approved medicaments, the user or his or her relatives may request relief pursuant to the Medicaments Injury Relief Act. Pharmaceutical firms have to allocate between 0.2 and 10 per cent of their previous year’s sales revenue from medicaments to injury-relief funds. The Medicaments Relief Foundation was established in 2001 to manage contributions from pharmaceutical firms and to handle medicaments relief claims.

As for an injury caused by the use of medicaments not deemed to be a medicaments injury, the user who suffered the injury would have to claim damages against the relevant pharmaceutical firms on the basis of tort law; it is possible that any dispute that arises would have to be resolved through civil litigation. The user would have to prove that he or she did suffer injury, that the injury was caused by the use of medicaments and that the damages claimed were well grounded. There have been cases in which patients have sued pharmaceutical firms based on the Consumer Protection Act (CPA) by arguing that the medicaments, although approved by the MoHW, did not meet the appropriate standards and that, as pharmaceutical firms are obliged to ensure their products meet these standards, the firms should compensate users of these products. The courts, however, generally hold the view that because the MoHW has set in place a complex system of review of medicaments, unless substantial evidence is provided, pharmaceutical firms cannot be deemed to have violated their obligations under the CPA.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Brand-name pharmaceutical firms will usually issue warning letters to healthcare providers informing them of patent disputes with generic firms. To distinguish between the proper exercise and abuse of intellectual property rights, the Taiwan Fair Trade Commission (TFTC) has promulgated the Guidelines on Reviewing Cases Involving Enterprises Issuing Warning Letters for Infringement on Copyright, Trademark and Patent Rights (the TFTC Guidelines) to provide necessary steps that a company must carry out before sending out warning letters to its competitors’ (potential) trading counterparts. In accordance with the TFTC Guidelines, brand-name pharmaceutical firms have to notify relevant generic firms requesting cessation of the infringement prior to or simultaneously with the issuance of the warning letter, and have
to state the precise content and scope of the patent rights concerned and the concrete facts of infringement in the warning letter so that healthcare providers have sufficient knowledge of the rights that could possibly be or are being infringed.

Generally speaking, even if a brand-name pharmaceutical firm loses a patent infringement litigation, the court will not deem that there has been patent abuse since the patentee should have the right to defend its rights through litigation. An important judgment, however, rendered by the Intellectual Property Court (the IP Court) in 2011 provides a standard for determining patent abuse. As a brand-name pharmaceutical firm, Takeda Pharmaceutical Co Ltd (Takeda) ought to have known of the fundamental inaccuracy contained in the patent infringement assessment report, given its professional background; however, it still filed the report to obtain the preliminary injunction and to deceive the judge, who did not have a technical background. The IP Court therefore held that Takeda’s conduct amounted to patent abuse and unduly affected fair trade by preventing Genovate’s product from entering the market.

As set out in Section II.vi, the patent linkage mechanism comes into force in August 2019, and the TFTC and TFDA are authorised to jointly promulgate the guidelines to deal with the potential pay-for-delay issue; developments in this area should be closely monitored.

**ii Transactional issues**

International pharmaceutical firms intending to terminate distribution licences with their local agents are often faced with the difficulty of regaining possession of the marketing approval. Under the PAA, an application to transfer marketing approval must be jointly filed by the original marketing approval holder and the new holder, but the agent (the original holder) will usually not cooperate with the licensor (the prospective holder).

Under these circumstances, international pharmaceutical firms would usually consider filing parallel marketing approvals. However, because the TFDA holds a conservative view on issuing parallel marketing approvals, the review process may be prolonged indefinitely. Therefore, if possible, it would be advantageous for an international pharmaceutical firm to set up a subsidiary in Taiwan for the purpose of holding marketing approvals. When mergers and acquisitions involve a transfer of marketing approval, it is essential to draft clauses to protect the acquirer’s right to obtain marketing approval as planned.

**VIII CURRENT DEVELOPMENTS**

The most drastic change in the life sciences sector is the implementation of patent linkage in August 2019. The originator companies have proceeded with the patent registration in recent months. However, the patent linkage mechanism is only applicable to generic application filed after patent registration; thus, the current practice of patent right enforcement would not be drastically changed. Having said that, the impact of patent linkage on the industries in the future should still be closely monitored.

As to the new Medical Devices Act, the Cabinet and TFDA may offer a grace period for the enactment in order to mitigate various impacts on the industry. While it is the view of some scholars that the contents of the new law would not fundamentally or suddenly change current practices in the medical devices industry, the development shall be closely monitored.
I INTRODUCTION

The Food and Drug Administration (FDA), established by the Ministry of Public Health (MOPH), is the government administrative and regulatory body governing consumable products in Thailand. Consumable products include foods, drugs, psychotropic substances, narcotics, medical devices, volatile substances, cosmetics and hazardous substances available in the country. To ensure the safety, quality and efficacy of consumable products, the FDA controls, regulates and administers the manufacture, distribution, advertisement and other matters in relation to the consumable products through five main divisions: the Bureau of Foods, the Bureau of Drug Control, the Medical Device Control Division, the Cosmetic and Hazardous Substance Control Division and the Narcotics Control Division.

The FDA’s five main roles and responsibilities are pre-marketing control, post-marketing control, development of a surveillance programme for consumers’ safety, consumer education and provision of technical support and cooperation with other agencies.

By law, certain important issues are decided by committees, whose members – all experts in their respective fields – are appointed by the Minister of Public Health. Currently, there are seven committees, for: foods, drugs, psychotropic substances, narcotics, medical devices, cosmetics and hazardous substances. In addition, to support the development of drugs, foods and chemical substances, the Cabinet has appointed three additional committees, which are the National Drug Committee, the National Food Committee and the National Chemical Safety Committee.

---

1 Jessada Sawatdipong is a managing partner, Pranat Laohapairoj is a counsel, and Suphakorn Chueabunchai and Noraseth Ohpanayikool are associates at Chandler MHM Limited.
II  THE REGULATORY REGIME

i  Classification

The consumable products under the responsibility of the FDA are each governed by eight specific Acts: the Drug Act B.E. 2510 (1967); the Psychotropic Substance Act B.E. 2518 (1975); the Food Act B.E. 2522 (1979); the Narcotic Act B.E. 2522 (1979); the Emergency Decree on Prevention of Abuse of Volatile Substances B.E. 2533 (1990); the Hazardous Substance Act B.E. 2535 (1992); the Medical Device Act B.E. 2551 (2008); and the Cosmetic Act B.E. 2558 (2015), issued specifically for the enforcement, supervision and control over the use, manufacture, distribution, import, export, advertisement, suspension and/or revocation of required licence, imposition of penalties in case of violation of the act, and determination of governmental fees of the consumable products under the responsibility of the FDA. Each specific Act provides a definition and classification (if any) in its introductory section.

The decisions on classification and categorisation of consumable products into different types or subcategories are undertaken by each responsible Bureau or Department under the control of the FDA. For instance, the classification and categorisation of drugs is undertaken by authorised officers of the Bureau of Drug Control. If a product is considered as a ‘drug’ under the definition set forth under the Drug Act, it is then further sub-classified into different categories of drugs (e.g., modern drug or traditional drug).

ii  Non-clinical studies

Studies of animals are governed by the Animals for Scientific Purposes Act B.E. 2558 (2015). The implementation and enforcement of this Act is carried out by the Supervisory and Promotional Committee on the Use of Animals for Scientific Purposes. This Act aims to raise awareness about the ethics of, and impose certain ethical standards on, animal testing, as well as to ensure that the testing will be carried out under proper standards, implementation and monitoring.

The Supervisory and Promotional Committee on the Use of Animals for Scientific Purposes issued a Notification determining ethics for the use of animals for scientific purposes. The ethics set forth under such Notification clearly promote the value of life of animals, and clearly specify that the use of animals for scientific purposes can be undertaken only when the users have thoroughly considered that the experiment in question shall be for the maximum benefits for the development of humans’ and animals’ lives, the development of academic progress, or both. After the end of a scientific experiment, the animal subjects shall be put to death in a peaceful manner to promote animal welfare and humane treatment.

5  ibid.
7  Chapter 1 of the Notification of the Supervisory and Promotional Committee on the Use of Animals for Scientific Purposes Re: Determining Ethics for the Use of Animals for Scientific Purposes, announced on 29 February 2016.
iiii Clinical trials

Currently, there is no regulation outlining guidelines for conducting clinical trials. However, according to Section 9 of the National Health Act B.E. 2550 (2007), if a public health professional practitioner demands to use a service receiver as a subject of an experiment in their research, the written consent of the service receiver shall be granted in advance, and such consent can be revoked by the service receiver at any time.

In addition to the National Health Act, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice (ICH/GCP) which was translated by the FDA in 2000, is used as guidance for conducting clinical trials in Thailand. Although this guidance does not have legal enforceability in Thailand, the criteria for the independent ethics committee or institutional review board for considering clinical trials relating to drugs shall be in line with such guidance.8

iv Named-patient and compassionate use procedures

There are no regulations permitting the distribution of medicines or medical devices without prior issuance of a marketing authorisation or other permission for commercial distribution. Thailand does not have exceptions for the registration of named-patient and compassionate use.

v Pre-market clearance

Under the Drug Act, pre-market clearance covers three main steps: licensing, registration and advertising control.

The Drug Act requires that a person who wishes to sell, produce or import drugs into Thailand obtain a licence from the FDA. The government fee for each licence varies depending on the type of licence and product from between 300 and 10,000 baht.9 The approval process will take 10 to 30 days depending on type of licence and product. In addition, such person shall also register the drug formulas with the competent official.10 The registration procedure is to ensure efficacy, safety and quality of drugs sold in Thailand. Upon receipt of a drug registration certificate, the drug can be lawfully marketed. Note that the application shall be submitted to the FDA upon making a reservation for the submission via the FDA's website, phone contact or walk-in contact. However, the registration of certain drug formulas (i.e., pharmacopoeia with new chemical entities) shall be submitted using the eCTD (electronic Common Technical Dossier) only.11 The consideration process shall be approximately 220 working days and the applicant shall prepare a fee of 500 to 2,000 baht for the registration. In addition, for the registration of a new chemical entity or new biological entity, the applicant shall prepare a consideration fee for the total amount of 185,000 baht. The administrative date and product information as well as the documents specifying the quality of the drugs shall comply with guidelines set forth by the FDA, which follows the rules of the ASEAN

8 Clause 6.3 of the Notification of the Drug and Food Administration Re: Rule Method and Criteria for Approving the Ethics Committee for Considering the Clinic Trial Project in Relation to Drugs, dated 10 September 2018.
Harmonization on Pharmaceutical Registration. The newly approved drug formulas shall be monitored and subject to at least a one-year safety monitoring programme (SMP) depending on the risk level of the drug.\(^\text{12}\)

Moreover, advertisement of any drug shall be approved by the FDA before being disseminated. The process will take 15 to 30 days.

Under the Medical Device Act, medical devices are categorised into three subcategories, each with different prerequisite obligations.\(^\text{13}\) Generally speaking, though, any person wishing to import medical devices is required to either obtain a prior licence, notify the relevant authorities, or notify and register the medical device prior to the importation, as the case may be.\(^\text{14}\)

\section*{vi Regulatory incentives}

The Trade Secrets Act contains a provision governing the duties of the state to maintain trade secrets of drugs, which are in the form of testing results or information of drugs which is prepared, discovered or created by an applicant, and such applicant has requested the state agencies to maintain the information as trade secrets.\(^\text{15}\) However, under such provision, only one notification was issued specifically to protect pharmacopoeia information of modern drugs, which use new chemicals that have never been registered in Thailand.\(^\text{16}\) The notification provides guidelines on the safe keeping of the approved and registered pharmacopoeia information as trade secrets for five years from the approval date.\(^\text{17}\)

Thailand has no special provisions to encourage the development of products for rare diseases, diseases that are prevalent in developing countries, or paediatric use.

\section*{vii Post-approval controls}

The Post Marketing Bureau of Drug Control, under the control of the Drug Control Bureau, is mainly responsible for the control and supervision of post-approval controls. The Post Marketing Bureau of Drug Control has two main duties: to monitor manufacturing facilities and drug safety and quality after the applicant has obtained the required approval from the FDA. Manufacturing facilities that have been approved are inspected in accordance with the relevant Ministerial Regulations and Notifications. Facilities must be in compliance with the Pharmaceutical Inspection Co-operation Scheme (PIC/S).\(^\text{18}\) For the monitoring of product safety and quality, officers of the Post Marketing Bureau of Drug Control are vested with the authority provided by the relevant Act, Notifications or Ministerial Regulations to conduct certain actions to ensure that drugs approved for distribution are safe and comply with the

\begin{flushleft}
\footnotesize
\begin{itemize}
\item 13 Section 6 of the Medical Device Act B.E. 2551 (2008).
\item 14 ibid.
\item 15 Section 15 of the Trade Secrets Act B.E. 2545 (2002).
\item 16 Clause 3 of the Rule of the Ministry of Public Health Re; the Keeping of Pharmacopoeia Registration Information B.E. 2550 (2007).
\item 17 Clauses 18 and 19 of the Rule of Ministry of Public Health Re: the Keeping of Trade Secrets of Pharmacopoeia Registration Information B.E. 2550 (2007).
\end{itemize}
\end{flushleft}
required standards under the law. For instance, a Notification issued under the Medical Act allows the officers to order the manufacturer, importer or distributor to recall unsafe drugs, or provide such drugs to the officers for further inspection and disposal.19

For medical devices, the Medical Device Act provides obligations to be complied by manufacturers, distributors and importer.20 Post-market controls on medical devices involve surveillance of medical devices to prevent injury that may be the result of the use of the medical device, as well as to allow the users the opportunity to file a complaint in relation to the medical device for the FDA’s further inspection.21 In addition, a Notification was issued to provide procedures for the submission of a device defect report or adverse event report as well as the ensuing field safety corrective report.

viii Manufacturing controls
As mentioned in subsection v, the Drug Act requires that any person who wishes to manufacture drugs in Thailand obtain a licence from the FDA.22 In this regard, the applicant shall provide the required evidence (i.e., the floor plan of the manufacturing facility, which is approved by the FDA, evidence of ownership over the assets and properties, affidavit if the applicant is a juristic person, and other required evidence, such as factory licence or building construction permit if the facilities fall within the size and manufacturing power as required under the relevant laws).23 After obtaining a licence for the manufacture of modern drugs, the manufacturer must have at least two pharmacists to manage the operations and to monitor drugs at the premises during business hours.24

Regarding medical devices, any person wishing to manufacture any category of medical device in Thailand must have its place of business operation registered with the FDA25 and also obtain a manufacturing licence.26

ix Advertising and promotion
The Consumer Protection Act generally governs the content of advertisements as well as labelling requirements. However, the Drug Act and Medical Device Act specifically contain chapters governing the advertisement of drugs and medical devices respectively.27 Both Acts set forth two fundamental requirements for advertising drugs and medical devices.

20 Section 41 of the Medical Device Act B.E. 2551 (2008).
21 ibid.
26 Section 17 of the Medical Device Act B.E. 2551 (2008).
First, a party must obtain prior approval for the content of the advertisement before such advertisement can be disseminated.\textsuperscript{28} In addition, there is also an obligation to obtain an advertising licence for the purposes of advertisements that contain information related to medical devices.\textsuperscript{29}

Second, both Acts provide guidelines set forth by the FDA, whereby the content of an advertisement shall not contain information that is false, exaggerated, misleading, or different from the details approved by the FDA.\textsuperscript{30}

In addition to the Drug Act and the Medical Device Act, other rules and Ministerial Regulations issued under both Acts provide additional requirements as to the advertisement of drugs and medical devices. For instance, the FDA issued a rule governing presentation of drug names, drug properties, and recommendations for usage and warnings.\textsuperscript{31} The FDA also issued a Notification that provides details regarding prohibited content and other requirements in the advertisement of medical devices, and rules and guidelines for the references to academic studies or research to support information in advertisements related to medical devices.\textsuperscript{32}

\section*{Distributors and wholesalers}

The sale of modern drugs is prohibited unless a licence has been granted by the FDA.\textsuperscript{33} The Notification Re: Permission and Issuance of a License to Sell Modern Drugs B.E. 2556 (2013) prescribes the application form and other obligations that an applicant must comply with in order to receive a distributing licence or a wholesaler licence. Generally, depending on the type of licence, the facilities for distribution or storage of drugs must be in compliance with the Notification. A distributor or wholesaler is also required to produce purchase reports, as well as to generate sales reports for submission to the FDA as required. There are also other obligations that must be complied with (i.e., the distributor shall have a pharmacist present during business hours to distribute drugs and monitor activities).

Distribution of medical devices is prohibited unless a licence for the distribution of such medical device has been granted.\textsuperscript{34} The Notification Re: the Permission and the Issuance of Medical Device Distribution Licences B.E. 2555 (2012) was issued to govern the issuance of licences and imposition of obligations on the applicant.

\begin{itemize}
\item[\textsuperscript{28}] Section 88 \textit{bis} of the Drug Act B.E. 2510 (1967), and Section 57 of the Medical Device Act, B.E. 2551 (2008).
\item[\textsuperscript{29}] Section 57 of the Medical Device Act B.E. 2551 (2008).
\item[\textsuperscript{30}] Section 88 of the Drug Act B.E. 2510 (1967), and Section 59 of the Medical Device Act B.E. 2551 (2008).
\item[\textsuperscript{31}] Rules of the Food and Drug Administration Re: Rules on Advertisement of Drugs B.E. 2545 (2002).
\item[\textsuperscript{32}] Notification of the Food and Drug Administration Re: Rules Procedures and Conditions on Advertisement of Medical Device B.E. 2553 (2010).
\item[\textsuperscript{33}] Section 12 of the Drug Act B.E. 2510 (1967).
\item[\textsuperscript{34}] Section 6 and Section 24 Paragraph 2 of the Medical Device Act B.E. 2551 (2008).
\end{itemize}
xi  **Classification of products**

Drugs are categorised as modern, traditional, dangerous, specially controlled, external-use, site-specific, household, packaged, and herbal. The MOPH, with advice from the Drug Committee, has the authority to classify drugs into one of these categories by making an announcement in the Royal Gazette.

The Medical Device Act provides classification of medical devices into different categories each with different restrictions and requirements. The MOPH, with advice from the Medical Device Committee, has the authority to classify medical devices based on risk and safety characteristics.

xii  **Imports and exports**

An import licence, granted by the FDA, is required to import drugs into Thailand.

Any person wishing to import medical devices is required to register a place of business operations with the FDA.

For exportation, both the Drug Act and the Medical Device Act do not impose an obligation on an exporter to obtain a licence for the exportation of drugs or medical devices. However, in practice, the Thai Customs Department will request an exporter to provide an export certificate. For example, an export of medical device certificate, issued by the FDA, is evidence specifying that the exporter (or the manufacturer) is the owner of the products. Such certificate also indicates the market status, and shows that such person has already obtained and complied with the requirements of the law in relation to the medical device.

xiii  **Controlled substances**

The Narcotics Control Division has control over import, export, commercial sale and possession of narcotics and psychotropic substances. It is also responsible for the approval, revocation and suspension of licences for import, export, commercial sale, and possession of narcotics and psychotropic substances. For instance, the Narcotics Act provides that no person shall import, export, commence commercial sale of or possess dangerous narcotics such as heroin.

xiv  **Enforcement**

One of the main responsibilities of the FDA involves surveillance of products in order to maintain product quality and standards, and to prevent violation under the Drug Act and the Medical Device Act. In this regard, FDA officers will, from time to time, initiate random spot checks to ensure that the products (i.e., drugs and medical devices) remain in compliance.
with the law. If a spot check reveals any failure to comply with the law, or in the case of a complaint made to the FDA, the enforcement phase will commence, which could lead to penalties for the violation as provided in the aforementioned Acts.

III PRICING AND REIMBURSEMENT

In Thailand, procurement by government agencies, including public hospitals, is subject to the criteria and requirements under the Public Procurement and Management of Supplies Act, B.E. 2560 (2017). In this regard, drug prices for public hospitals are prescribed by the National Drug System Development Committee. The latest list was announced in the Government Gazette on 22 April 2019.

Regarding reimbursement, Thailand has three types of the public health coverage: the Civil Service Welfare Systems for central and local civil officers and their family, Social Security for eligible employees in the private sector, and the Universal Coverage Scheme (UC) for all other Thai nationals.41

The benefits packages, payment systems and funding for each programme are different from one another. The Civil Service Welfare Systems is funded and regulated by the Comptroller General’s Department of the Ministry of Finance or the Ministry of Interior (for local officers), Social Security is funded by the Social Security Office, while the UC is funded by the National Health Security Office under the National Health Security Act, BE 2545 (2002).

It is notable that all three programmes universally use the National List of Essential Medicines (NLEM) as a guideline for reimbursable drugs. The NLEM is a list of reimbursable drugs announced by the Drug System Development Committee, including the conditions (or lack thereof) for medical professionals to prescribe reimbursable drugs under the coverage. The drugs outside of the NLEM can also be reimbursed; however, only with a prescription by medical professionals in charge as necessary to cure the patient of a sickness.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Under the Drug Act, in the case that a drug licence is not granted or the authority does not renew an existing licence, an applicant has the right to appeal that decision to the Ministry of Public Health within 30 days from receipt of notice that such licence will not be issued or renewed. If an applicant does not appeal that decision within 30 days, the licence will be revoked.

Since there is no specific period for consideration of an appeal under the Drug Act, consideration for such an appeal with be as specified in the Administrative Procedure Act, B.E. 2539, meaning the consideration process shall be completed within 30 days from the date of receipt of the appeal.

For medical devices, if the authority does not issue an establishment registration certificate, licence or specifications declaration receipt, the applicant has the right to appeal the authority’s order in writing to the Minister of Public Health within 30 days from the date of receipt of notice of the non-issuance of establishment registration certificate, licence or specifications declaration receipt, as the case may be.

---

41 ‘10 Things in Health Security’ by National Health Security Office.
When considering an appeal under the Medical Device Act, the Minister of Public Health shall complete the appeal process within 120 days from the date of receipt of the appeal. If, due to necessity, consideration cannot be completed within such time period, written notice shall be sent to the appellant before the expiry of the time period. The period for consideration of an appeal may be extended for not more than 120 days from the expiry of the initial 120 day consideration time period.

Pursuant to both Acts, the judgment of the Minister of Public Health is considered to be final. However, if the appellant is not satisfied with the judgment of the Minister of Public Health, the appellant has right to file a case with the Administrative Court.

V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

Thai law regulates the purchase of medicines and medical devices by the government. For the most part, the organisations that generally make decisions concerning utilisation or reimbursement of medicines and medical devices in Thailand are the Government Pharmaceutical Organization (GPO), the Thai Red Cross Society and public hospitals.

These organisations need to comply with a set of rules regarding the procurement of such products. 42 Thus, there should be no financial relationships between product suppliers or prescribers.

Generally, procurement of products can be done by three methods: the general solicitation method, the selection method and the specific method. The general solicitation method can be done through e-market, e-bidding or examination of price.43 The e-market method is used when procurement of products will cost more than 500,000 baht and such products do not have complex or specific characteristic and the details and specifications are provided in the e-catalogue system of the Comptroller General’s Department.44 The e-bidding method applies to the procurement of products costing more than 500,000 baht and the specifications are not provided in the e-catalogue system in accordance with the methods specified by the Comptroller General’s Department.45 The examination of price method must be done in the case of procurement of products costing more than 500,000 baht and there is no internet connection within the area of the relevant government organisations.46 Under the selection method, a government agency will solicit at least three business operators who possess specific qualifications determined by the relevant agency to submit a proposal, unless there are fewer than three business operators who possess such qualifications.47 Under the specific method, a government agency may solicit a single business operator who possesses specific qualifications determined by the relevant agency to submit a proposal, or to bargain prices where the cost does not exceed 500,000 baht for a single procurement.48

---

44 Article 30 of the Ministry Regulation re: Public Procurement and Management of Supplies B.E. 2560 (2017).
47 Section 55(2) of the Public Procurement and Management of Supplies Act B.E. 2560 (2017).
48 Section 55(3) of the Public Procurement and Management of Supplies Act, B.E. 2560 (2017).
On March 2019, the Committee that analysed issues in regard to public procurement and management of supplies issued guidelines for the purchase of medicines and medical devices for relevant government agencies.\[49\] Under such guidelines, when a government agency intends to purchase medicines or medical supplies under the Thailand National List of Essential Medicines (NLEM) that the GPO or the Thai Red Cross Society produces and distributes, that government agency is required to procure such medicines and medical supplies using the specific method. However, the government agency may purchase such products from any other suppliers when the GPO or the Thai Red Cross Society is not able to produce and distribute the products within the specified period according to the annual plan submitted by the relevant government agency.\[50\]

With regard to the purchase of medicines or medical supplies by the private sector, the authorised private sector entity may purchase such products certified by the FDA from any suppliers without restrictions.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

As there is no specific compensation system for persons injured by medicines or medical devices in Thailand, the general principles of law regarding tort and product liability apply.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

There is no specific rule or law on the settlement of patent disputes between an originator and generic manufacturers provided under intellectual property laws. Also, there is no specific provision targeting drug or medical device markets under the current antitrust law.

ii Transactional issues

There is no specific law governing licensing or strategic collaborations, joint ventures or mergers and acquisitions in relation to medicines and medical devices.

VIII CURRENT DEVELOPMENTS

i Amendment to the Drug Act

Effective as of 16 August 2019, the key amendments to the Drug Act (No. 6) are as follows:

\[a\] Involvement of experts, either as external organisations, government agencies or private entities both in Thailand or overseas, who meet the requirements set forth by the MOPH, to evaluate academic documents, conduct product analysis, as well as evaluate place of business and operation on behalf of the FDA, in order to facilitate and accelerate the drug approval process.

---

\[49\] The most urgent letter of the committee on analysing the problems on Public Procurement and Management of Supplies the Comptroller General’s Department No. GorKor. (GorWorJor) 0405.2/Wor 119 dated 12 March 2019.

\[50\] Clause 3.1.1 of the Most Urgent Letter of the Committee on analysing the problems on Public Procurement and Management of Supplies the Comptroller General’s Department No. GorKor. (GorWorJor) 0405.2/Wor 119 dated 12 March 2019.
b Payment fee collected from the expert's enrolment shall be kept by the FDA and used for the FDA's operation. This includes development of the FDA's organisation and development of the drug approval process.

c The FDA may announce usage or allow usage of foreign and international standards for manufacture, distribution or import of drugs, provided that the international standards adopted shall not be below the standards set forth by the FDA.

d Amendment to the validity period of a drug registration licence is seven years from the issue date. In this regard, drug registrations issued before the amendments to the Act became effective will remain valid for a period of between five and nine years depending on the year the drug registration licences were issued.

e A revision of the rate of fees in the attachment of the Drug Act was made, whereby the rates of the fees for licences, substitute licences and substitute certificates issued under the Drug Act have been increased.

**Draft Ministerial Regulations issued under the amended Drug Act**

a Draft Ministerial Regulation issued under the amended Drug Act (amendment to the Notification Re: Rules Conditions and Procedures for the Manufacture of Modern Drugs B.E. 2546). The key amendments are as follows:

- update to the process and evidence required for the application for a licence to manufacture modern drugs;
- establishment of additional obligations for an authorised person to manufacture modern drugs (i.e., provide an annual report regarding the manufacturing of modern drugs);
- sets requirements regarding the renewal of a licence to manufacture modern drugs; and
- allows authorised persons to increase their place of business for the storage of drugs.

b Draft Ministerial Regulation issued under the amended Drug Act (amendment to the Notification No. 16 issued under Drug Act B.E. 2510). The key amendments are as follows:

- provides additional requirements to be followed by an authorised person (i.e., to comply with rules and regulations on the keeping of drugs and the distribution of drugs);
- allows the Ministry of Public Health to determine characteristics and the amount of equipment that is required under Notification No. 16, as well as the rules in relation to the place for drug storage; and
- provides additional requirements for the renewal of a licence to import modern drugs into the Kingdom.

**ii Amendment to the Medical Device Act**

Effective as of 27 April 2019, the amendments to the Medical Device Act (No. 2) contain key amendments as follows:

a Revision of the definition of ‘medical device’, as well as to further define the terms ‘supporting equipment’ and ‘informant’ in order to comply with the ASEAN Agreement on Medical Device Directive.

b Determination and grouping of medical devices or a group of medical devices into different categories based on the level of risk of harm to health, body, or life of humans.
or animals or impact public health in general. In this regard, different obligations are imposed on different groups of medical devices (i.e., prior approval, and prior notification obligations). This categorisation is made in order to impose further obligations to any person who wishes to manufacture or import medical devices that may cause harm to health, body, or life of human or animals or impact public health in general.

c Adjustment of control measures for the import and export of medical devices. The Ministry of Public Health is authorised under the amended Act to determine a place of examination of a medical device to be imported in or exported out of the Kingdom.

d Involvement of experts – either external organisations, government agencies or private entities both in Thailand or overseas, who meet the requirements set forth by the Ministry of Public Health – to evaluate academic documents, conduct product analysis, and evaluate place of business and operations and approvals of licences and/or consideration of an application for a licence, notification letters, notification-approval letters, and other matters in relation to medical device on behalf of the FDA, in order to facilitate and accelerate the medical device approval process.

e Determination of the validity period and renewal period of the notification-approval letter. In this regard, the notification-approval letter shall be valid for a period of five years from the issue date. In addition, the amendment set forth a rule preventing any person from manufacturing, distributing, importing or exporting certain medical devices until such person has obtained an approval letter.

f Revision to the rate of fees in the attachment of the Medical Device Act was made. The revision was made to set a fee rate for the application to receive an approval letter for the manufacture or import of medical devices, and a fee for the registration of the place of import of medical devices.

**Draft Ministerial Regulations issued under the amended Medical Device Act**

a Draft Ministerial Regulation Re: Application and Issuance of Medical Device Licence. The key provisions are as follows:
- determination of the list of evidence an establishment registrant who wishes to manufacture or import medical devices must provide;
- licences for the manufacture or import of medical devices shall be renewed using the form provided by the FDA; and
- the application form, licence form, renewal form and amendment form shall be as provided by the FDA.

b Draft Ministerial Regulation Re: Notification and Issuance of Notification-Approval Letter. The Notification will provide a list of evidence required to be submitted to the FDA for any establishment registrant who wishes to manufacture a certain group of medical devices or medical devices that require a prior notification and prior receipt of an approval letter.

c Draft Ministerial Regulation Re: Notification of Details and Issuance of Approval of Explanation of Medical Device Letter. The Notification will provide the list of evidence required to be submitted to the FDA for any establishment registrant who wishes to manufacture or import a certain group of medical devices or medical devices that require prior notification.

d Draft Ministerial Regulation Re: Determination of Fees in Relation to Medical Devices. This Notification will provide a newly updated list of fees in relation to medical devices.
Chapter 31

UNITED ARAB EMIRATES

Melissa Murray and Surabhi Singhi

I INTRODUCTION

The UAE biotechnology and pharmaceutical industries are subject to stringent regulation – primarily by rules and regulations at the federal level and, to a lesser degree, at the individual Emirate level. Abu Dhabi and Dubai have the most developed rules and regulations of the seven emirates with respect to biotechnology and pharmaceutical matters, and the other Emirates usually follow their respective cues as regards policy and legislation.

As the United Arab Emirates (UAE) has now evolved as a member of the globalised economy, it has endeavoured to make itself a global destination for healthcare. Accordingly, much of its new legislation reflects the influence – and direction – of jurisdictional trends of international market players in the pharmaceutical and medical industries. There has been a growth phase in the healthcare sector in the past few years, which has helped the UAE move towards becoming a hub for medical tourism. The nation’s strategy also aims to guide and support the industry by building sustainable public-private partnership models in the healthcare sector.

II THE REGULATORY REGIME

To be supplied in the UAE, therapeutic goods must be vetted by the Registration and Control Department (RCD) of the Ministry of Health and Prevention (MOHP). The importer, exporter, manufacturer or seller of medicine or medical devices must satisfy the requirements of the RCD before they can be disseminated for public consumption within the UAE.

i Classification

The RCD regulates medication and medical devices (which includes a delineation for devices that include a pharmaceutical component). The RCD further oversees the examination and registration of dietary supplements (including vitamins and herbal extracts), medicated cosmetics, antiseptics and disinfectants, and all other products that contain a pharmaceutical component or medical claim that cannot otherwise be appropriately classified as a medication. Foodstuffs and general consumer products are not regulated by the RCD provided they assert no medical or therapeutic value or claims.

The RCD and the MOHP have the unilateral right to pull or ban any products that they may later deem to be unsafe for public consumption based on studies or recent cases within the UAE.

---

1 Melissa Murray is a partner and Surabhi Singhi is a senior associate at Bird & Bird (MEA) LLP.
ii Non-clinical studies

Use of animals

UAE Federal Law No. 16 of 2007 (on animal protection) states, at Article 12, that the use of animals for scientific purposes must be approved by the applicable governmental authority. Further, animals are protected from neglect, abuse and cruel treatment by applicable UAE law.

The law specifically states ‘scientific purposes’, which seems to implicate medical or pharmaceutical testing and does not directly address or contemplate the use of animals for the testing of (non-medicated) cosmetics or household products. The governmental approval process is always at the discretion of the concerned director, who may reject any request deemed excessive, unnecessary or generally harmful.

Embryos

UAE Federal Law No. 11 of 2008 (on the licensing of fertilisation centres) contained several provisions that allowed for the freezing of embryos, which were overturned a few years later by a directive of the UAE government and, as a result, hospitals and clinics were ordered to destroy or otherwise dispose of any frozen embryos in their custody. Now, only unfertilised eggs may be stored at appropriately accredited and licensed facilities.

The UAE Federal National Council approved the draft regulations relating to embryo freezing, with a particular focus on keeping pace with the other regions of the world that allow for this protocol.

IVF regulation

IVF clinics are regulated pursuant to UAE Federal Law No. 11 of 2008 (on the licensing of fertilisation centres). Governmental approvals are contingent upon satisfaction of numerous requirements, including facilities, equipment and staffing with appropriate professional personnel. There are numerous IVF clinics throughout the UAE.

Stem cells

There are no specific regulations (and, therefore, no restrictions) with respect to stem cell therapies in the United Arab Emirates. In 2010, the MOHP licensed its first stem cell practitioner, a specialist in spinal cord and brain injuries, and a facility to perform stem cell therapies within the UAE. There have been reports of autologous stem cell treatment on two patients with degenerative diseases. However, general stem cell transplants have been permitted on a restricted, alternative basis, although the storage of stem cells has been permitted. The Dubai Health Authority (DHA) approved the first stem cell and regenerative medical centre in Dubai in 2018.

The Department of Health – Abu Dhabi (DoH), the regulator of the healthcare sector in Abu Dhabi, alongside the Abu Dhabi Health Services Company and the United Arab Emirates University, signed a memorandum of understanding (MoU) with a Swedish company, Takura in September 2019, with the aim of bringing the entities together to develop and implement several revolutionary cell therapy treatments in the hope of aiding the treatment of several chronic diseases including cancer, diabetes and dementia.

The UAE has further announced the intent to inaugurate a new cancer treatment and research centre by 2020, which will also have a state-of-the-art bone marrow transplant division.
Organ transplants

The UAE federal law permitting organ transplantation became effective in March 2017. The law allows the transplant of tissue or organs from either live or deceased patients for the care of patients in need of the same. However, the law prohibits the sale of human tissue or organs, the funding of transplantation if this results from such sale, and the unlicensed advertising of transplantation services.

The DHA announced in November 2018 that a local committee will be formed to regulate the transport and transplantation of organs and tissues in Dubai.

Clinical trials

All clinical and research trials within the UAE require human subject consent, as well as the written approval of the MOHP, or other concerned governmental authorities, after a review of an application for such trials.

The Guidance of the Drug Control Department (DCD) of the MOHP states that the sponsor of a specific clinical trial or experimental protocol is required to secure all the necessary agreements between the concerned parties.

Designated clinical trial centres should establish independent institutional ethics committees (IECs), which are then tasked with reviewing the relevant proposals of the sponsors. These IECs will review the proposals for clinical trials and experimental protocols, taking into consideration the soundness of the objectives and the medical protocols and practices.

The IECs will render recommendations as whether or not to commence a clinical trial based upon the information provided. The findings and recommendation will then be provided to the applicable governmental authorities for their final, official approvals.

In the respective proposal, the sponsor is to set forth the compensation (if any) for the investigators and the subjects of a clinical trial in its proposal to the IEC. Furthermore, the IEC is to review and approve the proposal of the sponsor with respect to insurance coverage, indemnities or other forms of compensation in case of subject injury.

The investigator may also be the sponsor of a clinical trial, provided it independently plans, conducts and assumes full responsibility for the clinical trial.

All amendments to protocols and all unexpected or serious adverse reactions to drugs administered during the clinical trial are to be reported immediately to the Ethics Committee.

While the clear letter of the law states that no unregistered drugs may be used within the UAE, there are certain circumstances where the MOHP or other governmental departments have approved the use of unregistered drugs (discussed in further detail in subsection iv, below).

The Guidance further states that all clinical trials should follow the Helsinki Declaration to safeguard the rights of individuals subject to a clinical trial.

Named-patient and compassionate use procedures

In exceptional circumstances, governmental authorities in the UAE have permitted the importation and use of unregistered medicine into the country. The MOHP has recently put forth an approval process that allows such importation, under any of the following circumstances:

- to extend the life of a patient in an emergency situation;
- certain heart or cancer treatment medication that is not available in the UAE and cannot be dispensed in hospitals;
c other medication that has not yet been regulated by the MOHP, but which the MOHP has determined may be of benefit in emergency or other circumstances;
d medications that have been previously registered but have been cancelled by the local agent as a result of lack of market demand; or
e unregistered narcotic or psychotropic drugs for use in specialised hospitals with specific protocols.

Because of the nature of the UAE’s regulated market, applications to obtain or use unregistered medication or devices must be tailored for specific patients, trials or protocols, and exigent circumstances. As a result, the quantity of unregistered medication should be limited to a specific hospital or clinic capacity, and for existing or anticipated patients per the application. The MOHP has the discretion to reject, approve, or approve with modifications any application for unregistered medication.

Furthermore, the application to the MOHP must include the following documents or information: (1) a signed undertaking letter from the concerned hospital or clinic that it shall bear all liability for the use of the unregistered medicine; (2) a certification that the medicine is registered in the country of origin or an approved jurisdiction, such as the United States, the European Union or the Gulf Cooperation Council; and (3) a registration certificate from the manufacturer listing the chemical components of the medication.

v Pre-market clearance
To be supplied in the UAE, medication, pharmaceuticals and medical devices must be vetted and cleared by the MOHP. A foreign manufacturer of medication, pharmaceuticals and medical devices must appoint a local representative and a local agent (which may be the same person) for the sale and distribution of these products within the UAE.

Unless there are exigent circumstances (as described in subsection iv, above), there are virtually no exceptions to expedite or accelerate the approvals process. The approval of a new medication, for example, would take, on average, no less than two years from submission of an application to the relevant authorities.

Medicines and biologicals
The UAE is a signatory to international conventions on narcotics and psychotropic substances. When a medication is approved and registered for use in the UAE, the method of dispensation is also agreed. This is based on the level of control in the source country, as well as the level of control of the active ingredient pursuant to UAE law.

Pricing for medications are fixed by UAE law, and the MOHP provides an updated pricing list for these periodically. Attempts by manufacturers and agents to circumvent the fixed pricing may be subject to fines, bans or other legal recourse by the UAE government.

Devices
Medical devices must also be approved by the MOHP before they can be sold or distributed in the UAE. The law defines a medical device as any such device that is used to diagnose, monitor or treat an illness. UAE laws and regulations make a distinction between devices that provide therapeutic benefit through purely mechanical or non-pharmaceutical means and those devices that have a pharmaceutical component (i.e., devices that dispense a drug therapy). The latter may be subject to pricing controls similar to those of medication.
Currently the UAE is largely dependent on import of sophisticated medical equipment. However, recently, there has been development in the nascent medical products industry. In the near future, the UAE may play a leading role in 3D printing in the medical products sector, which could involve developing 3D-printed teeth, bones, artificial organs, medical and surgical devices, and hearing aids.

vi Regulatory incentives
Patents are registerable for pharmaceuticals for a period of up to 20 years, with no extension period allowed.

However, unlike other jurisdictions in the region, the UAE recognises the patentability of second-use medical inventions under the law, and has registered a number of these.

There are no remarkable regulatory incentives within the UAE with respect to the marketing, developing or production of pharmaceuticals at this time.

vii Post-approval controls
Under UAE law, the foreign manufacturer of a drug must appoint a local authorised representative within the UAE. The representative may also be the distributor of the medication within the UAE. The representative will be tasked with handling all complaints or recalls relating to the medication, as well as fulfilling all requirements with respect to placing the product in the market. The post-market obligations include the obligation to maintain distribution records, complaint-handling procedures and incident-reporting processes, and implement processes to execute investigations and recalls in respect of defective or potentially defective products promptly.

The RCD or MOHP have the discretion to recall any medication based on any information or incident reports directed to them.

viii Manufacturing controls
The relevant governmental authorities must approve a pharmaceutical manufacturing plant within the UAE. A foreign shareholder cannot own more than 49 per cent of the shares of a pharmaceutical manufacturing company within the UAE.

The proposed facility must be approved as far as its layout, infrastructure, manufacturing capacities, and its storage and handling of chemicals. The government reserves the right for site inspections and for assessing penalties upon non-compliant facilities.

The UAE Federal Law No. 19 of 2018 (the FDI Law) introduces the framework under which the UAE Cabinet will exercise its powers in respect of permitting increased levels of foreign ownership in companies operating in certain sectors of the economy but specifically excludes medical retail (including pharmacies) and blood banks, quarantines, and venom and poison banks. On 1 July, 2019, His Highness Sheikh Mohammed bin Rashid Al Maktoum, Vice President and Prime Minister of the UAE and Ruler of Dubai, announced that ‘a resolution allowing 100 per cent foreign ownership in UAE’s 122 economic sectors was adopted, giving foreigners 100 per cent ownership of their investment’. There is a list of 122 activities, purportedly the ‘positive list’, available in the public domain. The purported positive list also highlights various criteria, such as a minimum capital requirement, use of advanced and latest technology and participating in the Tawteen Partners Club at the Ministry of Human Resources & Emiratisation to be complied with to allow a maximum of 100 per cent foreign ownership in mainland UAE. We mention here that ‘medical and dental practice activities’, ‘hospital activities’ and ‘other human health activities’ are some
of the activities in the purported positive list which should benefit from the new FDI Law. Please note, however, that no formal resolution has been published in the Official Gazette yet in this regard and therefore there may be some changes to the final list. While the process to obtain approval for establishing 100 per cent ownership has not yet been formalised, we are aware that the governmental authorities are considering ad hoc applications from large multinational groups for processing approvals for an increased level of foreign ownership.

ix Advertising and promotion

Healthcare and medical advertising are strictly regulated by governmental authorities and there are stringent guidelines to ensure transparency and honesty, and to stamp out misleading marketing practices. All forms of medical and pharmaceutical advertising require governmental pre-approval before publication. Comparative advertising is usually not permitted and, given other considerations (mainly relating to potential criminal liability for libel or harm to business reputation), most companies steer clear of any advertising pitting themselves against their competitors. Even advertisements on discount websites for businesses such as laser hair removal or dermal fillers require Ministry of Health approval and carry a requisite warning to customers relating to efficacy or potential risks of such procedures.

Additionally, advertisements must not violate public morals, decency, UAE customs or Islamic values and traditions. Medical advertising cannot be false, deceptive or misrepresent the quality or type of medical treatment or product presented. Further, it cannot mislead potential patients regarding the efficacy of certain medication treatment, therapy or protocol, or that the aforementioned will have no potential side effects.

Advertising for telemedicine companies should clearly state what services they are and not authorised or licensed to provide. Advertisements geared towards children are prohibited.

Incentives to healthcare workers for the sale of specified medications, procedures or devices are not permitted by any medical or healthcare advertisement.

x Distributors and wholesalers

The UAE has a number of provisions within its Agency Law, Civil Code and Commercial Code that provide a number of protections to local agents and distributors. Some pharmaceuticals or medical equipment may, in certain circumstances, require a registered ‘commercial agent’ be the importer on record. Such registered commercial agents enjoy wide protections under the UAE’s Agency Law, including exclusivity within the UAE market.

A registered agency under the Agency Law makes it difficult for a foreign principal to terminate. Often, a registered agency will only agree to deregister a registered agency (and, hence, allow the principal to distribute products through other agents or resellers) upon an agreed and substantial financial settlement.

xi Classification of products

In addition to the basic definition of ‘prescription’ medication, the MOHP recognises the following three classifications: narcotics, CDA and CDB.

Narcotics are defined based upon their active ingredients and composition. Additionally, CDA medications are defined by their active ingredients, as well as their potential for abuse or diversion for illegal use. CDB medications are defined as those that are used for psychiatric conditions, avoid narcotic controls and restrictions owing to their chemical formulation, or require stricter control than simply those medications that are designated as ‘prescription’.
Medical devices are classified in order of risk:

- **Class I** medical devices are considered to be of low risk to patients. A declaration of conformity is usually accepted from the manufacturer.
- **Class II** medical devices are considered of medium risk because of the invasive nature of the device; however, these devices are only applied to the body's natural orifices.
- **Class III** medical devices are considered to be of medium risk to patients and are partially or wholly implantable within the human body, and may modify the biological or chemical composition of body fluids.
- **Class IV** medical devices are considered to be of high risk to patients. They involve clinical trials and product certification. These devices affect the functioning of vital organs or life-support systems. These devices are usually life-sustaining, life-supporting and invasive.

That being said, the vast majority of medication or medical devices that fall outside the categories of stricter scrutiny are available for sale and distribution over the counter.

---

**xii Imports and exports**

To import medicine or medical devices into the UAE, a UAE company must obtain a medical warehouse licence or a UAE national must obtain a medical importer licence with the relevant government authorities. The law was amended to permit companies with mixed UAE and foreign shareholding to obtain a medical import licence.

Re-exportation of imported goods can occur within six months of importation – provided the goods are in unused and otherwise exportable condition and the applicable documentation relating to the goods is current.

The UAE’s Boycott of Israel Law prevents the direct importation of any goods from Israel (referred to as the ‘primary boycott’). The law also prohibits the importation of goods that may have even relatively minor components manufactured in Israel (‘the secondary boycott’). Currently, however, the UAE usually enforces the primary boycott alone.

---

**xiii Controlled substances**

Controlled substances are heavily regulated and monitored in the UAE. In most circumstances, narcotics or psychotropic substances can only be administered within the confines of a hospital or clinic, or dispensed exclusively from a government hospital upon submission of a valid prescription.

The MOHP has a list of controlled substances that cannot be brought into the UAE by people visiting or entering the country, regardless of whether the person has a valid prescription for the medication in the country of origin. Following changes in October 2018, the MOHP announced that all tourists and residents entering the UAE will be required to complete an electronic form to obtain prior online approval to carry narcotic, psychotropic and controlled medication into the UAE for personal use. A Ministerial Decision of 2019 has laid out that a unified electronic platform shall be established for the prescription and dispensing of narcotics and controlled and semi-controlled medications, in coordination between the Ministry of Interior, the MOHP and the concerned health departments and entities.
Enforcement

The UAE governmental authorities have broad powers of regulation and sanction for the violation of any laws or regulations relating to medication and medical devices. These include: warning, fining, banning of distribution of certain products, blacklisting of manufacturers or medication, suspension or deregistration of local representatives or agents, and closing operations of pharmaceutical plants. The fines may be substantial, and imprisonment may be warranted in cases of intentional criminal activity.

The UAE has recently enacted the New Health Data Protection Law (UAE Federal Law No. 2 of 2019), with the objective of addressing the protection of health data originating in the UAE. This law derives principles from the European Union's General Data Protection Regulation, including purpose limitation, accuracy, integrity and confidentiality. Any health-related information and data that originates in the UAE may not be stored, processed, generated or transferred outside the UAE. This has a direct effect on foreign companies that provide cloud-based services, in addition to local companies that use these services. With regard to enforcement, healthcare providers that violate certain provisions of the New Health Data Protection Law may face fines ranging from 1,000 to 1 million dirhams, effective from May 2019. Although the legislation has the clear intent of enforcement, it is not clear whether the MOHP and relevant authorities will take immediate action. It is appropriate to assume that a grace period will be given to companies to overcome technological hurdles in order to comply with the law.

III PRICING AND REIMBURSEMENT

Pricing of medication is fixed and regulated by applicable laws, with specified margin limits. Hospitals and clinics must sell medication to the public at the prices specified by the MOHP, and cannot give discounts on medication outside the margins fixed by law. Bonus schemes between manufacturers and distributors are strongly discouraged (if not prohibited by law).

Since 2010, and under the direction of Abu Dhabi, the UAE has been moving towards a diagnostic rate group (DRG) system for insurance billing and reimbursement. One of the intended purposes of switching to the DRG system is to lower medical costs in the UAE (where the vast majority of medication is imported). The Emirate of Dubai announced a substantial rollout of DRG for 2018, with the projection that all healthcare facilities will be DRG-compliant by 2020.

The DRG system requires new billing systems within hospitals and clinics, and the requisite staff training for documenting and coding applicable medical services. One potential benefit of the installation and implementation of the DRG system UAE-wide is providing transparency and avoiding excess payments or overbilling.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The UAE Medical Liability Law (UAE Federal Law No. 4 of 2016 read together with the implementing regulation of 2019) gives patients the right to report any form of medical malpractice or medical negligence by their service providers or by pharmaceutical companies directly to the MOHP, or its applicable departments. The complaints are to be referred to medical liability commissions, formed by the MOHP, or the chairman of the local health authority.
The relevant commission will review the complaint with all the applicable documentation, and make an adjudication on the existence of malpractice and, if applicable, the causes and results of that malpractice.

The decisions made by the commissions are appealable by the patients, doctors or providers within 30 days to a higher liability commission, formed by the UAE Cabinet. After review of the file, the decisions of such higher commission are final and binding upon all parties.

V  FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The Emirates of Abu Dhabi and Dubai have instituted mandatory health insurance schemes upon all employers. Additionally, the DOH introduced a standard provider contract mandating that all contracts between insurers and providers meet required standards. One such requirement is that reimbursement of healthcare fees are made in accordance with a mandatory tariff, which specifies the price for basic services. Ideally, such requirement is an attempt to discourage or stop commissions or kickbacks between providers.

DOH previously issued a directive relating to kickbacks in medical laboratory services and testing. This directive was the result of complaints from patients who were often directed to a medical laboratory that a specific doctor had an agreement with, to be billed for examinations, diagnostics or treatments that were unnecessary. The doctor was given a portion of any fees generated from such visits.

Additionally, local insurers have recently taken a novel approach in requiring that providers sign an undertaking letter to the effect that providers would comply with the spirit and letter of contractual requirements of their binding contract, with a sworn statement that no volume incentives or commissions are being paid for obtaining services. Violation of the undertaking letter could result not only in a material breach of the underlying contract justifying termination, but would allow the insurer to petition DOH or another concerned governmental authority for redress.

Efforts to stem the flow of kickbacks are much more likely to have a significant impact on smaller secondary care providers (e.g., medical laboratory service providers or specialist diagnostic centres) that generate much of their revenue from larger hospitals or clinics. One way to ensure referrals is the payment of kickbacks. If kickbacks are no longer available through this route, companies will need to become more competitive.

The DRG billing system (as discussed in Section III) may be a further tool in the future to combat kickbacks and illegal commissions.

VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Other than the remedies delineated in Section IV, there are no special liability or compensation systems contemplated in applicable law.

VII  TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

UAE Federal Law No. 4 of 2012 on the regulation of competition (the Competition Law) became effective in 2013 and regulates competition within the UAE market. The Competition Law specifically exempts the pharmaceutical industry from competition (as stated elsewhere,
the pricing of medication and pharmaceuticals is fixed by UAE law. However, the Law does not exempt the pharmaceutical industry from other monopolistic practices. Therefore, agreements between competitors to divide territories, allocate or boycott customers, or limit or cease production are all prohibited by the Competition Law.

ii Transactional issues

With respect to the sale of pharmaceutical manufacturing plants, companies or patents in the UAE, generally, these would follow the rules and requirements contained in the UAE Commercial Companies Law or Commercial Transactions Law. Approval of the relevant health department (DOH or DHA) or the Ministry of Health may be required depending on the specific activity on the licence of the company.

With respect to patent licensing, a patent licence cannot be transferred to a third party unless ownership of the licensed item has been assigned and approved by the respective court.

VIII CURRENT DEVELOPMENTS

Many of the legal and regulatory reforms contemplated herein strongly convey the desire of the UAE to be at the forefront of medical care. The ultimate objective of the UAE (the Emirates of Abu Dhabi and Dubai in particular) to be able to manufacture or provide the medication and healthcare that rivals that of any country around the world. This also includes a renewed focus on research and development, and attracting qualified medical professionals and researchers.

During the past few years, the UAE has ramped up its investment strategy in the pharmaceutical industry. The UAE intends to attract more than 75 major pharmaceutical firms by 2021 – nearly 20 more than exist in the UAE today – with investments upwards of 2 billion dirhams per year. The number of pharmaceutical factories increased from 14 in 2014 to 18 in 2017, and is expected to reach 36 in 2020. A recent industry report shows that investments in healthcare in the UAE reached 62.2 billion dirhams in 2017 and are expected to be 118.1 billion dirhams in 2027. This augmented investment strategy is propelled to focus on one of the significant national agenda items (i.e., to achieve a world-class healthcare system in the UAE).
This chapter summarises the UK regimes governing medicines and medical devices. Since, at time of writing, the United Kingdom is still an EU Member State and has implemented the EU medicines and medical devices regimes, we will not repeat much of the substantive content of the European Union chapter. We will focus on unique features of the UK regimes and the chapter should be read in conjunction with the European Union chapter. As noted below, the regulatory position in the United Kingdom is likely to change significantly in the near future as a result of the United Kingdom’s decision to leave the EU (Brexit), but the precise impact on the regulation of medicines and medical devices in the United Kingdom is uncertain at this stage.

I INTRODUCTION

Medicines for human use are regulated primarily by the Human Medicines Regulations 2012 (the Medicines Regulations). The Medicines Regulations implement Directive 2001/83/EC and most other EU medicines laws into UK law. The Medicines Regulations also consolidated most UK medicines legislation – including the majority of the Medicines Act 1968 – into one statutory instrument to provide a comprehensive regime for the authorisation, manufacture, import, distribution, advertising, sale and supply of medicinal products for human use. However, the Medicines Act 1968 continues to regulate some aspects, such as pharmacies and the dispensing of medicines.

Medical devices are regulated by the Medical Devices Regulations, which implement the three EU Medical Devices Directives into UK law (pending the implementation of Regulation (EU) 2017/745 on Medical Devices, and Regulation (EU) 2017/746 on In

---

1 Grant Castle and Sarah Cowlishaw are partners at Covington & Burling LLP.
2 The Human Medicines Regulations 2012 (SI 2012/1916), as amended.
4 The Medicines Act 1968 (Chapter 67), as amended.
5 The Medical Devices Regulations 2002 (SI 2002/618), as amended.
Vitro Diagnostic Medical Devices, which both entered into force on 25 May 2017 and, subject to any changes introduced as a result of Brexit, will apply as of 26 May 2020 and 26 May 2022 respectively. For further details, see the European Union chapter.

The Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the Department of Health and Social Care, is the United Kingdom’s national competent and enforcement authority for the regulation of both medicinal products and medical devices. However, the ‘licensing authority’ is responsible for the granting, renewal, variation, suspension and revocation of licences, authorisations, certificates and registrations under the Medicines Regulations. The licensing authority comprises either or both of the Secretary of State for Health and the Minister for Health, Social Services and Public Safety, acting on the advice of the MHRA. Likewise, the Secretary of State exercises certain powers under the Medical Devices Regulations. The ‘enforcement authority’ comprising relevant ministers is responsible for authorising inspectors and for bringing enforcement actions.

II THE REGULATORY REGIME

i Classification

The MHRA has primary responsibility for determining whether borderline products are medicinal products or medical devices. It does so case by case, having regard to the legal definition of a medicinal product and a medical device set out in EU law and implemented in the United Kingdom.

The MHRA’s Borderline Section considers each product on its merits and any information that may have a bearing on the product’s status; for example, its mode of action, pharmacological properties of the product’s ingredients, the claims made for the product, whether there are any similar regulated products on the market, and how the product is presented through labelling, packaging, promotional literature and advertisements.

The Borderline Section provides informal, written advice on classification in response to specific enquiries about potential borderline issues. However, it will also exercise its enforcement powers following complaints about a particular product or based on its review of a product. In the latter scenario, the Borderline Section has a range of powers available to it to require removal of the product from the market (e.g., because it is an unlicensed medicine or a medical device that does not conform to the Medical Devices Regulations). However, the MHRA’s usual approach is to serve a provisional determination notice advising that the MHRA considers the product a medicinal product or a medical device. A provisional determination must set out the reasons for the Agency’s position and the options available to the person served with the notice should that person disagree with the determination. The options include the right to request an independent (advisory) review panel to review the determination and associated documentation. After considering the panel’s advice, the MHRA makes a final determination. There is no right of appeal against a final determination, other than via the courts and judicial review. It is a criminal offence not to comply with the conditions of a final determination.
ii Non-clinical studies
The Animals (Scientific Procedures) Act 1986⁹ implemented Directive 2010/63/EU¹⁰ into UK law from 1 January 2013. It permits research involving animals only in premises licensed by the Home Office, by appropriately qualified staff and in accordance with procedures designed to minimise animal pain and suffering.

The Good Laboratory Practice Regulations 1999¹¹ transpose Directive 2004/10/EC¹² into UK law. They require that all animal studies be conducted in accordance with sound standards of good laboratory practice. These standards reflect the Organisation for Economic Co-operation and Development requirements.

iii Clinical trials
Medicines
Clinical trials of medicines for human use are regulated under the Medicines for Human Use (Clinical Trials) Regulations 2004 (the Clinical Trial Regulations),¹³ which implement Clinical Trials Directives 2001/20/EC¹⁴ and 2005/28/EC¹⁵ into UK law. Clinical trials of medicinal products in humans are generally only permitted if the MHRA has granted a clinical trial authorisation (CTA) and an ethics committee has issued a favourable opinion. A CTA is not required for ‘non-interventional’ trials, but the definition of a non-interventional trial is very narrow. It covers only trials involving approved medicines used on-label where there are no changes to routine medical care, including prescribing decisions or additional monitoring or information-gathering procedures.

CTA approval process
Applicants for a CTA must first have obtained a EudraCT number and must then submit the relevant application form, the investigational medicinal product dossier (IMPD) and supporting documentation to the MHRA. The MHRA aims to assess applications within 30 days from receipt of a valid application, but there are accelerated review times for certain studies. The Agency aims to review applications for Phase I trials in healthy volunteers within 14 days and there is also a 14-day notification scheme for clinical trials that involve an authorised medicinal product and meet certain conditions.

---

⁹ The Animals (Scientific Procedures) Act 1986 (Chapter 14), as amended.
¹¹ The Good Laboratory Practice Regulations 1999 (SI 199/3106), as amended.
¹² Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, as amended.
¹³ The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.
¹⁵ Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
Applications for a positive ethics committee opinion are usually considered in parallel with applications for a CTA and are made via the National Research Ethics Service, which is part of the Health Research Authority. Following the adoption of the new Clinical Trials Regulation (EU) No. 536/2014,16 the United Kingdom is currently working towards the establishment of a system for the granting of a single approval for a clinical trial, encompassing both MHRA and ethics committee review.

All investigational medicinal products must have been manufactured or imported by the holder of a manufacturer’s authorisation in the European Economic Area (EEA). The manufacturer or importer must ensure that a qualified person has performed batch release of the products for clinical-trial use, which is only possible if the product is manufactured in accordance with an appropriate standard of good manufacturing practice (GMP) and if the product conforms with the specifications in the IMPD.

Sponsors must submit reports of suspected unexpected serious adverse reactions (both United Kingdom and non-United Kingdom) relevant to a UK trial to the MHRA and the relevant research ethics committee. There is also a requirement to submit annual safety reports. They must provide investigators with information on safety issues relevant to whether they enrol patients or allow them to continue with the study.

The Clinical Trial Regulations require sponsors to provide adequate insurance or indemnity to cover liabilities that may arise in relation to the clinical trial. The MHRA expects that a sponsor’s insurance policy or indemnity will reflect the form recommended by the Association of the British Pharmaceutical Industry (ABPI) Clinical Trial Compensation Guidelines. The ABPI has also published specific insurance and compensation guidelines for Phase I clinical trials.

Assessment process

The MHRA will assess the application within 30 days of receipt of a valid submission unless the applicant indicates that the study is eligible for the shorter 14-day assessment time.

Medical devices

Clinical investigations of medical devices are governed by the Medical Devices Regulations. In addition to obtaining research ethics committee approval, the manufacturer must notify the MHRA prior to the conduct of a clinical investigation involving a non-CE-marked medical device. The MHRA assesses notifications within 60 days of receipt of a complete notification.

There is a different process for performance evaluation of a non-CE-marked in vitro diagnostic medical device (IVD). Manufacturers must draw up a declaration and follow the procedure set out in Annex VIII of the IVD Directive 98/79/EC and must also register details of the IVD for performance evaluation with the MHRA.

Manufacturers must report serious adverse events involving a device under clinical investigation to the MHRA. The MHRA requires manufacturers to provide insurance for subjects in clinical investigations of medical devices.

If and when effective in the UK, the new Medical Devices Regulation (EU) 2017/745 and In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 will introduce more stringent requirements for device clinical investigations than the current framework. For further details, see the European Union chapter.

iv Named-patient and compassionate-use procedures

Medicines

Regulation 167 of the Medicines Regulations implements the named-patient exemption under Directive 2001/83/EC into UK law. It allows the supply of unlicensed medicines in response to a bona fide unsolicited request by a healthcare professional to meet the unmet clinical needs of an individual patient. Medicinal products supplied under the named-patient exemption are known as ‘specials’. A special may not be advertised (although price lists may be made available) and they should not be supplied if an equivalent authorised product is available. The responsibility for patient safety remains with the prescribing clinician.

If a special is manufactured in the United Kingdom, the manufacturer must hold a manufacturer’s (specials) licence granted by the MHRA. Importers of specials must hold the appropriate wholesale dealer’s or manufacturer’s authorisation. In addition, importers must notify the MHRA 28 days prior to importing a special.

There are record-keeping requirements and serious adverse drug reactions must be reported to the MHRA.

The compassionate use exemption under Article 83 of Regulation (EC) No. 726/2004 applies directly in the United Kingdom.

The MHRA’s Early Access to Medicines Scheme (EAMS) provides another exemption to the requirement for a medicinal product to have a marketing authorisation prior to being placed on the market. The EAMS has been adopted to enable patients with ‘life-threatening or seriously debilitating conditions’ to have early access to medicines that have yet to receive a marketing authorisation. The process for joining the scheme involves a two-stage evaluation by the MHRA: step I is the promising innovative medicine (PIM) designation, and step II is the EAMS scientific opinion. For medicines to qualify for the EAMS, they must meet the following criteria:

a the product is needed to treat a life-threatening or seriously debilitating condition, and there is a high unmet need;
b the medicinal product is likely to offer significant advantages over methods currently used in the United Kingdom;
c the potential benefits of the medicinal product outweigh the adverse effects; and
d the applicant is able to supply the product and to manufacture it to a consistent quality standard of GMP.

Medical devices

The Medical Devices Regulations permit the supply of custom-made medical devices that meet the essential requirements but have not been CE-marked, and also devices that do not meet the essential requirements, provided that the MHRA authorises their use.

The use of an individual non-complying medical device, for a single named patient, is permitted only in exceptional circumstances; for example, where no alternative CE-marked devices are available or where it has been demonstrated that the morbidity or mortality of patients is significantly reduced with the use of the device in question as compared to those using alternative available treatment. The MHRA requires that an application be made for each patient, which includes information from the manufacturer and relevant clinician.

v Pre-market clearance

Medicines

Regulation 46 of the Medicines Regulations implements Article 6(1) of Directive 2001/83/EC, which requires that a medicinal product has a marketing authorisation prior to being placed on the market. It is an offence for any person to sell or supply, or offer to sell or supply, an unauthorised medicinal product or a medicinal product otherwise than in accordance with the terms of a marketing authorisation.

The MHRA is the UK national competent authority for review of marketing authorisation applications under the national, mutual recognition and decentralised procedures, although the relevant ministers acting through the licensing authority grant the authorisations.

Medical devices

The EU chapter summarises the conformity assessment and CE-marking procedures for medical devices. Since there is little regulatory pre-market review and approval of medical devices (with the exception of European Medicines Agency review of devices incorporating medicinal products and blood products), the MHRA has no involvement in the process leading up to CE marking.

However, the Medical Device Regulations require that manufacturers and authorised representatives based in the United Kingdom that are placing Class I or custom-made devices on the market to register details of themselves and the medical devices with the MHRA. Manufacturers or authorised representatives for IVDs must register themselves and their IVDs via the EU database, Eudamed.

vi Regulatory incentives

Medicines

The Medicine Regulations implement the EU periods of eight years’ regulatory data exclusivity (during which generic applicants cannot file) followed by two years’ market exclusivity (during which regulators may review generic applications, but generic manufacturers cannot launch) under Directive 2001/83/EC for products for which qualifying national applications were submitted after 30 October 2005. For complete free-standing applications submitted on or before that date, UK marketing authorisation holders would benefit from 10 years of data exclusivity protection, during which generic applicants cannot file. These regulatory exclusivity periods begin when the product is first approved anywhere in the EEA, not necessarily in the United Kingdom.
The additional data exclusivity provisions for ‘orphan medicinal products’ and for products with paediatric indications developed in accordance with an approved paediatric investigation plan under Regulation (EC) No. 141/2000\(^\text{18}\) and Regulation (EC) No. 1901/2006,\(^\text{19}\) respectively, apply directly.

In the United Kingdom, the Intellectual Property Office is responsible for granting supplementary patent certificates for medicinal products that meet the criteria under Regulation (EC) No. 469/2009.\(^\text{20}\)

**Medical devices**

UK legislation does not provide specific regulatory exclusivity periods for medical devices. A device may be protected by a UK patent if it satisfies the requirements for patentability under the Patents Act 1977.\(^\text{21}\) A UK patent is granted initially for four years and is renewable annually thereafter up to a maximum of 20 years from the filing date of the patent application.

**vii Post-approval controls**

The United Kingdom’s post-approval controls over marketing authorisation holders for medicines and manufacturers of medical devices closely mirror the EU requirements.

**Transfer of marketing authorisations for medicines**

Marketing authorisation holders may apply to the MHRA to ‘transfer’ ownership of their marketing authorisations to third parties. If satisfied that the recipient is suitable to hold the approval, the MHRA will grant the transferee a new marketing authorisation. It will usually also allow the original authorisation to remain in force for a transitional period. This avoids interruptions in supply by allowing a product in the name of the original authorisation holder to be placed on the market until the new product is widely available.

**Revocation, suspension or variation of marketing authorisations**

The licensing authority, acting through the MHRA, has the power to revoke, suspend or vary a marketing authorisation. Companies that are unhappy with the proposal have the right to appeal to the appropriate committee, then to an independent review panel in accordance with Schedule 5 of the Medicines Regulations. However, these procedures do not apply when the product is centrally approved or has been subject to either the mutual recognition procedure, the decentralised procedure or an EU referral. Under those circumstances, the relevant procedures are governed by EU law.

---


\(^{21}\) The Patents Act 1977 (Chapter 37), as amended.
viii  Manufacturing controls

The substantive requirements governing the manufacture of medicinal products, including the need for a manufacturing or import authorisation, a qualified person and compliance with GMP, are discussed in the European Union chapter.

The MHRA regulates pharmaceutical manufacturing operations within the United Kingdom, although the licensing authority actually grants, suspends and revokes manufacturing authorisations. The MHRA will conduct inspections of manufacturing facilities before authorisation and periodically thereafter.

Changes to UK manufacturing and wholesale distribution authorisations require variations to be submitted to the MHRA. A change of name of the licence holder, if it remains the same legal entity, requires a simple administrative notification to the MHRA. Transfers of authorisations from one legal entity to another require submission of a change of ownership application signed by both the transferor and the transferee. The MHRA will only accept such change of ownership applications if there is no substantive change to premises, operations or personnel. If there are any substantive changes, the MHRA will treat the application as an application for a new licence.

ix  Advertising and promotion

Medicines

The Medicines Regulations implement the EU advertising rules into UK law. These include the general requirements that advertisements should not be misleading, that they should be substantiated and that they should be accompanied by appropriate prescribing information. There is also a prohibition on pre-approval or off-label promotion of medicines, advertisements of prescription-only medicines to the general public, and illegal inducements to prescribe. Guidance from the MHRA, called the Blue Guide on Advertising and Promotion of Medicines in the UK (the Blue Guide), supplements the Regulations and is intended to provide additional clarification on the interpretation and application of the law. The MHRA is the statutory enforcement body for these rules and requires pre-vetting of advertising material in some circumstances, for example, new active substances granted marketing authorisations.

The statutory scheme is supported by a long-standing system of self-regulation based on the ABPI Code of Practice for the Pharmaceutical Industry (the ABPI Code). The ABPI Code is enforced by a self-regulatory body called the Prescription Medicines Code of Practice Authority (PMCPA), which adjudicates complaints by competitor companies and individuals, but can also bring proceedings itself.

The ABPI Code governs the advertising of prescription-only medicines to health professionals, relevant administrative staff and to the general public. It only applies to companies that are members of the ABPI or that have formally agreed to abide by the ABPI Code. The success of this self-regulatory scheme has meant that the MHRA has not needed to exercise its statutory enforcement powers against legitimate pharmaceutical companies for nearly 30 years.

The provisions of the ABPI Code are consistent with the Medicines Regulations and in some instances more stringent. For example, under the ABPI Code, promotional material must not be issued unless its final form has been certified on behalf of the company by a person...
that is a registered medical practitioner or a UK-registered pharmacist. It also significantly limits companies’ ability to provide promotional aids and seeks to regulate certain company interactions with the National Health Service (NHS).

Medical devices

The United Kingdom has no specific device advertising legislation. Medical device advertising is subject to general advertising rules, requiring that advertisements be substantiated, factual, balanced and not misleading.

The Association of British Healthcare Industries (ABHI) has incorporated advertising guidelines into its Code of Business Practice (the ABHI Code). The provisions of the ABHI Code only apply to ABHI members and companies that have formally agreed to abide by the ABHI Code. There is a complaints procedure, but at the time of going to press, the Complaints Adjudication Panel has yet to hear a complaint.

Distributors and wholesalers

Medicines

As under EU law, distributors of medicinal products must hold a wholesale dealer’s licence, and must operate appropriate facilities and staff under the supervision of an appropriately qualified responsible person. They must comply with good distribution practices (GDP) and maintain appropriate batch records.

The Medicines Regulations define wholesale dealing as ‘selling or supplying it, or procuring or holding it or exporting it for the purposes of sale or supply’ to a person who receives it for the purposes of selling or supplying it, or administering it or causing it to be administered to a human being, in each case in the course of a business carried on by that person. Thus, the sale of a medicine without physically handling the product constitutes wholesale dealing, for which a distributor’s authorisation is required.

The licensing authority, acting through the MHRA, is responsible for issuing, suspending and revoking wholesale dealers’ licences in the United Kingdom. The MHRA will conduct inspections prior to the grant of such a licence and then periodically thereafter.

Consistent with EU law, the Medicines Regulations also regulate ‘brokers’, meaning persons who engage in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person. UK-based brokers must comply with GDP and must be registered with the MHRA.

Medical devices

The United Kingdom currently has no specific rules governing the distribution or wholesale of medical devices.

If and when effective in the UK, the new Medical Devices Regulation (EU) 2017/745 and In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 will introduce new regulatory obligations on distributors and other economic operators in device supply chains, such as verifying that any devices distributed are compliant with regulations. For further details, see the European Union chapter.
xi Classification of products

Medicines

The Medicines Regulations presuppose that new medicinal products are generally restricted to use under medical supervision and made available only on prescription. There is also scope for imposing additional restrictions, such as requiring that certain products are prescribed only by specialists, or in hospitals. Non-prescription status is appropriate only for products with an appropriate level of safety and where self-diagnosis and treatment is appropriate without a healthcare professional’s intervention or supervision.

There are two classes of non-prescription or over-the-counter drugs in the United Kingdom. Consumers must obtain pharmacy supply products bearing the designation ‘P’ from pharmacies, where they are dispensed under the supervision of a registered pharmacist. General sale list products may be sold through general retail channels, such as supermarkets, convenience stores, petrol stations and the like. These products bear the designation ‘GSL’.

Medical devices

There are no UK rules governing the classification of medical devices that restrict their sale to the public.

xii Imports and exports

The United Kingdom’s regulations governing the import and export of medicinal products reflect those at EU level. Unless products are intended only for trans-shipment via the United Kingdom, they must be imported by the holder of a manufacturer’s authorisation. Products may only be exported by authorised manufacturers or distributors.

xiii Controlled substances

The Misuse of Drugs Act 197122 and subordinate legislation, including the Misuse of Drugs Regulations 2001,23 implement the UN Single Convention on Narcotic Drugs 1961 and the UN Convention on Psychotropic Substances 1971 into UK law. A ‘domestic licence’ is required to produce, possess, supply or offer to supply any controlled substance. Any person that intends to import or export a controlled substance must also obtain an import or export licence for the particular consignment, as applicable. The Home Office is responsible for issuing controlled substances licences in England and Wales. A domestic licence holder may only supply controlled substances to persons authorised to possess such substances; for example, registered pharmacists.

xiv Enforcement

Medicines

A breach of the Medicines Regulations is in most cases a criminal offence, and the MHRA has an Enforcement Division that considers and manages prosecutions. When the MHRA identifies a potential breach of the legislation, a letter is sent to the individual outlining the Agency’s provisional view. The letter will generally list the potential breach or breaches and any public health risk identified where appropriate, along with any action the MHRA requests

---

22 The Misuse of Drugs Act 1971 (Chapter 38), as amended.
23 The Misuse of Drugs Regulations 2001 (SI 2001/3998), as amended.

© 2020 Law Business Research Ltd
the company to take. The process to resolve these issues tends to be informal, with individuals agreeing to take voluntary action, so prosecutions are rare. Offences under the Medicines Regulations are usually triable either way (i.e., in summary proceedings before magistrates or on indictment before a crown court judge and jury, depending on the seriousness of the breach). They usually carry a penalty of a fine on summary conviction, or an unlimited fine and the possibility of up to two years in jail on indictment. The historic limit of £5,000 for fines on summary conviction was removed for offences committed after March 2015.

When the PMCPA Panel rules there is a breach of the ABPI Code under the self-regulatory scheme, the company concerned must give an undertaking not to repeat the offending advertisement or activity. The company, whether a member of the ABPI or not, must also pay an administrative charge of £3,500 per matter (or £4,500 per matter for non-members) where it accepts the Panel’s decision that it breached the Code. The charge increases to £12,000 per matter (or £13,000 per matter for non-members) where the company appeals the Panel’s decision and is unsuccessful. At the conclusion of a case, the PMCPA will also publish a detailed case report in its Code of Practice review and on its website.

### Medical devices

The MHRA is responsible for ensuring compliance with the Medical Devices Regulations. For enforcement purposes, an offence under these Regulations is often treated as a breach of a safety regulation under the Consumer Protection Act 1987.24 A person who contravenes the Medical Devices Regulations is liable for a penalty of six months’ imprisonment or a fine per breach.

The main sanction under the ABHI Code for non-compliance is negative publicity. An administrative charge is also payable. However, there have been no complaints procedures under the Code and the level of the administrative charges payable has not yet been determined.

### III PRICING AND REIMBURSEMENT

The NHS is primarily funded by general taxation. The NHS consists of four individual systems: NHS England, Health and Social Care (HSC) in Northern Ireland, NHS Scotland and NHS Wales. In England, the Department of Health and Social Care controls the NHS.

#### i Medicines

The NHS pricing and reimbursement process is essentially a free pricing model for innovative medicines. There are separate schemes for generic medicines. Manufacturers set the reimbursement price of products, usually having consulted the Department of Health and Social Care (DHSC). This price is published in the Drug Tariff. The Secretary of State has the power to impose price reductions under the National Health Service Act 2006, but most companies historically have participated in the voluntary Pharmaceutical Price Regulation Scheme (PPRS) (for branded medicines), which provided for a system of price controls or rebates negotiated between the ABPI and DHSC. Companies that did not participate in the PPRS instead had to participate in a statutory scheme whereby the DHSC imposed price reductions. As detailed further below, the PPRS has now been superseded by the Voluntary

---

24 The Consumer Protection Act 1987 (Chapter 43), as amended.
Scheme for Branded Medicines Pricing and Access (Voluntary Scheme). In addition, the National Institute for Health and Care Excellence (NICE) assesses medicinal products to determine whether they are cost-effective and should be reimbursed by the NHS. NHS health service providers are expected to make funding available for products recommended by NICE.

ii Voluntary Scheme for Branded Medicines Pricing and Access

The 2014 PPRS was superseded on 1 January 2019 by the 2019 Voluntary Scheme, which builds on many of the principles set out in the previous PPRS. The Voluntary Scheme is an opt-in arrangement negotiated between the DHSC25 and the branded pharmaceutical industry represented by the ABPI. The ABPI historically has negotiated the PPRS (in one form or another) approximately every five years to agree a price reduction or payment that participants must deliver during the term of the next scheme, with the reduction based largely on profits companies have generated on NHS sales. Similarly, the latest Voluntary Scheme is valid for five years up until the end of 2023. Historically, participants were able to deliver the price reduction in a number of ways; for example, through uniform price reductions, by selectively reducing the price of certain products and even by making a payment in lieu of a proportion of the reduction. Under the latest Voluntary Scheme, companies will be expected to deliver savings by making payments to the government, although those who are regarded as small or medium-sized companies, or have products that contain new active substances, may qualify for certain exemptions. The Voluntary Scheme also prevents companies increasing their product list price without the prior approval of the DHSC.

iii National Institute for Health and Care Excellence

NICE performs technology appraisals of medicines and medical devices and draws up clinical guidelines to assist the NHS in England and Wales. There are analogous procedures for other parts of the United Kingdom.

Under the National Health Service Act 2006, NHS entities should reimburse medicines used in accordance with a favourable appraisal determination, but are not precluded from reimbursing products that NICE has not recommended.

NICE appraises individual or multiple products, technologies and procedures and develops guidelines on the instructions of the Department of Health and Social Care or the Welsh Assembly government. Where necessary, it commissions an independent academic centre known as an assessment group to review available evidence, including submissions by manufacturers, and prepare an evaluation report. A NICE appraisal committee then produces an appraisal consultation document (ACD), which includes NICE’s provisional view on the cost-effectiveness of a product and its recommendations. NICE has a fairly rigid approach to assessing cost-effectiveness. It determines the quality-adjusted life year (QALY) associated with a technology and uses that to calculate the cost per QALY saved (i.e., incremental cost-effectiveness ratio (ICER)). NICE will favour interventions with a lower ICER. If the ICER is less than £20,000, NICE will usually recommend reimbursement. For ICERs up to £30,000, it will often exercise its discretion to recommend a product, but above this threshold, it is unlikely to recommend a product unless there are extenuating circumstances.

25 Pursuant to the powers conferred upon the Department of Health by Section 262 of the National Health Service Act 2006 (Chapter 41), as amended.
Stakeholders and commentators have four weeks to comment on the ACD. After considering comments on the ACD, the appraisal committee makes its final recommendations in the final appraisal determination (FAD). Stakeholders can appeal against the final recommendations in the FAD to the NICE Appeal Panel. If there are no appeals, or an appeal is not upheld, the final recommendations are issued as NICE guidance.

NICE has developed a highly specialised technology (HST) process, which is a variation of its existing processes designed to evaluate technologies for extremely rare conditions, essentially ultra-orphan medicines. NICE will recommend funding for HSTs with an ICER of less than £100,000 per QALY gained although it has discretion in certain circumstances to recommend products above that threshold, usually up to ICERs of £300,000. However, a medicine can only be appraised through the HST process if it satisfies narrow criteria. These include not only that the product is ultra-orphan but also that treatment is concentrated in very few centres in the NHS.

Finally, a partnership between NHS England, NICE, Public Health England and the Department of Health and Social Care also operates the Cancer Drugs Fund (CDF). NICE can recommend a drug for use in the CDF if it has the potential to satisfy the criteria for the standard health technology assessment process, but where there is significant clinical uncertainty that needs further investigation (i.e., through data collection in the NHS or clinical studies). The CDF provides an interim funding mechanism, often while a company gathers additional data to demonstrate the cost or clinical effectiveness of its drug.

NICE is currently contemplating whether to move to a more flexible ‘value-based’ approach to health technology assessment, perhaps for medicines for small patient populations.

iv Medical devices

There is no formal scheme in the United Kingdom that governs the pricing and reimbursement of medical devices. Some devices are listed in the Drug Tariff, but these are largely consumable devices used by outpatients. Many other devices are reimbursed as part of the cost of NHS procedures under the Payment by Results system of tariffs. However, NICE performs some technology appraisals of medical devices.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

It is possible to challenge the decisions of national public authorities, such as the MHRA or NICE, by judicial review. This is a procedure by which courts examine the decisions, actions or failures to act of a public body, subject to general principles of administrative law. Before seeking judicial review, the applicant must have exhausted all other avenues of redress, such as internal or administrative appeal procedures. In addition, the relevant act and body must be amenable to review, the claimant must have ‘sufficient interest in the matter to which the application relates’, or legal standing, and the claim must be commenced ‘promptly and in any event not later than three months after the grounds to make the claim first arose’.

26 Section 31(3) of the Senior Courts Act 1981 (Chapter 54).
The grounds for judicial review are constantly evolving but, in general, the courts will consider whether decisions or acts of a public body are illegal, irrational or procedurally unfair.28

There are three specific discretionary remedies for judicial review proceedings: quashing orders, prohibiting orders and mandatory orders. A claimant may also seek a declaration, a stay or injunction and, in certain circumstances, damages. Claimants typically seek a quashing order to set aside the public body's decision, together with a mandatory order directing the public body to take the decision again in accordance with the court's judgment.

Where national judicial review proceedings involve matters of EU law, national courts may refer questions of EU law to the Court of Justice of the European Union (CJEU). The CJEU will issue a preliminary ruling, which the national court can use as a basis for its judgment.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

i Medicines
Regulations 293 to 300 of the Medicines Regulations implement into UK law the EU rules on the promotion of medicinal products and interactions between pharmaceutical companies and healthcare professionals. The legal position concerning communications or activities of pharmaceutical companies involving prescribers and payers is therefore the same in the United Kingdom as in the European Union, and contains a broad prohibition on the offer to healthcare professionals of unlawful inducements to prescribe. However, the prohibition excludes financial trade practices, such as discounts, that were in common use in the industry before 1 January 1993.

The Blue Guide and the ABPI Code clarify or establish additional requirements governing interactions with payers and prescribers. For example, the ABPI Code also governs the offer of inducements to administrative staff and prohibits promotional aids, except for inexpensive items for patient support. The ABPI Code also contains guidelines governing certain interactions between companies and NHS entities.

ii Medical devices
There are no specific UK rules that govern the interaction between medical devices companies and healthcare professionals.

The ABHI Code includes guidelines and a question-and-answer document on the minimum standards device companies should comply with when interacting with healthcare professionals, including payers. The provisions of the ABHI Code are based on the EU code of practice (the Eucomed Code) and therefore the national principles reflect the EU position on ethical communications and interactions with prescribers and payers.

28 Council of the Civil Service Unions v. Minister for the Civil Service [1985] A.C. 374. The list of grounds for review cited is not exhaustive and may be added to in the future.
iii Anti-bribery legislation
Most healthcare professionals, administrative staff and payers in the United Kingdom are government officials, employees or contractors. Companies should therefore also be mindful of anti-bribery legislation, such as the UK Bribery Act 2010.29

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

i Medicines
With the exception of a specific vaccine injury compensation scheme and the implementation of EU rules governing compensation for clinical-trial related injuries, there are no specific pharmaceutical injury compensation rules in the United Kingdom.

The Vaccine Damage Payments Act 1979 (VDPA)30 provides a statutory compensation scheme for individuals who can demonstrate that they have suffered a severe mental or physical disability caused by a vaccination against a specific disease. The VDPA scheme applies only to vaccinations for specified diseases listed in the VDPA or diseases recommended by the Secretary of State for Health as falling under the scope of the VDPA scheme.31 The diseases are typically those for which vaccination is recommended.

Under the VDPA, individuals must show that they were at least 60 per cent disabled by the vaccination to be entitled to a tax-free payment of £120,000. The scheme is rarely used because of the requirement for 60 per cent disability before a claim can be made and limitation periods under UK law.

ii Medical devices
There is currently no national scheme or system to compensate individuals injured by medical devices.

If and when effective in the UK (pending clarification regarding Brexit), the new Medical Devices Regulation (EU) 2017/745 and In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 will require the UK to ensure there is a national system in place (e.g., for insurance, guarantees or similar) to compensate anyone who suffers damage from participating in medical device clinical investigations.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law
Since, at time of writing, the United Kingdom is still an EU Member State and because the provisions of the UK Competition Act 1998 closely reflect those found in Articles 101 (anticompetitive agreements) and 102 (abuse of dominant market position) of the Treaty on the Functioning of the European Union, many of the considerations and issues outlined in the European Union chapter apply equally in the United Kingdom.

The Competition and Markets Authority (CMA) is the body with responsibility for policing activities that affect trade within the United Kingdom, or regions within the United Kingdom. The CMA has recently been reviewing certain pricing practices in the

29 The Bribery Act 2010 (Chapter 23).
30 The Vaccine Damages Payments Act 1979 (Chapter 17), as amended.
31 Section 2 of the VDPA.
pharmaceutical industry, particularly the practice of de-branding (or genericising) drugs so that they are no longer subject to price regulation through normal control mechanisms, such as the PPRS. For example, at the end of 2016, the CMA fined pharmaceutical companies Pfizer and Flynn Pharma nearly £90 million for abusing their dominant position by charging excessive prices to the NHS for an anti-epilepsy drug. An appeal was brought to the CAT, which ruled against the CMA’s decision. The CMA has received permission to appeal the CAT’s decision to the UK Court of Appeal. A number of other investigations relating to excessive and unfair prices are ongoing in the United Kingdom. The CMA has also focused on ‘pay-for-delay’ agreements, issuing its first pay-for-delay infringement decision on 12 February 2016. It fined GlaxoSmithKline (GSK), Generics UK Limited (GUK), Merck KGaG (GUK’s former parent company), Actavis UK Limited, Xellia Pharmaceuticals ApS and Alpharma LLC a total of £45 million for delaying market entry of generic versions of GSK’s anti-depressant Seroxat (paroxetine) in the United Kingdom. The decision has been appealed to the UK Competition Appeal Tribunal, which has made a referral to the CJEU. The CMA also investigated a discount scheme that Merck Sharp & Dohme (MSD) operated for its product Remicade, among suggestions that it might have restricted competition for ‘biosimilar’ versions of infliximab. However, on 14 March 2019, the CMA closed its investigation because MSD’s scheme was not likely to have exclusionary effects.

The CMA’s predecessor, the Office of Fair Trading (OFT), also brought a number of proceedings against companies in the life sciences sector. For example, the OFT found that Genzyme abused its dominant position by bundling the list price of its drug Cerezyme with the price of home-care services. The OFT imposed directions requiring that the NHS list price for Cerezyme be a stand-alone price for the drug, exclusive of any home-care services, and that the price at which the drug was supplied to third parties be no higher than the stand-alone price for the drug.

Napp Pharmaceuticals and other manufacturers were investigated for fixing the prices of opiate drugs. The OFT found that Napp abused a position of dominance approaching monopoly in the UK market for the supply of morphine tablets by charging excessively low, predatory or exclusionary prices in the hospital segment of the market, and excessively high prices in the community segment of the market. The OFT ordered Napp to cut the price of its morphine products to the community and reduce the difference between community and hospital prices.

### Transactional issues

The considerations and issues outlined in the European Union chapter apply equally in the United Kingdom.

### VIII CURRENT DEVELOPMENTS

In March 2017, the United Kingdom issued a formal notice in accordance with Article 50 of the Treaty on the Functioning of the European Union that put the United Kingdom on course for Brexit on 29 March 2019. This deadline has subsequently been pushed back twice and at time of writing Brexit is now anticipated to occur by 31 January 2020.

Brexit is likely to have significant implications for the pharmaceutical and medical devices industries in the United Kingdom and for international companies operating in...
the United Kingdom. Its impact will very much depend on the form a post-Brexit United Kingdom will take, the relationship that the country chooses to have with the European Union, and indeed the relationship that the European Union is willing to accept.

The European Union (Withdrawal) Act 2018 (the Withdrawal Act) received royal assent on 26 June 2018. In overview, the Withdrawal Act (as amended) will repeal the European Communities Act 1972 at 11pm on 31 January 2020, with generally all ‘Direct EU-legislation’ and ‘EU-derived domestic legislation’ (each as defined within the Withdrawal Act) that is operative as part of UK law the day before continuing to have effect in the United Kingdom on and after Brexit until otherwise amended or repealed by the UK Parliament to reflect any negotiated Brexit outcome.

An updated draft withdrawal agreement (the Draft WA), representing the latest proposed agreement reached between the United Kingdom and EU negotiating parties, and proposed political declaration on the future relationship between the United Kingdom and EU, were both published by the UK government and the European Commission in October 2019.

The Draft WA sets out a proposed transition period between the date the agreement enters into force (upon the United Kingdom’s exit from the EU), until 31 December 2020, during which time EU law will ‘be applicable to and within’ the United Kingdom. The Draft WA also details that the United Kingdom must transfer all documentation relating to ongoing procedures led by a UK competent authority in accordance with Directive 2001/83/EC, and, if reasonably requested by the European Medicines Agency or an appropriate Member State authority, make available any UK-authorised medicinal product marketing authorisation dossier to that authority before the end of the transition period. Similarly, the relevant Member State authorities must also make available to the United Kingdom any medicinal product marketing authorisation dossier approved by that body, when requested by the United Kingdom before the end of the transition period. UK conformity assessment bodies must also make available the information they hold (such as in relation to medical devices) to any notified body of a Member State as indicated by the certificate holder before the end of the transition period.

While the Draft WA was endorsed by the 27 EU Member States on 19 October 2018, the UK Parliament has to date withheld its approval to implement the Draft WA into UK law. As such, at the time of writing, the exact nature of the UK’s departure from the EU continues to be debated, and very significant uncertainty remains regarding the eventual post-Brexit relationship between the European Union and the United Kingdom. EU and UK regulators are continuing to plan for all eventualities, as are companies that Brexit may affect. Since August 2018, both the DHSC and MHRA have published a series of ‘no Brexit deal’ guidance and proposed contingency planning (available on the UK government website). Increasingly, potentially affected pharmaceutical companies have taken actions to move regulatory approvals from the UK to other Member States, and adjusted their pharmaceutical

32 The European Union (Withdrawal) Act 2018 (Chapter 16), as amended.
33 The European Communities Act 1972 (Chapter 68).
34 Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community (published 19 October 2019).
35 Political Declaration setting out the framework for the future relationship between the European Union and the United Kingdom (published 19 October 2019).
supply chains in preparation for a potential ‘hard’ Brexit. If the United Kingdom, in lieu of EU membership, does not join either the EEA or the European Free Trade Association, the extent to which the United Kingdom continues to participate in the EU regulatory schemes will need to be defined in new bilateral trade agreements.
I  INTRODUCTION

The United States accounts for about 35 per cent of the global pharmaceutical market and is the largest single investor in research and development of new products. The National Institutes of Health, the primary federal agency that funds biomedical research, will have a budget of more than US$30 billion for 2019, and manufacturers based in the United States spend substantially more than that each year on research and development.

The principal federal regulatory authority for medicines and medical devices is the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services. The FDA, which has a staff of more than 17,000 and an annual budget in excess of US$6 billion, regulates human drugs, human biological products, medical devices, foods, cosmetics, veterinary medicines, animal feeds, radiation-emitting products and tobacco. A substantial part of the agency’s budget comes from ‘user fees’ imposed on some of the industries it regulates (including drug and device manufacturers); these may include registration fees for marketing authorisation applications as well as annual fees for marketed products.2

The FDA is headed by a Commissioner of Food and Drugs, who is appointed by the president with the approval of the Senate. Only a handful of the Commissioner’s subordinates are political appointees; the rest are career civil servants. Approximately half of the FDA’s staff are located in the Washington, DC, metropolitan area, many serving in ‘centres’ that supervise the principal industry sectors that the agency regulates. Among these are the Center for Drug Evaluation and Research (CDER), which regulates small-molecule drugs and most therapeutic protein products; the Center for Biologics Evaluation and Research (CBER), which regulates vaccines, blood products, gene and tissue therapies and certain other biological products; and the Center for Devices and Radiological Health (CDRH), which regulates medical devices and radiation-emitting products. The Office of Regulatory Affairs,
headed by an associate commissioner, manages the agency’s inspection and enforcement programmes, staffed by several thousand employees who are located in regional, district and field offices around the United States.\(^3\)

The main statute administered by the FDA is the Federal Food, Drug and Cosmetic Act (FDCA), originally enacted in 1938, which governs foods (including dietary supplements), drugs, devices, cosmetics, veterinary drugs, radiation-emitting products and tobacco.\(^4\) The statute prohibits ‘adulteration’ and ‘misbranding’ of regulated products and imposes numerous other requirements for specific types of products (e.g., pre-market approval or clearance procedures for certain drugs and medical devices). The FDA also administers parts of the Public Health Service Act (PHSA), including requirements for licensing biological products, as well as numerous other regulatory statutes.\(^5\)

The Drug Enforcement Administration (DEA), an agency within the Department of Justice, administers the Controlled Substances Act and other statutes relating to narcotics, psychotropics and other drugs with potential for abuse. Manufacturers of controlled substances are licensed and inspected by the DEA and may be required to obtain permits for specific activities (e.g., import and export licences and manufacturing and import quotas for certain products).

United States attorneys, located in every state, can bring cases to enforce the FDCA and other regulatory statutes governing drugs and devices. Federal prosecutors may act on referrals from the FDA or on their own initiative.

The Federal Trade Commission (FTC) regulates the advertising of non-prescription drugs and non-restricted medical devices and plays a major role in supervising compliance with the antitrust laws within the medical products industry.

The Office of Inspector General (OIG) in the Department of Health and Human Services investigates allegations of fraud, kickbacks and other abuses affecting federal healthcare programmes, including Medicare (for the elderly and disabled) and Medicaid (for indigent persons). It has the power to exclude companies or individuals from participation in those programmes if they are found to have committed specified offences.

The state governments also have the power to regulate drug and device manufacturers. Many states have enacted ‘mini’ food and drug acts, as well as statutes prohibiting healthcare and consumer fraud. The states also maintain Medicaid fraud control units to investigate abuses by manufacturers, providers and beneficiaries under that programme.

---

\(^3\) The FDA website (www.fda.gov) contains information on the agency as well as links to relevant statutes, regulations, guidances and other documents.

\(^4\) The FDCA is codified at 21 USC, Section 301 et seq. It replaced the Food and Drugs Act, originally passed in 1906.

\(^5\) The relevant provisions of the PHSA are set out in 42 USC, Section 262. Requirements for federal licensing of establishments that manufacture biologics were originally enacted in 1902.
II    THE REGULATORY REGIME

i    Classification

The FDCA defines foods, drugs, devices, cosmetics, dietary supplements and certain other types of products, and the PHSA defines biologics. However, the same product may be covered by two or more definitions and thus be subject to multiple regulatory requirements. Many of the classifications depend on the ‘intended use’ of an article, which is ordinarily determined by statements made in advertising, labelling or other materials issued by the seller. Thus, a fluoride toothpaste for which anti-cavity claims are made is regulated as a drug, because it is intended to prevent tooth decay, and as a cosmetic, because it is intended to clean teeth and improve their appearance.

For certain borderline products that may be subject to more than one regulatory review process or for which the product category is unclear or in dispute, the FDA has issued regulations and guidelines to determine which review centre will take the lead, and it has established an Office of Combination Products to assign products. These regulations and processes apply to drugs, devices, biological products and combinations thereof, known as ‘combination products’. They do not apply to combinations of two drugs, two devices or two biologics, or to other combinations of regulated products.

The FDA can initiate enforcement actions against borderline products that it believes are marketed without required prior approval. For many years, the FDA often initiated enforcement actions against dietary supplements for which therapeutic claims were made, on the basis that those products were unapproved new drugs. These actions have been less frequent since the Dietary Supplement Health and Education Act of 1994 created a separate legal framework to govern those products. The agency continues to monitor the advertising and labelling of cosmetics for which anti-ageing claims are made.

ii    Non-clinical studies

Non-clinical safety studies that are intended to be submitted to the FDA in support of clinical research applications or marketing authorisation applications generally must be conducted in compliance with good laboratory practice (GLP) regulations. These are fundamentally the same as the principles established by the Organisation for Economic Co-operation and Development, which were based on the FDA rules.

---

6 Under the FDCA, the term ‘drug’ includes articles recognised in official pharmacopoeias; articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; and articles (other than food) intended to affect the structure or any function of the body (21 USC, Section 321(g)). The term ‘device’ is defined in substantially similar terms, but applies to articles that do not achieve their primary intended purposes ‘though chemical action within or on the body…’ and which are not ‘dependent upon being metabolised for the achievement of their primary intended purposes’ (21 USC, Section 321(h)). Under the PHSA, the term ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product or arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment or cure of a disease or condition in human beings (42 USC, Section 262(i)(1)).

7 21 CFR, Part 3.

8 21 CFR, Part 58.
The Animal and Plant Health Inspection Service (APHIS) within the Department of Agriculture administers regulations under the Animal Welfare Act that govern research facilities using covered species. Facilities must be registered and comply with applicable welfare requirements and are subject to inspection by APHIS.

Clinical trials
The FDA maintains separate regulatory systems for clinical trials of drugs and medical devices. Both are subject to requirements for the protection of human subjects, including rules on informed consent and independent ethical review, performed by organisations known as institutional review boards (IRBs).10 FDA regulations also establish requirements for financial disclosures by investigators who conduct clinical trials submitted to the FDA in support of applications for drugs or medical devices.10 Disclosure must be made if an investigator has a substantial financial interest in the product under investigation or the company that sponsors a trial, subject to detailed criteria set out in the rules.

Drugs
Clinical trials of unapproved new drugs or biologics generally must be carried out under an investigational new drug application (IND).11 The application contains information about the manufacturing process and formulation of the investigational product, non-clinical and existing clinical safety data, the protocol for the proposed trial, a copy of the investigator brochure and information about the investigators who will carry out the trial. The FDA ordinarily requires INDs to be submitted in the electronic common technical document (eCTD) format established by the International Conference on Harmonisation (ICH). The IND submission must clearly identify any obligations that the sponsor intends to delegate to another person, including contract research organisations (CROs). If the sponsor does not reside in or have a place of business in the United States, the application must be countersigned by an agent or attorney in the United States.

Review of an IND is supervised by a division within the CDER or CBER that specialises in the therapeutic area or product type to which the proposed study relates. That division will have lead responsibility for reviewing a marketing authorisation application if one is submitted and will retain supervisory control over the product after approval. As a result, there is considerable continuity in the review process from the earliest stages of clinical development.

Assuming that approval is granted by the relevant IRB, the sponsor may commence a clinical trial 30 days after the agency accepts the application for filing, unless the FDA informs the sponsor that it may commence the trial earlier or imposes a clinical hold. The rules establish several grounds for a clinical hold, but the main focus is on the safety of human subjects. The sponsor has the right to receive a prompt written statement of the reasons for a clinical hold and to make an appeal, which must be acted upon within 30 days. Once an IND is in effect, new protocols and substantial protocol amendments must be submitted to the FDA before they are initiated, but studies can commence as soon as IRB approval is

---

9 21 CFR, Parts 50, 56.
10 21 CFR, Part 54.
11 See generally, 21 CFR, Part 312.
received. Throughout the process, however, the FDA has the right to impose a clinical hold on studies under the IND if it believes that there is a risk to the safety of human subjects or if certain other criteria apply, subject to an appeal by the applicant.

A sponsor may seek informal, non-binding advice from the FDA at any time during the pendency of the IND. It may also seek advice through an ‘end-of-Phase II’ meeting, which is held to agree the design of the protocols for the pivotal clinical trials, or, for certain studies, a special protocol assessment. In either case, barring a significant scientific development, studies conducted in accordance with the agreement will be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

Sponsors and investigators are required to comply with provisions of good clinical practice (GCP), including requirements for informed consent, IRB review, monitoring, record-keeping and reporting. Studies conducted in accordance with ICH\(^{12}\) GCP guidance will normally be acceptable to the FDA. There is no requirement for sponsors to maintain insurance or compensate subjects for injuries during clinical trials, but informed consent documents must make clear whether such arrangements have been made. There are requirements for annual reports and expedited reports of serious, unexpected adverse events when there is a reasonable possibility that they are drug-related and of certain significant findings in non-clinical studies.

The FDA will accept data from foreign clinical trials not conducted under a US IND in support of a marketing authorisation application, provided the trials are performed in accordance with GCP and the FDA is able to validate the data through an on-site inspection, if necessary. It is possible to obtain approval for a drug entirely on the basis of foreign clinical data, but in practice it is ordinarily desirable to carry out at least some part of the pivotal trials in the United States.\(^{13}\)

**Devices**

Sponsors of device clinical trials conducted in the United States must comply with the FDA’s investigational device exemption (IDE) regulations. The regulatory requirements for a trial differ depending on whether the device is ‘significant risk’ (SR). SR devices are defined as those that present a potential for serious risks to the health, safety or welfare of subjects (e.g., implants and life-supporting and life-sustaining devices).\(^{14}\) Before beginning an investigation of an SR device, the sponsor must obtain FDA approval of an IDE application. The application has some similarities to an IND (e.g., it must contain the investigational plan and report prior studies of the device). The FDA may disapprove an IDE if the risks to subjects are not outweighed by the anticipated benefits to the subjects and the importance of knowledge to be gained, among other bases for disapproval. The FDA may not disapprove an IDE because the study may not support clearance or approval of the device. The FDA has the authority to put a device investigation on clinical hold. Sponsors of SR investigations must also comply with the requirements of the IDE regulations, including requirements relating to IRB approval, informed consent, selection of investigators, monitoring, record-keeping and reporting.

\(^{12}\) The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

\(^{13}\) See 21 CFR, Section 312.120.

\(^{14}\) 21 CFR Section 812.3(m); see also FDA, Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies (January 2006).
‘Abbreviated’ IDE requirements apply to investigations of non-significant risk devices (i.e., those that do not meet the regulatory definition of SR). The sponsor must obtain IRB approval and informed consent and comply with record-keeping and reporting requirements, but need not submit or obtain FDA approval of an IDE before commencing the study. Further, some device investigations are exempt from the IDE and abbreviated IDE requirements, including investigations of certain non-invasive diagnostic devices.

Device sponsors may obtain informal advice from the FDA on study design and other issues through a ‘pre-submission’ process (formerly the pre-IDE process). In September 2017, the FDA issued a revised final guidance on the pre-submission programme.15

The FDA will accept foreign studies not conducted under an IDE to support a device pre-market approval application (PMA) if the data are valid and the investigators conducted the studies in accordance with the Declaration of Helsinki (1983 version) or the laws of the country where the research is conducted, whichever provides greater protection of trial subjects.16 In 2012, Congress codified the FDA’s approach in Section 569B of the FDCA. In February 2018, the FDA issued a final rule amending the criteria for acceptance of foreign data in device submissions (including data to support an IDE, PMA, premarket notifications, humanitarian device exemption, and de novo classification) that are collected in accordance with GCP and subject to the FDA’s ability to validate the data through an inspection.17 The FDA has also issued final guidance providing proposed recommendations on how to develop foreign data that are adequate to support approval or clearance of the device in the United States.18

iv Named-patient and compassionate use procedures

There are several procedures under which drugs or devices can be made available to treat patients even though they have not been cleared for commercial distribution.

Drugs

The FDA has established rules for ‘expanded access’ to investigational drug products that are intended to treat serious or life-threatening diseases. These include provisions for emergency INDs that permit physicians to treat individual patients following relatively simple applications to the FDA and treatment INDs, which provide for larger-scale use of investigational products. In certain cases, the FDA can authorise sponsors to charge for investigational drug products under treatment INDs; prices are limited to recovery of the direct costs of manufacture and distribution. Treatment INDs require prior submission to the FDA, and sponsors must comply with requirements for informed consent, IRB review and reporting of adverse events.

Pharmacists may prepare ‘compounded’ products as part of the practice of the profession of pharmacy. In 1997, Congress enacted a detailed statutory regime to govern

---

15 FDA, Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance (September 2017).
16 21 CFR, Section 814.15(b).
17 83 Fed Reg 7366 (21 February 2018).
18 FDA, Guidance for Industry and Food and Drug Administration Staff: Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions (February 2018).
pharmacy compounding but the Supreme Court held that a provision of that regime that forbade compounders from advertising their services violated the First Amendment to the US Constitution, which guarantees freedom of speech. The lower courts disagreed on the question of whether the Supreme Court’s ruling invalidated the entire statute or only the prohibition on advertising. Reports of severe injuries associated with the use of injectable compounded products that were contaminated with infectious organisms led to enactment of legislation to clarify the FDA’s authority. The Compounding Quality Act, signed by the president in November 2013, establishes a new category of compounders in addition to traditional compounders, which prepare products at the request of physicians for specific patients. The new regulated entity, which is known as an ‘outsourcing facility’, prepares compounded products in larger quantities that are not necessarily intended for specific patients. Traditional compounders are regulated primarily by state boards of pharmacy, while outsourcing facilities are regulated by the FDA. If a compounder voluntarily registers with the agency as an outsourcing facility, submits to agency inspections and complies with other requirements, its products will not be subject to certain statutory requirements, including for pre-market approval. The new provisions added to the FDCA by the Compounding Quality Act apply only to drugs and do not contain any exemption from requirements for pre-market licensure of biologics. The FDA has indicated in guidance, however, that the agency does not intend to take action against the mixing, diluting or repackaging of licensed biological products as a violation of the PHSA’s licensure requirement, provided certain conditions are satisfied.

Certain products for the prevention or treatment of pandemic diseases or to protect against bioterror agents can be sold under an emergency use authorisation (EUA). EUAs can only be approved if the Secretary of Health and Human Services declares an emergency or material threat, and authorisations remain valid only while the declaration is in effect.

In May 2018, the President signed the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act. The law permits ‘eligible patients’ to receive wholly unapproved ‘eligible investigational drugs’ outside of a clinical trial and expanded access setting without violating federal law, subject to specified conditions. Eligible patients must have, among other things, been diagnosed with a life-threatening disease or condition. The law remains in the early stages of implementation, but to date, drug sponsors generally have continued to use the expanded access framework to provide access to drugs outside of clinical trials.

Devices
Similar procedures apply to investigational devices intended for serious and immediately life-threatening diseases and conditions. The compassionate use framework permits access for individuals and small groups of patients who do not meet trial inclusion criteria. Prior

---

19 21 USC, Section 353a.
20 Thompson v. Western States Medical Center, 535 US 357 (2002).
21 The FDA has issued guidance implementing the new legislation, which appears on the agency’s website at www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm.
22 FDA, Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2018).
FDA approval and certain patient protection measures (e.g., informed consent, IRB chair concurrence and institutional clearance) are required. The treatment IDE provisions permit wider use of an investigational device, although treatment use may not begin until completion of clinical trials if the disease is serious but not immediately life-threatening. The sponsor must submit an application for treatment use, and treatment use may begin 30 days after the FDA receives the application unless the FDA objects. As with treatment INDs, sponsors of treatment IDEs must comply with requirements for informed consent, IRB review and reporting of adverse events. Sponsors generally may not charge for the device any more than necessary to recover the costs of manufacturing, research, development and handling. EUAs are also available for devices.

‘Custom devices’ that meet certain criteria are exempt from the requirements for an approved PMA and compliance with performance standards under Section 520(b) of the FDCA. Traditionally, the FDA interpreted this exemption narrowly and many patient-matched devices are not exempt ‘custom devices’. In 2012, Congress enacted clarifying changes to Section 520(b), including a provision that states that production of custom devices ‘is limited to no more than 5 units per year of a particular device type’. The FDA has issued final guidance implementing the amended custom device provision.

Laboratory-developed tests (LDTs) present special regulatory issues. LDTs are diagnostic tests that are developed, validated and performed within a single laboratory but not commercially distributed. Clinical laboratories performing LDTs are subject to the requirements of the Clinical Laboratory Improvements Amendments of 1988, including the requirements to validate the LDTs and obtain certifications to perform testing. Historically, the FDA asserted that LDTs are devices subject to regulation under the FDCA but exercised enforcement discretion and did not require pre-market approval or clearance for LDTs. In June 2010, the FDA announced that it intended to exercise authority over LDTs. In the FDASIA, Congress required the FDA to notify Congress 60 days before issuing a draft or final guidance document regarding the regulation of LDTs. In 2014, the FDA provided this notice and published two draft guidances describing a proposed regulatory framework for LDTs. Congress also began considering several different potential legislative approaches to address LDTs and other diagnostics. The FDA stated that it intended to publish final guidance on the issue in 2016; however, in November 2016, following the presidential election, the FDA announced that it would not move forward with efforts to finalise the draft guidances. In January 2017, the FDA did publish a discussion paper summarising comments

24 21 USC, Section 360j(b).
25 FDA, Guidance for Industry and Food and Drug Administration Staff: Custom Device Exemption (September 2014).
on the guidance and a proposed revised approached for regulation of LDTs. While the agency has not taken further action to regulate LDTs under the Trump administration, Congress is expected to continue to consider potential legislation addressing LDTs.

The FDA does not require in vitro diagnostic products labelled for research use only (RUO) and certain in vitro diagnostic products labelled for investigational use only (IUO) to comply with most regulatory controls, including pre-market clearance requirements. In November 2013, the agency issued final guidance describing its current thinking on when products are properly labelled and distributed as for RUO or IUO.

v Pre-market clearance

Drugs other than biologics

‘New drugs’, which are defined as drugs that are not generally recognised as safe and effective for their labelled conditions of use or that are so recognised but have not been used to a material extent or for a material time, may not be introduced into interstate commerce unless they are subject to a new drug application (NDA) or abbreviated new drug application (ANDA) approved by the FDA. Drugs that are not new may be marketed without pre-market approval.

In practice, the great majority of non-prescription drug products, which contain old, well-established active ingredients, are marketed in accordance with ‘monographs’ issued under the Over-the-Counter (OTC) Drug Review. Monographs, which govern therapeutic categories (e.g., antacids, topical antimicrobials or ophthalmic drug products), specify permitted active ingredients, dosages and instructions for use. Products in compliance with monographs can be marketed without any prior submission to the FDA. Many therapeutic categories are subject to proposed rather than final OTC monographs, and there are complex procedures for determining which products can be marketed while rule-making procedures are under way. Newer OTC drug products and virtually all prescription drug products are marketed under approved NDAs or ANDAs.

An NDA for an innovator product must contain information on the manufacturing process and formulation of the product, full reports of non-clinical studies and clinical trials.
demonstrating the safety and effectiveness of the product and proposed labelling.\textsuperscript{35} The FDA now requires that most submissions be made electronically (in the eCTD format); this requirement became effective for drug marketing applications on 5 May 2017. The FDA also requires submission of tabulations of all patient data from the principal clinical trials, as well as copies of case report forms (CRFs) for patients who died during clinical trials or withdrew because of adverse events, and it can demand CRFs for all patients in pivotal clinical trials. An applicant that does not maintain a place of business in the United States must appoint a US agent, who signs the application and receives official communications from the agency.\textsuperscript{36}

Legislation originally enacted in 1992 and known as the Prescription Drug User Fee Act (PDUFA)\textsuperscript{37} requires sponsors of original products to pay fees upon the submission of NDAs, as well as annual fees for products that are subject to the user fee requirement. The fees are adjusted each year according to a formula set out in the law.\textsuperscript{38} As part of the process leading to enactment of each version of the PDUFA, the FDA has made commitments to Congress in the form of performance goals for the NDA review process, including (among many other things) requirements to hold prompt meetings with applicants prior to and during the NDA review process, timelines for the completion of reviews and procedures for appeals of negative decisions. Under current PDUFA commitments, the FDA aims to review non-priority applications for new molecular entities within 12 months of submission and priority applications within eight months.\textsuperscript{39} The review process is carried out by an interdisciplinary team under the direction of the relevant therapeutic review division within the CDER. The FDA may consult with one or more independent expert advisory committees. At the end of a review cycle, the FDA issues either an approval or a ‘complete response’, informing the applicant why approval was not granted and identifying additional information required for approval.\textsuperscript{40}

To approve an NDA, the FDA must determine that the product will be safe and effective for the conditions of use recommended in its labelling, that the manufacturing

\textsuperscript{35} An NDA may rely on information contained in another NDA, an IND or a drug master file, subject to a right of reference from the submitter of that information. FDA regulations provide for submission of DMFs for active substances, inactive ingredients and drug packaging materials, as well as other types of information by prior agreement with the agency (21 CFR, Section 314.420).

\textsuperscript{36} Regulations governing the content and review of NDAs are set out in 21 CFR, Part 314.

\textsuperscript{37} The PDUFA sunsets every five years unless re-enacted by Congress. The most recent enactment, passed in August 2017 as part of the FDA Reauthorization Act (FDARA), is commonly referred to as ‘PDUFA VI’.

\textsuperscript{38} For fiscal year 2020, the fees are as follows: for an application containing clinical data, US$2,942,965; for an application that does not contain clinical data, US$1,471,483; and the programme fee, US$325,424.

\textsuperscript{39} Priority designation is granted if FDA determines that a drug would represent a significant improvement in the treatment, diagnosis or prevention of a disease as compared with existing therapies. There are provisions under which the sponsor of an NDA for a rare paediatric disease, a material threat medical countermeasure, or a drug for a designated tropical disease may obtain a transferable priority review voucher, which can be sold to another company to enable it to obtain priority review of a product that would not otherwise be eligible for priority review.

\textsuperscript{40} If the sponsor elects to resubmit the NDA with additional studies or other information to correct the deficiencies identified in the complete response, the FDA is ordinarily obligated to act on the resubmission within two or six months, depending on the complexity of the submission. In lieu of resubmitting the NDA, the sponsor may invoke its right to a formal evidentiary hearing, which will eventually lead to a decision by the Commissioner of Food and Drugs that can be appealed to a federal court of appeals. Sponsors rarely invoke this right because the process is time-consuming and seldom leads to a change in the outcome.
process and facilities are adequate and in compliance with requirements for the current good manufacturing practice (GMP), and that the labelling is not false or misleading. Proof of effectiveness must be based on ‘substantial evidence’ consisting of reports of adequate and well-controlled clinical investigations.41

As interpreted by the FDA, the Drug Price Competition and Patent Term Restoration Act of 1984 (often called the Hatch-Waxman Act) establishes two pathways for less-than-full applications that refer to prior approvals: ANDAs, submitted under Section 505(j) of the FDCA,42 which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2),43 which rely on the finding of safety and effectiveness for a reference product but contain clinical data or other information in support of a change (e.g., a new indication or dosage form, a new combination of active substances or a different salt or ester of an active moiety). The starting point for such submissions is an FDA publication known as the Orange Book, which lists all products subject to approved NDAs with information on relevant patents and regulatory exclusivity periods (described in more detail below).44

A generic product for which an ANDA is submitted must (1) ordinarily be the same as the reference product in terms of active ingredients, dosage form, route of administration and strength; (2) contain safe and suitable inactive ingredients; (3) bear the same labelling as the reference product except for changes owing to differences in manufacturer (e.g., in inactive ingredients or composition of the product); and (4) be bioequivalent to the reference product. ANDAs must contain full information on the composition, manufacturing process and manufacturing facilities for the generic product.

The FDA permits labelling for generic products to ‘carve out’ indications or other statements in labelling when necessary to comply with regulatory protection periods or patents for the reference product. Minor changes in dosage form (e.g., a capsule instead of a tablet) and certain other product characteristics may be accepted if their safety and effectiveness can be demonstrated solely on the basis of bioequivalence studies and they are first determined to be acceptable by means of a ‘suitability petition’ approved by the FDA.

Responding to staff shortages and major delays in the FDA review process for ANDAs, in 2012, Congress enacted user fee legislation for generic drugs. Under the reauthorisation of the Generic Drug User Fee Act enacted in 2017, the FDA will collect fees for original applications and drug master file submissions, annual programme fees for sponsors with approved ANDAs, and annual fees for certain facilities.45 There is a 10-month target for standard review of new applications, and priority review is now also available for certain generic applications.

41 Many NDAs must contain data on paediatric use, unless the FDA grants a waiver or deferral of the requirement or the application is exempt (most orphan drugs).
42 21 USC, Section 355(j).
43 21 USC, Section 355(b)(2).
44 The official name of the publication is Approved Drug Products with Therapeutic Equivalence Determinations.
45 Application fees for fiscal year 2020 are US$176,237 for new ANDAs; US$57,795 for DMFs; US$44,400 for domestic facilities that manufacture active substances; US$59,400 for foreign facilities that manufacture active substances; US$195,662 for domestic facilities that manufacture finished products; and US$210,662 for foreign facilities that manufacture finished products.
Biologics

Biological products are subject to a separate statutory approval system under Section 351 of the PHSA. Sponsors of original products submit biologics licence applications (BLAs) that contain essentially the same information as NDAs in the eCTD format. The review process is substantially the same as for NDAs and is subject to the same user fees and performance goals under the PDUFA. To be approved, products must be ‘safe, pure and potent’ and be produced in manufacturing facilities that meet standards designed to ensure that they continue to comply with these standards. The statute does not expressly require ‘substantial evidence’ of effectiveness (i.e., reports of adequate and well-controlled clinical investigations), and the FDA to an extent, therefore, has more discretion in determining whether efficacy has been demonstrated. In practice, however, the agency has ordinarily demanded the same evidence of efficacy for biologics as it expects for ordinary drugs.

In 2010, Congress enacted legislation establishing an approval process for follow-on versions of biological products, or ‘biosimilars’. Such a product must:

a. be ‘highly similar’ to a reference product ‘notwithstanding minor differences in clinically inactive components’;

b. have no clinically meaningful differences from a reference product in safety, purity or potency;

c. be labelled for a condition of use for which the reference product is approved;

d. have the same route of administration, dosage form and strength as the reference product; and

e. be manufactured in facilities designed to ensure safety, purity and potency.

The legislation contemplates that the showing of biosimilarity will ordinarily be based on analytical tests, non-clinical studies and clinical trials, but the FDA has discretion to waive any of these requirements if it finds that the data are unnecessary. Additional showings are required for the FDA to make a determination that a biosimilar product is ‘interchangeable’ with a reference product. In 2019, the FDA released final guidance describing its expectations for data and information, including from switching studies, needed to support interchangeability.

Although user fees for biosimilar applications were previously the same as those for original products, they are now subject to their own user fee framework. The FDA sets the amount of each type of biosimilar user fee via publication in the Federal Register. In addition to fees for original applications and product fees now called a ‘programme’ fee, a biosimilar developer also must pay a fee when it seeks development advice from the FDA and, thereafter, an annual fee as a biosimilar development fee. Unlike under the previous law, the initial and annual fees are no longer subtracted from the user fee due when the sponsor


47 A small number of biological products, including recombinant insulin and somatropin, were originally approved under the FDCA rather than the PHSA and were therefore eligible for submission of follow-on applications under Sections 505(b)(2) and 505(j) before the BPCIA was enacted. The FDA approved an application under Section 505(b)(2) for a follow-on version of recombinant somatropin in 2006, based on a substantial package of non-clinical and clinical data. Subsequently, the FDA has approved applications under Section 505(b)(2) for follow-on insulin analogues. In 2020, the proteins approved under the FDCA generally will transfer to the PHSA. Id. Section 7002(e).

48 FDA, Guidance, Considerations in Demonstrating Interchangeability With a Reference Product (May 2019).
submits its application. The FDA has issued final and draft guidance covering a number of issues relating to the implementation of the BPCIA and, in March 2015, approved its first biosimilar. Nevertheless, the programme is still at an early stage — for instance, the FDA has not approved any biosimilars as interchangeable with their reference products.

**Expedited programmes**

The FDCA and FDA regulations establish special procedures for the approval of drugs and biologics for serious or life-threatening diseases that provide meaningful benefits over existing therapies. For instance, pursuant to accelerated approval, effectiveness may be demonstrated on the basis of surrogate or intermediate clinical endpoints, with a commitment to carry out post-marketing studies to confirm the validity of those endpoints as predictors of clinical outcomes. The FDA may impose special restrictions on such drugs (e.g., pre-submission of promotional materials or restrictions on distribution). If post-marketing studies fail to confirm clinical benefit, approval may be withdrawn through an expedited procedure.

**Medical devices**

The pre-market clearance requirements for a device depend on the device’s class, which in turn depends on the level of risk that the device presents. Class I devices present the least risk and, generally, they are exempt from pre-market review. Class II devices present moderate risk, and most require FDA clearance of a pre-market notification under Section 510(k) of the FDCA (510(k)) prior to marketing. Class III devices — the highest-risk category — typically require approval of a PMA before marketing. Devices that have not yet been classified are automatically in Class III. For devices that present a low or moderate risk, the manufacturer can request classification into Class I or II through the de novo classification process.

To obtain clearance of a 510(k), the submitter must show that its device is ‘substantially equivalent’ to a legally marketed ‘predicate’ device. A predicate device may be a pre-amendments device, a device already cleared through the 510(k) process, or a device reclassified into Class I or II. To demonstrate substantial equivalence, the submitter must show its device has the same ‘intended use’ as the predicate device, and either has the same technological characteristics as the predicate device, or has different technological characteristics, but is as safe and effective as, and does not raise different questions of safety and effectiveness than, the predicate device. The 510(k) must contain, among other things, proposed labelling, a device description and the submitter’s rationale for concluding that the device is substantially equivalent to the predicate device. In some cases, it may need to contain clinical data. In addition to a traditional 510(k), the FDA also permits two other types of 510(k) submissions: Special 510(k) and Abbreviated 510(k).\(^{49}\) A Special 510(k) can be used when a manufacturer makes certain modifications to its own device. An Abbreviated 510(k) relies on adherence to guidance documents, special controls, and/or FDA-recognized consensus standards to demonstrate substantial equivalence and facilitate 510(k) review. The Abbreviated 510(k) and Special 510(k) programmes were originally developed in 1998, and in 2019, the FDA issued updated guidances clarifying these programmes.\(^{50}\) Also, in 2019, the

---


50. FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Abbreviated 510(k) Program (September 2019); FDA, Draft Guidance for Industry and Food and Drug Administration Staff: The Special 510(k) Program (September 2019).
FDA issued a guidance describing the Safety and Performance Based Pathway, an expansion of the concept of the Abbreviated 510(k) pathway for certain well understood device types. The FDA has issued draft guidances describing proposed performance criteria to support use of the Safety and Performance Based Pathway for spinal plating systems, cutaneous electrodes for recording purposes, conventional Foley catheters, orthopaedic non-spinal metallic bone screws and washers and magnetic resonance coils. The submitter of a 510(k) must pay a modest user fee for the submission. By statute, the FDA must act on 510(k) notifications within 90 days and the FDA has agreed to performance goals for acting on them. The submitter may not market the device until the FDA has ‘cleared’ the 510(k) notification, even if the FDA misses the applicable deadline.

For low and moderate risk devices that lack an appropriate predicate or where the FDA determines that a 510(k) submission has not demonstrated the device is substantially equivalent to the predicate device, the submitter may submit a de novo classification request. If the FDA grants the request, the agency will classify the device into Class I or Class II and authorise the marketing of the device (which then also serves as a predicate device for subsequent 510(k) submissions). The statute calls for the FDA to rule on a de novo request within 120 days, although historically the time to FDA action was often up to a year. FDARA added a user fee for de novo requests, and the FDA agreed to corresponding performance goals for the agency’s review. In December 2018, the FDA issued a proposed rule to implement the de novo classification process. The proposed rule largely aligns with the agency’s existing guidance on the submission and review of de novo requests.

The PMA pathway has some similarities to the NDA pathway for drugs. The PMA must contain manufacturing information, information regarding the device components and principles of operation, proposed labelling and full reports of all information regarding investigations conducted to assess the device’s safety and effectiveness. The PMA must contain valid scientific evidence, which typically requires clinical trial data, demonstrating the safety and effectiveness of the device, and the applicant must pay a substantial user fee. To be approved, the application must show that there is a reasonable assurance that the device is safe and effective for the proposed conditions of use. The FDA generally refers PMAs for novel devices to an advisory panel for review and input. As with NDAs, the FDA agrees to performance goals for acting on PMAs. Action may take the form of an approval or a deficiency letter.

In April 2015, the FDA published a final guidance proposing a voluntary programme to expedite access to devices that ‘demonstrate the potential to address unmet medical needs for life-threatening or irreversibly debilitating diseases or conditions’ and are subject either to PMAs or de novo classification requests. The 21st Century Cures Act, enacted in December 2016, amended the FDCA to establish a new priority review programme for ‘breakthrough’

51 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Safety and Performance Based Pathway (September 2019).
54 FDA, Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (October 2017).
55 FDA, Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions (April 2015).
devices, formally codifying and expanding the programme described in the agency’s final guidance. A device subject to a PMA, de novo classification or 510(k) may qualify as a breakthrough device if it represents a breakthrough technology or offers the potential, compared to existing alternatives, to reduce or eliminate the need for hospitalisation, improve patients’ quality of life, facilitate patients’ ability to manage their own care, or establish long-term clinical efficiencies. The programme, which was modelled partly on the expedited programmes for medicines, features more interactive communications with the agency during device development. The FDA published final guidance on the breakthrough devices programme in December 2018.\(^\text{56}\)

The FDA also may reclassify devices under a procedure that was streamlined in the FDASIA. Prior to the FDASIA, the FDA use notice-and-comment rule-making to recategorize devices, and this proved burdensome. As amended by the FDASIA, the statute permits the FDA to reclassify a device by administrative order ‘[b]ased on new information respecting [the] device’ and ‘following publication of a proposed reclassification order in the Federal Register, a meeting of a device classification panel [. . .] and consideration of comments to a public docket’.\(^\text{57}\) Although this language suggests the three activities must occur in chronological order, in a proposed rule to amend the governing regulations to conform to the FDASIA, among other things, the agency stated: ‘The panel meeting must occur before the final order is published, and may occur either before or after the proposed order is published.’\(^\text{58}\)

vi Regulatory incentives

Drugs

The United States has established a complex series of regulatory incentives to encourage the development of innovative medicines and follow-on products. These may be best explained in their chronological order of enactment.

The Orphan Drug Amendments to the FDCA, originally passed in 1983, establish incentives for development of drugs and biologics to treat rare diseases, including a seven-year period of market exclusivity (i.e., protection against approval of the same drug for the same indication). Orphan drug designations may be granted on the basis of prevalence (i.e., that the drug is intended for a disease that affects fewer than 200,000 persons in the United States) or an economic criterion (which has rarely been applied in practice). The FDA recently revoked one of the few orphan-drug designations granted on the economic basis many years after its initial grant and based on a conclusion that it erred in granting the designation.\(^\text{59}\) FDA regulations establish detailed criteria for determining when competitive products may be approved during the orphan exclusivity period, including rules for determining when subsequent products are not the ‘same’ as first entrants (e.g., because of differences in the composition of their active substances or because they are clinically superior).\(^\text{60}\) As part of FDARA, Congress codified the FDA’s practice of requiring an applicant seeking orphan-drug exclusivity for a drug that is the ‘same’ as a previously approved drug to show clinical

\(^{56}\) FDA, Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program (December 2018).

\(^{57}\) FDASIA, Section 608 (amending FDCA, Section 513(e)).


\(^{60}\) See 21 USC, Sections 360n-360ff; 21 CFR, Part 316.
superiority to that prior drug, even if the prior drug never had orphan-drug exclusivity or it expired.\(^{61}\) Litigation pending before the United States Court of Appeals for the DC Circuit raises the issue of whether the FDA can apply the clinical superiority requirement to a product designated and approved before enactment of FDARA; the district court had ruled that the FDA must recognize orphan-drug exclusivity without proof of clinical superiority in this case.\(^{62}\)

The Hatch-Waxman Act establishes several incentives for development of original products, as well as a significant incentive for development of certain follow-ons. First, the statute provides for patent term extensions to restore a portion of the patent life that is lost during clinical development and FDA review of new drugs and biological products. Credit is given for half the time spent in the IND process and all of the time spent in the NDA or BLA review process (subject to a reduction for any period during which the applicant was not pursuing development with due diligence), with a maximum extension of five years and a maximum effective patent life, following FDA approval, of 14 years.\(^{63}\)

Second, the statute provides for periods of data exclusivity (i.e., protection against submission or approval of ANDAs and Section 505(b)(2) applications) for original products approved under the FDCA. New chemical entities (NCEs) receive a five-year protection period, while changes in approved products (e.g., new indications or dosage forms) and approvals of non-NCE drugs receive three years if they are required to be supported by clinical investigations other than bioequivalence studies. Except as noted below, follow-on applications for NCEs may not be submitted until expiry of the five-year period, so that the effective period of protection includes the time required for review and approval of a follow-on product. Follow-on applications relating to changes in approved products or non-NCE drugs can be submitted during the three-year period but approvals cannot be made effective for the innovator drug's conditions of approval until the period expires.\(^{64}\) The FDA was recently involved in litigation addressing the meaning of 'conditions of approval'.\(^{65}\) In a decision on remand, the FDA construed this phrase to mean the innovative change for which the new clinical investigations were essential for approval of the active moiety, which the FDA determines principally by asking what unique clinical question or questions about the moiety's safety or effectiveness did the clinical investigations answer for the first time?\(^{66}\)

Third, the statute contains complex provisions linking the approval of follow-on products to patents for reference drugs approved under the FDCA. Sponsors of original products are required to submit patent information for their products, including expiry dates, which the FDA includes in the Orange Book. Sponsors of follow-on products are required to make one of four patent certifications:

- \(a\) that no patents are listed for the reference product;
- \(b\) that all listed patents have expired;
- \(c\) that a patent is listed and has not expired, but the applicant wishes that approval of its product be made effective upon expiry; or

---

63 35 USC, Section 156.
64 21 USC, Section 355(j).
that the listed patent is invalid or unenforceable or will not be infringed by the applicant’s product.

Submission of a certification under the last provision (a ‘Paragraph IV’ certification) has two consequences: if the reference product is an NCE with an unexpired period of data exclusivity, the follow-on application may be submitted at the end of the fourth year following approval of the original product, instead of the fifth year; and the follow-on applicant must submit a notification to the patent holder (and NDA sponsor) for the reference product, including a statement of reasons why the patent is invalid or unenforceable or will not be infringed. Submission of a follow-on application with a Paragraph IV certification is deemed an act of infringement under the patent laws, and if the patent holder initiates an infringement action within 45 days of receiving the notification, approval of the follow-on product is stayed for 30 months or until the court rules that the patent is invalid, unenforceable or not infringed.67

Finally, the Hatch-Waxman Act provides for a 180-day period of generic marketing exclusivity for the first ANDA applicant that submits a substantially complete application that contains and lawfully maintains a Paragraph IV certification. The provision, which was intended to create an incentive to challenge patents for reference products and clear the way for early entry of generic products, has been complicated to administer in practice, and the rules have been modified to reduce the potential for abuse or other unintended results.

Legislation originally enacted in 1997, as part of the FDA Modernization Act, provided regulatory incentives for paediatric studies of drugs. An applicant that carries out such testing in compliance with a written request from FDA can receive a six-month extension of every form of regulatory exclusivity pertaining to its product, including five-year and three-year exclusivity under Hatch-Waxman, seven-year orphan-drug exclusivity and protection against approval of ANDAs or Section 505(b)(2) applications after patent expiry.68

The Generating Antibiotic Incentives Now Act, which was included in the FDASIA, established procedures under which certain new antibacterial or antifungal drugs intended for serious or life-threatening infections can receive five-year extensions of the four-year, five-year and three-year exclusivity under the Hatch-Waxman Act and seven-year orphan-drug exclusivity.69

**Biologics**

Under the BPCIA, applications for biosimilar products may not be filed until four years, and may not be approved until 12 years, after first licensure of the reference product. Those periods can be extended by six months if the sponsor of the reference product licence carries out paediatric studies in compliance with an FDA request. A ‘first licensure’ provision limits availability of new exclusivity periods for modified versions of previously authorised reference products. In general, it allows for a new exclusivity period when the licence application for the subsequent product is submitted by an entity that is not related to the sponsor of the earlier product, or when the subsequent product differs from the earlier product in structure and in safety, purity or potency. In July 2018, the FDA sought public comment on whether

---

67 If the Paragraph IV notification is submitted before the end of the fifth year following approval of the reference product, the period of the stay is adjusted so that the follow-on product may not be approved until seven-and-a-half years after the approval of the reference product.

68 21 USC, Section 355a.

69 21 USC, Section 355f.
it should adopt an ‘umbrella’ exclusivity policy for biologics as it has for drugs. Under such a policy, new uses, dosage forms and other modifications to exclusivity-protected products that do not independently qualify for reference product exclusivity will benefit from the balance of reference product exclusivity on the first-licensed product.

The BPCIA does not provide for patent linkage of the type established by the Hatch-Waxman Act, but it does contain provisions for exchange of information between sponsors of biosimilar and reference products and early resolution of some patent issues. In a June 2017 opinion, the United States Supreme Court interpreted the BPCIA’s information-sharing provision as not enforceable by injunction under federal law and remanded to the Federal Circuit to determine whether a state law injunction was available. The Supreme Court also held that a biosimilar applicant may give notice of commercial marketing contemplated by the BPCIA before the FDA licenses the biosimilar. In December 2017, the Federal Circuit held that the BPCIA pre-empts state law remedies for a biosimilar applicant’s failure to comply with the BPCIA’s information sharing provision.

**Devices**

A six-year regulatory exclusivity period applies to devices approved pursuant to PMAs. After that exclusivity period expires, the FDA may use safety and effectiveness data in a PMA, but not trade secrets, to approve another device, establish special controls for a class of devices, or classify or reclassify other devices, inter alia. However, in practice, given the nature of innovation for devices, device manufacturers very rarely seek to rely on data in another approved PMA and this exclusivity period typically does not have a significant impact on the submission of subsequent PMAs for similar technologies. Patent term extension is also available for PMA-approved devices.

The humanitarian device exemption (HDE), rather than regulatory exclusivity, is available for sponsors of devices for rare diseases or conditions. It exempts the device from compliance with the effectiveness requirements of Section 515 of the FDCA, relating to PMA approval, and Section 514, relating to performance standards. To qualify, the sponsor must show that the device (1) is intended for diagnosis or treatment of a disease or condition affecting fewer than 8,000 individuals in the United States; (2) will not be available to these patients without the exemption, and no comparable device (other than another a humanitarian use device (HUD)) is available for them; and (3) will not expose patients to an ‘unreasonable or significant risk of illness or injury’, and the probable benefit from using the HUD outweighs its risks. IRB approval is required before use of HUDs. Sponsors may charge a commercial, rather than cost-recovery, price for an HUD intended for use in a paediatric population or subpopulation, or a disease or condition that is very rare or non-existent in children, if certain conditions are met. For example, the number of devices distributed annually cannot exceed the ‘annual distribution number’ (i.e., the number of devices reasonably needed to treat, diagnose or cure 8,000 people in the United States).

---

vii  Post-approval controls

Drugs

FDA regulations establish requirements for the reporting of adverse events associated with approved drugs and biologics, including expedited (15-day) reports of serious, unexpected events as well as periodic adverse drug experience reports (PADERs). In lieu of PADERs, the FDA will grant waivers to permit submission of periodic safety update reports (PSURs) in the CIOMS\(^73\) format as well as the more recent ICH format for periodic benefit risk evaluation reports. Special rules apply to reports of adverse events associated with non-prescription products that are marketed under OTC drug monographs rather than NDAs.

Holders of approved NDAs and BLAs must also submit reports when they discover defects in products released for commercial distribution. The criteria for making such reports and the deadlines and procedures for their submission are different for drugs and biologics.\(^74\) Manufacturers of approved drugs and biologics are also required to notify the FDA of discontinuance or certain interruptions in production of life-supporting and life-sustaining drugs, as well as drugs ‘intended for use in the prevention or treatment of a debilitating disease or condition,’ and NDA and ANDA holders are subject to an additional notification requirement for product withdrawals and products not available for sale.\(^75\)

As part of the approval process, the FDA can impose requirements for risk evaluation and mitigation strategies (REMS), which may include special labelling or ‘elements to assure safe use’, such as patient testing and restricted distribution. The effectiveness of the REMS must be periodically evaluated after approval. The FDA can also impose requirements for post-marketing tests and changes in certain labelling of approved drug products. Sponsors may invoke informal dispute resolution procedures to challenge imposition of these requirements, but there is no provision for formal hearings.

BLAs may impose requirements for testing and certification of each batch of a biologic by the FDA before it can be released for commercial use. These requirements are imposed on many vaccines and certain other products regulated by the CBER.

FDA regulations establish detailed rules for changes in products that are subject to approved NDAs or BLAs.\(^76\) Major changes (e.g., addition of new indications, new manufacturing facilities or significant changes in the manufacturing process) require submission and approval of a supplemental NDA or BLA (a prior approval supplement (PAS)). Less significant changes can be made after submission of a changes-being-effected supplement; in some cases, the applicant is required to wait 30 days before implementing a change, but certain changes can be made immediately upon submission.\(^77\) Minor changes (e.g., minor editorial changes in labelling) can be notified in annual reports to the NDA or

\(^73\) Council for International Organizations of Medical Sciences.
\(^74\) 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).
\(^75\) 21 USC, Section 356c, 356i; 21 CFR Section 600.82.
\(^76\) 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).
\(^77\) The regulations permit sponsors to add or strengthen a contraindication, warning, precaution or adverse reaction to the prescribing information without prior approval from FDA, provided there is reasonable evidence of a causal relationship to the drug (21 CFR, Sections 314.70; 601.12(f)(2)). The FDA traditionally advised that this regulation did not apply to generic drugs, because their labelling must be the same as that of reference products. In 2013, however, the agency proposed amendments to its regulations that would establish a procedure for generic manufacturers to add new safety information to the labelling for their products (78 Fed. Reg. 67985 (13 November 2013)). The FDA subsequently withdrew the proposal. 83 Fed. Reg. 64299 (14 December 2018).
BLA file. For drugs, the FDA has issued detailed guidance on classification of changes in the quality aspects of products (manufacturing facilities, manufacturing processes, components, containers, etc.), and in 2017 released draft guidance which addresses this topic for certain biologics.78

Ownership of NDAs can be transferred by submission of a letter to the FDA, although related changes may require supplemental applications, including prior approval supplements for new manufacturing facilities. Transfer of ownership of BLAs is somewhat more complex and typically requires prior consultation with the FDA, as well as supplemental applications for related changes.

Under the provisions of the FDCA, the FDA cannot ordinarily withdraw approval of an NDA without first affording the sponsor notice and an opportunity for an administrative hearing, a process that can last several years. The Secretary of Health and Human Services can, however, suspend approval of a drug pending completion of the required administrative hearing, if it is determined that the drug presents an imminent hazard to public health.79 Although the PHSA does not contain provisions governing revocation of BLAs, FDA regulations establish a system that is similar to the one for NDAs: the sponsor is ordinarily entitled to notice and an opportunity for a hearing, but the licence may be suspended if there is a danger to health. In practice, when significant safety issues arise, sponsors often withdraw products from the market voluntarily in response to a request from the FDA.

Special procedures apply to drugs and biologics authorised under the accelerated approval procedure (e.g., on the basis of surrogate endpoints). If required post-marketing studies fail to confirm the safety or effectiveness of such a product, the FDA can withdraw approval after an informal hearing before a specially constituted advisory committee.

Devices

The FDCA’s ‘general controls’ apply to all devices, including Class I devices exempt from pre-market review.80 The general controls include prohibitions on adulteration and misbranding, as well as requirements for device labelling, establishment registration and device listing and for compliance with the FDA’s medical device reporting (MDR) regulations and the quality system regulation (QSR).

Under the MDR regulations, a manufacturer must file a report if it becomes aware of information that reasonably suggests that its marketed device may have caused or contributed to a death or serious injury, or malfunctioned, and recurrence of this malfunction in the device (or any similar device marketed by the manufacturer) would be likely to cause or contribute to a death or serious injury.81 Importers must report deaths and serious injuries to the FDA and the manufacturer, and they must report malfunctions to the manufacturer. User facilities must report deaths to the FDA and the manufacturer, but need to report only

80 Some Class I devices are exempt from certain elements of the quality system regulation.
81 21 CFR, Section 803.50(a).
serious injuries to the manufacturer. Manufacturers must make their reports within 30 days of becoming aware of the information, although this is shortened to five days for events that require remedial action to prevent an unreasonable risk of substantial harm to public health.82 Importers must complete their reports within 30 days; for user facilities, the deadline is 10 days.83 In November 2016, the FDA issued a final guidance document on MDR reporting for manufacturers, which generally takes a broad view of the situations in which reporting is appropriate.84 Also, in December 2016, the FDA issued a final guidance describing when and how the agency will provide public notice of emerging post-market safety signals for devices.85

The FDA also requires manufacturers and importers to report certain corrections and removals of devices in the field within 10 working days of initiating the action. Corrections include actions taken to repair, relabel, destroy or remediate a device at its point of use, whereas removals involve the physical removal of the device from its point of use to some other location for remediation or destruction.86 These actions are reportable if taken ‘to reduce a risk to health posed by the device’ or ‘to remedy a violation of the act that may present a risk to health’.87 In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.88

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.89 The agency may also establish a performance standard for a Class II or Class III device, under Section 514 of the FDCA, if the agency determines that such a standard is appropriate and necessary to provide reasonable assurance of the safety and effectiveness of the device. The FDA also may impose ‘special controls’ for Class II devices, which may include performance standards, patient registries and guidelines for the submission of clinical data in 510(k)s. The FDA also finalised regulations generally requiring the labels of devices to bear a unique device identifier.90

Different frameworks apply to post-approval changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.91 Major changes (i.e., those affecting safety or effectiveness) require approval of a PMA supplement. Certain other changes, including some labelling changes and some manufacturing changes, may be implemented with prior notice to the FDA. Other changes may be reported in periodic reports that are required as a condition of device approval. A different approach applies to 510(k)-cleared devices. Some modifications to these devices may be made without submitting a new 510(k), provided that the manufacturer documents the changes in a ‘letter to file’. Others require a new pre-market notification (not a supplement); certain modifications may

82 21 CFR, Section 803.40.
83 21 CFR, Section 803.10.
84 FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device Reporting for Manufacturers (November 2016).
85 FDA, Guidance for Industry and Food and Drug Administration Staff: Public Notification of Emerging Post-market Medical Device Signals (December 2016).
86 21 CFR, Section 806.2(d) and (i).
87 21 CFR, Section 806.10(a).
88 FDA, Distinguishing Medical Device Recalls from Medical Device Enhancements: Guidance for Industry and Food and Drug Administration Staff (October 2014).
89 FDCA, Sections 519(e), 522.
91 See 21 CFR, Section 814.39.
be submitted in a Special 510(k) rather than a traditional 510(k). Changes that require a new 510(k) are those that ‘could significantly affect the safety or effectiveness of the device’ (such as a major modification to the device’s design) or that involve a major change to the device’s intended use.92 In October 2017, the FDA issued two final guidances describing how manufacturers should determine whether a new 510(k) should be submitted for change to an existing device.93

As with drugs, ownership of PMAs may be transferred upon letter notification to the FDA. If the changes affect device safety or effectiveness or the conditions of approval, the new owner must obtain approval of a PMA supplement before marketing. In December 2014, the FDA published draft guidance regarding the procedures for notifying the FDA of a 510(k) transfer via compliance with the device-listing requirements.94

The FDA has statutory authority to withdraw approval of PMAs, IDEs and HDEs and to suspend an HDE approval after providing notice and an opportunity for a hearing.95 The FDA also may temporarily suspend approval of a PMA and an HDE pending completion of withdrawal proceedings in certain situations where there are serious risks to public health. The FDA has taken the position that it can rescind clearance of a 510(k) notification, although there is no specific statutory or regulatory basis for this position, and in 2001, the agency published a proposed rule describing when FDA may rescind a 510(k) clearance.96 In 2011, a device manufacturer challenged the FDA’s claimed authority in court. The district court found that the FDA has inherent authority to rescind a 510(k) clearance in ‘rare situation[s]’, if the agency acts within a ‘reasonable time’ and upheld the FDA’s rescission in that case, emphasising its conclusion that ‘procedural irregularities’ occurred throughout the clearance process for the device in question.97 On appeal, however, the DC Circuit Court of Appeals reversed. The Court reasoned that, because rescission of the 510(k) clearance resulted in automatic reclassification of the device into Class III, the FDA had to follow the statutory reclassification procedure rather than revoking the 510(k) based on claimed inherent rescission authority.98

viii Manufacturing controls

Drugs

Facilities that manufacture drugs or biologics for distribution in the United States, including foreign facilities, must be registered with the FDA, but the procedure is ministerial and there is no requirement for a manufacturing authorisation. NDAs and BLAs contain detailed information on manufacturing facilities, which are normally inspected by the FDA before marketing authorisations are granted. All facilities that manufacture drugs or biologics

92 21 CFR, Section 807.81(a)(3).
93 FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (October 2017); FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Software Change to an Existing Device (October 2017).
94 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Transfer of a Premarket Notification (510(k)) Clearance – Questions and Answers (December 2014).
95 21 USC, Sections 360e(e), 360j(g)(5), 360j(m)(5).
98 Ivy Sports Medicine, LLC v. Burwell, 767 F.3d 81, 87 (D.C. Cir. 2014).
(including ‘old’ drugs, such as monograph OTCs, for which prior approval is not required) must comply with regulations governing current GMP, which are supplemented by detailed guidances. Transfer of ownership of drug manufacturing facilities does not normally require prior approval from the FDA, but changes must be made in establishment registrations, and other changes resulting from a transfer of ownership may require supplemental applications for products made in an establishment.

**Devices**

The FDA also requires establishment registration for device facilities through a ministerial procedure. Devices must be manufactured in accordance with the FDA’s QSR, which includes provisions governing design control and validation, and GMP. PMAs must contain a detailed description of methods, facilities and controls used in manufacturing the device. The FDA frequently also conducts a pre-approval inspection of the manufacturing facility. In contrast, 510(k)s need not contain detailed manufacturing information, and their submitters typically do not undergo pre-market inspections. For PMAs, transfer of ownership of the manufacturing facility may require a PMA supplement. For 510(k)-cleared devices, the manufacturer must assess whether a facility change requires a new 510(k) (i.e., whether the change could significantly affect the device’s safety or effectiveness).

**ix Advertising and promotion**

**Drugs**

The FDA regulates advertising and promotional labelling for prescription drugs. Detailed rules govern the content of advertisements, including requirements for fair balance, adequate substantiation of claims, consistency with the approved prescribing information, inclusion of a ‘brief summary’ of the prescribing information and prominent disclosure of the non-proprietary name of the drug product. There is an exemption from some of these requirements for ‘reminder’ advertisements, which do not make claims; drugs with serious side effects for which ‘boxed warnings’ are required may not take advantage of this exemption.

Promotional labelling (e.g., brochures and similar materials used by sales representatives) is subject to similar requirements, except that the full prescribing information (in lieu of the brief summary) must accompany all such labelling (except for reminder labelling).

Direct-to-consumer (DTC) advertising of prescription drugs is permitted in the United States. Print advertisements must fully comply with the general rules on prescription drug advertising, using language that is understandable to the ordinary person. Broadcast advertisements, including television advertisements, must maintain fair balance, provide important safety information and incorporate mechanisms by which listeners or viewers can obtain complete information (e.g., websites, print advertisements or other measures). Although FDA pre-clearance of DTC advertisements is not ordinarily required, companies often submit television advertisements for FDA review prior to use.

---

99 21 CFR, Parts 210, 211.
100 21 CFR, Part 820.
101 21 CFR, Section 814.20(b)(4)(v).
102 21 CFR, Section 814.39(a)(3).
Oral statements by sales representatives and other agents of drug manufacturers may be taken as evidence of the intended uses of a drug product. If those statements recommend uses that are not included in the approved prescribing information, the FDA will take the position that the drug product is misbranded (and therefore in violation of the FDCA) because its labelling does not include adequate directions for such uses.104

The FDA maintains a number of policies that are intended to permit ‘free exchange’ of scientific information relating to unapproved drug products or new uses for approved products (e.g., drug company support for continuing medical education programmes for healthcare professionals, as well as responses to unsolicited requests from healthcare professionals for information on unapproved uses of drug products); it also permits disease awareness communications that do not promote specific drugs. In recent years, there has been growing concern that the agency’s policies prohibit drug companies from communicating truthful, non-misleading information concerning research on new uses for approved drug products, and that this prohibition infringes the right of freedom of speech guaranteed by the First Amendment to the US Constitution. Under pressure from the federal courts, the FDA has adopted guidance that permits drug companies to distribute reprints of articles from peer-reviewed medical journals and independent medical texts that contain information on unapproved uses of approved drug products.105 Decisions by the US Supreme Court in 2011,106 an influential federal court of appeals in 2012,107 and a federal district court in 2015,108 have clearly established the principle that communication of truthful, non-misleading information about unapproved uses of approved drugs and devices is protected by the First Amendment, and the FDA has issued guidance documents that are partly responsive to those decisions.109

The FDA regulates the labelling of non-prescription drug products, including brochures and point-of-purchase materials. These must be consistent with the terms of approved NDAs or applicable OTC drug monographs, and they must not contain false or misleading information. The FTC regulates the advertising of non-prescription drugs under general

104 See 21 USC, Section 352(f)(1) (requiring that drugs bear adequate directions for use); 21 CFR, Section 201.100 (requiring that the labelling for prescription drugs contain adequate directions for all purposes for which they are ‘intended’); and 21 CFR, Section 201.128 (defining the meaning of ‘intended uses’ to include all expressions of the objective intent of the seller, including oral or written statements).


106 Sorrell v. IMS Health Inc, No. 10-779, 131 S. Ct. 2653 (2011). The decision invalidated a state law that prohibited pharmaceutical marketing research companies, but not other persons, from collecting information from pharmacists on physician prescribing practices.

107 United States v. Caronia, 703 F. 3d 149 (2d Cir. 2012). The court reversed the conviction of a pharmaceutical sales representative for ‘misbranding’ an approved drug product by presenting information on unapproved uses in a conversation with a physician, where there was no allegation that the information was false or misleading.


109 The FDA held a two-day hearing in December 2016 to receive information from industry and the general public on regulation of off-label claims for approved drugs and devices. See 81 Fed. Reg. 60299 (1 September 2016). In January 2017, the FDA issued draft guidance documents on communications that are consistent with approved labelling for drugs and devices with communications with payers. In June 2018, FDA issued revised final versions of the guidance. FDA, Guidance for Industry and Review Staff, Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities - Questions and Answers (June 2018); FDA, Guidance for Industry, Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers (June 2018).
provisions of the Federal Trade Commission Act that prohibit unfair or deceptive practices in commerce and special provisions that govern false advertising of drugs. The FTC requires prior substantiation for claims as to the safety or effectiveness of non-prescription drugs.

**Devices**

The FDA and the FTC also share responsibility for regulating advertising and promotion of non-restricted devices. The FTC regulates their advertising and the FDA regulates their labelling (including promotional labelling). With respect to restricted devices, the FDA regulates both labelling and advertising.

The FTC’s approach to regulation of device advertising is parallel to its approach to regulating OTC drug advertising. The FTC focuses its efforts on ensuring that advertising claims are not deceptive and are substantiated by competent and reliable evidence.\(^{110}\) Similarly, the principles for the FDA’s regulation of device promotion and restricted device advertising are generally consistent with those for regulation of drug promotional labelling and advertising.\(^{111}\) For example, device promotional materials must be consistent with the device labelling and cannot promote the product for an unapproved or uncleared intended use. Important differences include a ‘valid scientific evidence’ standard for substantiation (rather than ‘substantial evidence’) and the lack of an express requirement for ‘fair balance’ in the regulations.\(^{112}\) Device promotion remains subject to the statutory prohibitions on false and misleading representations, however.\(^{113}\) The new guidances mentioned above also apply to device promotion.

**Distributors and wholesalers**

The FDA does not license distributors or wholesalers, but warehouses and distribution facilities used for drug products may be inspected for compliance with applicable requirements of GMP. Many states impose requirements for the licensing of pharmaceutical distributors and distribution facilities, and the FDA has issued guidelines for those states.\(^{114}\)

The FDA regulations implementing the Prescription Drug Marketing Act establish a number of requirements that apply to manufacturers, wholesalers and distributors, including provisions governing distribution of samples and drugs supplied to charitable institutions, documentation of the chain of distribution and requirements for manufacturers to maintain lists of authorised distributors.\(^{115}\) The Drug Supply Chain Security Act, signed in November 2013, provides for an electronic system to track and trace prescription drug products, to be implemented by the FDA over a 10-year period.

**Classification of products**

The FDCA establishes two legal classifications of drug products: prescription drugs, which can be dispensed or administered only on the prescription of or under the supervision of a physician or other licensed practitioner, and non-prescription (or OTC) drugs. There is

---

\(^{110}\) Michael S Labson, ‘Regulation of Advertising, Promotion, and Distribution of Drugs, Medical Devices, and Biologics’, Section 6.1.3, in Fundamentals of Life Sciences Law.

\(^{111}\) id.

\(^{112}\) id.

\(^{113}\) 21 USC, Sections 502(a) and (q).

\(^{114}\) 21 CFR, Part 205.

\(^{115}\) 21 CFR, Part 203.
no federal ‘third class’ of pharmacy-only non-prescription drugs. Some FDA officials have suggested that the process for switching drugs from prescription to OTC status might be facilitated if the agency had the authority to impose additional conditions on newly switched products, perhaps including a transition period during which they were available only after consultation with a pharmacist, but no concrete measures have been proposed.116 For prescription drugs, elements to ensure safe use, established as part of FDA-imposed REMS, can limit use of a product to certain medical specialties or settings (e.g., hospitals).

Devices, like drugs, may be limited to prescription status. The FDA may also classify a device as restricted and thus limit access and distribution of the device, if ‘there cannot otherwise be reasonable assurance of its safety and effectiveness’.117 Possible restrictions include training requirements for users, limiting use to certain facilities, and labelling requirements. The FDA may impose these restrictions by regulation or through a PMA approval order. Special controls for Class II devices may also limit sale, distribution or use of the device.

xii Imports and exports

The FDCA includes a limited exemption under which certain drugs, biologics and devices that do not fully comply with requirements for sale in the United States may be imported for the purpose of further processing and re-export. Otherwise, imported drugs and devices must fully comply with requirements for shipment in domestic commerce. If they are deemed adulterated or misbranded, or if they fail to comply with a requirement for pre-market clearance, they may be detained at the point of entry, and the FDA can issue import alerts that effectively block entry of a product to the United States. The importer of a detained product has the right to an informal hearing before local FDA officials, but in practice, the agency has great discretion in the use of the import detention power.

The FDCA includes complex provisions governing the export of drugs and devices that do not comply with requirements for shipment in domestic commerce. If such products are ‘adulterated’ or ‘misbranded’, they may be exported provided that they comply with the specifications of the foreign purchaser, do not conflict with the law of the country to which they are exported, are labelled for export and are not reintroduced into domestic commerce.118 The FDA has interpreted these provisions to impose requirements for record-keeping and other forms of documentation.

Exports of products that do not comply with requirements for FDA pre-clearance (e.g., NDAs and PMAs) are subject to much more elaborate rules.119

---

116 The FDA has approved one product (Plan B, an emergency contraceptive) for OTC use by women 17 years of age or older and as a prescription product for younger patients; in practice, both versions of the product are sold only in pharmacies. In 1985, Florida enacted a law that established a list of prescription drugs that could be dispensed by pharmacists without a physician’s prescription; but the procedure was seldom used, and the law was later repealed.

117 21 USC, Section 360j(e).

118 21 USC, Section 381(e).

119 21 USC, Section 382. See FDA Guidance for Industry: Exports under the FDA Export Reform and Enhancement Act of 1996 (23 July 2007). The FDA takes the position that foreign trade zones, which are exempt from customs requirements, are within the territory of the United States for purposes of the FDCA. Thus, goods that are produced within a foreign trade zone can only be exported in compliance with the provisions of the FDCA. See United States v. Yaron Laboratories, 365 F. Supp. 917 (N.D. Calif. 1972); FDA Compliance Policy Guide Sec. 110.200.
xiii  Controlled substances

Narcotics, psychotropics and other drugs that are liable to abuse are regulated under the Controlled Substances Act, which is administered by the DEA in the Department of Justice. Substances are assigned to one of five schedules under the statute, which determines the level of controls to be imposed. Schedule I comprises substances (e.g., heroin) that have a high potential for abuse and no currently accepted medical use in the United States, while Schedules II to V include substances with accepted medical uses and decreasing potential for abuse. The DEA issues licences for the manufacture, import, export, distribution, prescribing and dispensing of controlled substances and imposes requirements for security and record-keeping measures to protect against diversion of controlled substances. For certain controlled substances, the DEA issues import and manufacturing quotas based on estimates of legitimate medical needs. DEA agents inspect licensed facilities, and the statute includes multiple enforcement measures, including provisions for seizures of unlawful products and criminal prosecutions.

Companies that are developing new chemical entities with a potential for abuse inform the FDA at the time of submission of an IND or NDA. The FDA then makes a recommendation to the DEA for the appropriate scheduling of the product, although the actual rule-making to include a new substance in a schedule under the statute is conducted by the DEA.

In recent years, there have been significant developments relating to the legal status of cannabidiol (CBD) products in the United States, which now depends on the product’s intended use, the product source and where the product is sold.

120 21 USC, Section 801 et seq.

121 The FDA has required applicants to agree not to market new drugs containing controlled substances until the DEA issues a final scheduling regulation. In recent years, the DEA process has often not been completed until months after FDA approval, thus delaying access to the new drug and effectively depriving the applicant of the value of a portion of any period of market exclusivity. This led one manufacturer to sue the FDA, demanding a proportionate extension of its market exclusivity period, but the court ruled in the FDA’s favour. *Eisai Inc v. FDA*, Case No. 1:14-cv-01346-RCL, 2015 WL 5728882, at *12 (D.D.C. 30 September 2015). On 25 November 2015, however, Congress enacted legislation providing that approval of the NDA will not take effect until the DEA issues an interim final rule scheduling the drug. The legislation also imposes a 90-day deadline for the DEA’s scheduling action running from the later of (1) the date when the DEA receives the FDA’s scheduling recommendation, or (2) the date when the DEA receives notification that the FDA has approved the drug. Pub. Law No. 114-89 (2015).

122 There is one cannabidiol product approved for sale as a drug in the United States, and it remains a Schedule V controlled substance unless and until the DEA takes administrative action to reschedule the substance. Whether a person may sell a CBD product as a food, dietary supplement, cosmetic, or consumer product depends on federal and state law. Some CBD products are schedule I controlled substances and are prohibited from general commercial sale. On 20 December 2018, the Agricultural Improvement Act of 2018 (the Farm Bill) effectively descheduled CBD products derived from cannabis sativa containing no more than 0.3 per cent THC, but CBD derived from cannabis with more than 0.3 per cent THC remains a schedule I controlled substance. Pub. L. No. 115-334 (2018). Separately, the FDA restricts sales of CBD products as food or dietary supplement for humans and animals in the United States. The FDA takes the position that CBD was not used in dietary supplements or foods before the start of substantial drug clinical investigations on CBD and thus, is excluded from use in dietary supplements and foods under particular provisions of the FDCA. The FDA has indicated that it is considering whether it should issue a regulation allowing the use of CBD in a food or dietary supplement, but, until that time, the FDA’s position remains unchanged. See the FDA, FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD), https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-
Enforcement

The principal formal enforcement measures under the FDCA are seizures of non-complying goods, injunction actions to restrain future violations and criminal prosecutions. The FDA lacks authority to initiate these actions on its own, but must refer them to the Department of Justice. The statute has been interpreted to impose strict criminal liability for a misdemeanour (i.e., charges can be lodged against any person who stands in a responsible relationship to the enterprise that causes the violation, with no requirement for proof of intent, negligence or other form of mens rea).\textsuperscript{123} Felony penalties may be imposed subject to proof that a violation was committed with the intent to defraud or mislead or upon a second conviction for a strict liability offence.\textsuperscript{124} The FDA also has authority to impose civil monetary penalties for certain violations of the FDCA and the PHS Act, subject to judicial review in the federal courts. In practice, the FDA relies heavily on informal enforcement measures, including regulatory correspondence (‘warning’ and ‘untitled’ letters). The agency also issues public health alerts and other announcements to the news media that can have significant commercial effects on the products and companies to which they relate.

Investigations of pharmaceutical and medical device companies by the Department of Justice, often prompted by whistle-blower actions under the federal False Claims Act, have led to major civil and criminal penalties, in many cases based in whole or in part on alleged violations of the FDCA. Offences have included improper distribution of free samples, off-label promotion, manufacturing deficiencies and failure to comply with rules on safety reporting and clinical investigations.\textsuperscript{125} Convictions for certain offences under the FDCA may form the basis for mandatory or permissive exclusion of individuals and companies from participation in federal healthcare programmes.


\textsuperscript{124} The FDCA imposes penalties of US$1,000 and imprisonment for one year per violation for misdemeanours and US$10,000 or imprisonment for three years for felonies. General federal criminal legislation provides for significantly greater fines than those imposed under the FDCA.

\textsuperscript{125} It is estimated that total judgments in such cases over the past decade have exceeded US$20 billion. The largest settlement to date related to GlaxoSmithKline, which agreed to pay a total of US$3 billion in civil and criminal penalties to resolve allegations under the FDCA and the False Claims Act relating to multiple drug products in July 2012.
III PRICING AND REIMBURSEMENT

Reimbursement for prescription drugs in the United States is provided through a mixed system of private and public coverage. More than 65 per cent of all patients have private insurance, often provided through their employer,\footnote{United States Census Bureau, Health Insurance Coverage in the United States: 2018 (2019), https://www.census.gov/library/publications/2019/demo/p60-267.html.} which covers prescription drugs, although private insurance plans vary greatly as to the number and types of drugs that are covered and the share of costs for which the patient is responsible. Patients who are enrolled in government-sponsored health programmes, including Medicare, which provides healthcare for the elderly and disabled, and Medicaid, which provides healthcare for low-income individuals, receive drug coverage through these programmes. Beyond Medicare and Medicaid, a range of federal and state programmes offer drug benefits to individuals who meet certain eligibility criteria (e.g., TRICARE is a federal healthcare programme for military personnel and their dependants, and many states offer AIDS drug assistance programmes). These private and public programmes are known as ‘payers’ and generally do not purchase or dispense drugs directly but instead pay for the products patients receive from their physicians, retail or speciality pharmacies, hospitals and other distribution channels.

Both public and private payers use a variety of mechanisms to control drug prices and utilisation. Private payers typically contract with pharmacy benefits managers (PBMs) to manage their prescription drug benefits. PBMs negotiate prices and rebates with drug manufacturers, develop drug formularies (lists of drugs that a health plan will cover) and impose utilisation management techniques, such as prior authorisation and quantity limits. The manner in which public programmes will reimburse prescription drugs is often dictated by statute. For example, states may establish maximum allowable costs to cap payments for brand or generic versions of the same drug.\footnote{Most states have adopted rules under which pharmacists are permitted or required to dispense a lower-cost generic equivalent on a prescription for a brand-name product. These rules often rely on therapeutic equivalence evaluations made by FDA and published in the Orange Book. Similar laws exist for substitution of interchangeable biosimilars; however, the FDA has not yet approved any such products.}

Public programmes also use mechanisms to control costs similar to those used by private plans. Medicare Part D, which covers outpatient prescription drugs, imposes significant beneficiary cost sharing in a coverage gap known as the ‘donut hole’ (although subsequent legislation will close the donut hole by 2020). Drug manufacturers whose outpatient products are covered by Medicaid are required to pay rebates to states for their drugs to ensure that the Medicaid programme receives the manufacturer’s most favourable pricing. Likewise, states often negotiate supplemental rebates with manufacturers in exchange for placement of the manufacturer’s drugs on a preferred drug list. The federal government is not currently permitted to negotiate drug prices under Medicare Part D.\footnote{42 USC Section 1395w-111(g)(1) (Social Security Act Section 1860D-11(g)(1)) (providing that the HHS Secretary ‘may not interfere with the negotiations between drug manufacturers and pharmacies and PDP sponsors,’ and ‘may not require a particular formulary or institute a price structure for the reimbursement of covered part D drugs’).}

Despite the availability of public and private insurance, many people (approximately 27.5 million by one estimate) lack coverage in the United States.\footnote{United States Census Bureau, Health Insurance Coverage in the United States: 2018 (2019), https://www.census.gov/library/publications/2019/demo/p60-267.html.} The Affordable Care Act (ACA) was enacted in 2010 to provide health coverage for those individuals who

© 2020 Law Business Research Ltd
were not covered by other programmes. The ACA established minimum requirements for health insurance programmes, required most individuals to purchase insurance (although the individual mandate has since been repealed) and subsidised premiums for low-income individuals. In particular, the ACA established prescription drug coverage as an ‘essential health benefit’ that must be included in health plans offered by state health insurance exchanges and in the benchmark benefit packages for newly eligible adults under Medicaid.

The current administration and many members of Congress have undertaken significant efforts to repeal the ACA, and its future is uncertain. A Texas district court recently struck down the entire ACA as unconstitutional; the decision is on appeal to the United States Court of Appeals for the Fifth Circuit.

There are also significant efforts aimed at reducing drug prices in the United States. At the federal level, the current administration has announced numerous potential reform proposals, including indexing the prices of certain drugs reimbursed under Medicare to international prices and requiring the disclosure of drug list prices in direct-to-consumer television advertisements. As discussed more fully below, the FDA recently released a draft guidance and proposed rule to allow importation of drugs from Canada. Congress also is actively considering reform measures that could include international price indexing, list price disclosure in direct-to-consumer advertising, and other reforms such as federal government drug price negotiation and caps on price increases or rebates for increases greater than inflation. Many states have adopted measures aimed at increasing transparency regarding drug pricing activities. For example, Oregon requires manufacturers to submit annual reports and advance notice of price increases above a certain threshold, as well as notice upon the introduction of certain new high price drug products. A smaller number of states have enacted laws aimed at limiting manufacturers’ ability to increase drug prices. For example, in 2017 Maryland enacted a law that would have allowed the state’s Attorney General to sue manufacturers for significantly high price increases; while this law was struck down in federal court, the state has adopted a new measure creating a board to set upper payment limits for certain prescription drugs. Additional drug pricing reform efforts are ongoing.

---

132 See U.S. Dept of Health & Hum. Serv., Medicare Program; International Pricing Index Model for Medicare Part B Drugs, 83 Fed. Reg. 54546 (30 October 2018). The administration has indicated that it could expand this proposal to drugs reimbursed under Medicare Part D or could instead issue an Executive Order to this effect.
135 Or. H.B. 4005 (eff. 1 January 2019 and 15 January 2019); Or. H.B. 2658 (eff. 1 January 2020).
136 Md. H.B. 631 (eff. 1 October 2017).
137 Md. S.B. 759 (eff. 1 July 2019).
IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The FDCA and FDA regulations and policies provide several mechanisms for internal administrative review of agency decisions. Certain decisions (e.g., to refuse or withdraw approval of an NDA) may be contested under statutory procedures that include formal evidentiary hearings before an administrative law judge. However, the majority of disputes are resolved through less formal mechanisms. The FDA regulations establish a general right to informal review of any decision within the agency hierarchy. Certain FDA commitments made under the PDUFA (e.g., to decide appeals of ‘procedural or scientific matters involving the review of human drug applications and supplements’) include performance goals for completion. Nevertheless, the FDA recently issued final guidance providing that only appeals of ‘regulatory action[s] taken by the FDA that . . . ha[ve] scientific and/or medical significance’ are major disputes subject to the PDUFA goals and the FDA’s formal dispute resolution process and expressly excluded FDA advice given in meeting minutes and other correspondence from that definition, even though such advice can have great developmental significance.

Statutory provisions authorising the FDA to require REMS, post-approval studies and labelling changes afford sponsors a right to an informal dispute resolution procedure. Similarly, the FDCA provides for supervisory review of ‘significant decisions’ regarding medical devices and imposes a 30-day deadline for the sponsor to file its appeal. In guidance, the FDA describes its interpretation of ‘significant decision’ and strictly interprets the 30-day deadline for filing an appeal, noting that “[t]here is no provision in the statute for extensions or waivers, or for partial submissions or “placeholders”.”

Judicial review of final agency action by the FDA is ordinarily subject to review in the federal courts under provisions of the FDCA and the Administrative Procedure Act (APA). Certain agency decisions (e.g., the refusal or withdrawal of approval of an NDA following a formal evidentiary hearing) are subject to review in a federal court of appeals; the FDA’s findings as to facts are deemed conclusive if supported by substantial evidence in the administrative record. In most cases, however, judicial review is available in a federal district court.

138 21 USC, Section 355(d), (e).
139 21 CFR, Section 10.75. In certain circumstances, the person seeking review may request that a scientific controversy be submitted to an FDA advisory committee, although FDA is not required to grant such a request.
140 FDA, PDUFA VI Commitment Letter, Section I.E.
141 FDA, Guidance for Industry and Review Staff, Formal Dispute Resolution: Sponsor Appeals Above the Division Level (Nov. 2017).
142 21 USC, Sections 355(o), 355-1.
143 FDCA Section 517A(b).
144 FDA, Guidance for Industry and Food and Drug Administration Staff; Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A (July 2014); FDA, Guidance for Industry and Food and Drug Administration Staff; Center for Devices and Radiological Health Appeals Processes (May 2013).
145 5 USC, Section 501 et seq.
court under general provisions of the APA. The court may set aside agency action if it is arbitrary, capricious or otherwise contrary to law, contrary to constitutional right, in excess of statutory power or without observance of required procedure.146

The APA also permits judicial review of agency action unlawfully withheld or unreasonably delayed, but the courts will normally hear such cases only if the applicant has exhausted its administrative remedies and the matter is otherwise ripe for a decision. This can make it difficult to challenge general FDA policies that have not been set out in final regulations or guidances, although it is sometimes possible to obtain judicial review following the submission of a ‘citizen petition’ under the FDA’s procedural regulations.147 The courts have generally held that warning letters and other informal communications used by the FDA to secure voluntary compliance do not constitute final agency action and are not reviewable under the APA.148

A person seeking judicial review of FDA action must demonstrate the requisite legal interest (standing). In practice, the rules on standing followed by the federal courts are relatively liberal, and, depending on the facts, challenges to FDA actions may be permitted by competitors, trade associations, professional groups and consumer organisations that are directly affected by FDA decisions.149

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

With limited exceptions, the FDA does not enforce federal laws governing financial relationships between pharmaceutical and medical device companies and prescribers or payers.150 Instead, these are subject to provisions of law enforced by the Department of Justice and the Office of Inspector General (OIG) of the Department of Health and Human Services.

146 5 USC, Section 706. Subject to somewhat complex rules enunciated by the Supreme Court and the US Court of Appeals for the District of Columbia Circuit, the federal courts often defer to FDA’s interpretation of the statutes and regulations it administers, and in practice they also tend to give great weight to the agency’s findings on matters of science and medicine within its special areas of expertise.

147 21 CFR, Section 10.30. The regulation requires the FDA to respond to a petition within 180 days of receipt, but permits the agency to provide a ‘tentative response’ stating that it has been unable to deal with the matter; in practice, the agency sometimes takes several years to provide a final response. However, for certain citizen petitions – those that may delay approval of a pending follow-on or biosimilar application – the FDA must respond within 150 days of the petition being filed under Section 505(q)(1)(F) of the FDCA. In recent guidance, the FDA interprets this deadline to apply only in certain circumstances, including that a pending abbreviated application that could be delayed by the petition has a user fee goal date that is within 150 days of submission. FDA, Guidance for Industry, Citizens Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act (September 2019). Pre-enforcement review is available as to final regulations issued by the FDA. Abbott Laboratories v. Gardner, 387 US 136 (1967).


150 FDA requires a person submitting a marketing authorisation application for a drug or medical device to disclose specified financial interests of investigators who conducted clinical trials relied on in the application (21 CFR, Part 54).
The federal Anti-Kickback Statute\textsuperscript{151} prohibits the provision or acceptance of anything of value in an effort to induce or reward the referral of federal healthcare programme business. The law is enforced by criminal and civil penalties, coupled with the potential for exclusion from participation in federal healthcare programmes. There is no private right of action under the statute, but whistle-blowers (relators) may initiate qui tam lawsuits on behalf of the federal government under the False Claims Act.\textsuperscript{152} Such suits may result in penalties equal to three times the cost of unlawful activities to federal healthcare programmes plus a penalty for each false claim, and a significant portion of the damages may be awarded to the whistle-blower.

The OIG has established a number of ‘safe harbours’ to protect specific business practices, such as discounting arrangements and fee-for-service engagements, from enforcement actions under the Anti-Kickback Statute.\textsuperscript{153} In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers\textsuperscript{154} and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals, which the OIG has endorsed.\textsuperscript{155}

The states also maintain statutes governing improper payments and other forms of fraud affecting public healthcare programmes, and many impose similar controls on improper payments in connection with private healthcare programmes. These are typically enforced by state attorneys general and by state Medicaid fraud control units.

The federal Sunshine Act, passed as part of the ACA in 2010, requires pharmaceutical and medical devices companies to report payments to physicians and teaching hospitals to the Department of Health and Human Services for disclosure on a public website.\textsuperscript{156} The federal requirement pre-empts some, but not all, similar disclosure requirements that had previously been established in some states.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The United States has established several systems governing liability and compensation for injuries associated with drugs and biologics. The most important is the Vaccine Injury Compensation Program (VICP), originally enacted as part of the National Childhood Vaccine Injury Act of 1986.\textsuperscript{157} The VICP is a no-fault compensation system for injuries or death associated with vaccines listed in the vaccine injury table issued under the programme, funded by an excise tax on each dose of the listed vaccines. A vaccine is listed following a determination by the Department of Health and Human Services to recommend it for routine administration to children. Compensation claims are submitted to the US Court of Federal Claims and reviewed by special masters within what is popularly known as the Vaccine Court. Compensation may include:

\begin{itemize}
\item \textsuperscript{151} 42 USC, Section 1320a-7b.
\item \textsuperscript{152} 31 USC, Sections 3729-3733.
\item \textsuperscript{153} 42 CFR, Section 1001.952.
\item \textsuperscript{154} 68 Fed. Reg. 23731 (5 May 2003).
\item \textsuperscript{155} PhRMA Code on Interactions with Healthcare Professionals: www.phrma.org-guidelines/code-interactions-healthcare-professionals.
\item \textsuperscript{156} www.cms.gov/openpayments.
\item \textsuperscript{157} 42 USC, Section 300aa-10 et seq.
\end{itemize}
Claimants may reject awards in the no-fault system and bring suits for damages under state tort law, but the statute imposes significant limitations on those suits, including defences based on compliance with FDA standards for product design and labelling, limits on punitive damages and trial procedures designed to facilitate consideration of scientific evidence as to causation.

Section 304 of the Homeland Security Act of 2002\(^{158}\) established a special programme to protect covered persons (including doctors and pharmaceutical companies) from liability for injuries caused by a smallpox vaccine during a period of public health emergency declared by the Secretary of Health and Human Services. The Public Readiness and Emergency Preparedness (PREP) Act of 2005\(^{159}\) prohibits suits against specified persons (including pharmaceutical manufacturers) for injuries allegedly caused by covered countermeasures during the period of a pandemic declaration issued by the Secretary of Health and Human Services, except for suits alleging wilful misconduct, which may be brought only in the federal district court in Washington.\(^{160}\)

**VII TRANSACTIONAL AND COMPETITION ISSUES**

**i Competition law**

The interplay between the statutory mechanisms providing for approval of generic/biosimilar products and the US antitrust laws has produced a constant stream of antitrust issues in recent years. Government enforcers, generic developers and customer groups routinely challenge conduct that they allege prevents the development of competitive products that the drug and biologics regulatory regimes are intended to encourage.

To facilitate the marketing of generic products, the Hatch-Waxman Act incentivises generic applicants to challenge the patents of innovative companies at very little financial risk to themselves.\(^{161}\) And under the Hatch-Waxman Act, in the case of a patent challenge, patent holders that file an infringement suit within a specified period are provided with guaranteed protection of their intellectual property for a period of generally at least 30 months, during

---

158 42 USC, Section 233(p). Suits must instead be brought against the United States, which has a right to recover for gross misconduct or violations of contractual obligations on the part of covered persons.

159 42 USC, Section 247d-6d.

160 In December 2014, a PREP Act declaration was issued for designated vaccines under development for the Ebola virus disease.

which the FDA cannot approve the alleged infringer's product. But once the companies are embroiled in the lengthy, unpredictable patent litigation encouraged under the structure of the Hatch-Waxman Act, the companies often wish to resolve the litigation.

These settlements take many forms and may include consideration that flows to the generic company, such as manufacturing assistance from the innovative company, and an agreement that the generic may enter the market on a certain date prior to expiry of the innovative company's patent. Consideration does not usually flow the other way, aside from the value of settlement and the certainty that it brings, because the Hatch-Waxman Act results in infringement actions being filed before the generic company has entered the market (i.e., before infringing sales have been made). This is in contrast to other types of patent litigation, where the patent holder has a damages claim and where, as a result, consideration to settle a matter might be expected to flow from the alleged infringer to the patent holder.

The FTC has taken the position that settlements that involve consideration flowing back to the generic company are anticompetitive. In particular, the FTC has argued that but for the consideration given by the innovative company to the generic company, the generic company would have entered the market earlier, resulting in lower-cost generic drugs for consumers.162

Notwithstanding the FTC's concerns, most courts that considered the issue recognised the importance of settlement of Hatch-Waxman patent infringement cases to maintaining the careful balance established by the Act. The Federal, Eleventh and Second Circuits consistently held that the antitrust laws allow patent settlements that include consideration flowing from an innovative manufacturer to a generic manufacturer along with an agreed entry date for the generic product, so long as the settlement does not exclude competition beyond the scope of the patent.163 This conclusion flows from the courts' recognition that the patent grant provides the innovative company with the lawful right to exclude.

Thus, under the 'scope of the patent' standard, these settlements were lawful unless the patent was procured by fraud; the underlying infringement action was objectively baseless; or the settlement obtains more coverage than the patent grant, for example, by excluding products not covered by the patent from the market or by excluding products covered by the patent from the market until some point after the patent expires.164

The Third Circuit rejected the 'scope of the patent' standard in a significant 2012 decision, In re K-Dur Antitrust Litigation.165 The Third Circuit held that any payment from a patent holder to a generic patent challenger who agrees to delay entry into the market constitutes prima facie evidence of an unreasonable restraint of trade, and the patent holder then bears the burden of showing that the payment was for a purpose other than delayed

---

162 A 2010 analysis by the FTC asserts that reverse payment settlements cost consumers US$3.5 billion annually. FTC, 'Pay-for-Delay: How Drug Company Pay-Offs Cost Consumers Billions', at 8 (2010), available at www.ftc.gov/os/2010/01/100112 payfordelayrpt.pdf. The FTC estimates that one year after a generic product enters the market the generic captures over 90 per cent of the pioneer drug's sales and sells for 15 per cent of the price of the pioneer. Id.


164 See, e.g., In re Tamoxifen Citrate Antitrust Litig, 466 F. 3d at 213.

165 See In re K-Dur Antitrust Litig, 686 F. 3d 197 (3d Cir. 2012).
entry or offers some pro-competitive benefit. In adopting such a standard, the Third Circuit stated that the scope of the patent test ‘improperly restricts the application of antitrust law and is contrary to the policies underlying the Hatch-Waxman Act’. The Third Circuit’s explicit rejection of the standard applied by the majority of other courts to consider the issue generated considerable uncertainty as to how such settlements will be evaluated in future cases.

In June 2013, the Supreme Court rejected both the ‘scope of the patent’ standard and the more stringent approach taken by the Third Circuit in *FTC v. Actavis*.

The Actavis decision held that reverse payment settlements can in some circumstances violate the antitrust laws and that they should be evaluated under a traditional rule-of-reason analysis, which involves comparing the likely anticompetitive effects of the settlement versus any pro-competitive benefits. The application of the Actavis ruling to particular cases is extremely fact-intensive. Significant uncertainty remains as the lower courts evaluate a number of settlements now subject to renewed litigation following the Supreme Court ruling. One of the key issues that continues to be litigated is what constitutes a ‘large and unjustified’ reverse payment required by the Actavis decision to subject the settlement to antitrust scrutiny.

In addition to allegations based on settlement of infringement suits under the Hatch-Waxman Act, generic manufacturers have often brought antitrust suits against manufacturers of reference products that submitted citizen petitions to the FDA identifying scientific, medical or legal reasons why generic marketing authorisation applications should not be approved, or suggesting additional testing necessary to ensure the safety or effectiveness of generic products. Although petitions submitted to federal agencies are normally protected under the First Amendment to the US Constitution, which guarantees the right to petition the government for redress of grievances, generic manufacturers have argued that citizen petitions relating to their products are a sham intended solely to delay market entry. Amendments to the FDCA enacted in 2007 impose specific requirements for submission of petitions relating to the generic drug approval process and expressly prohibit the FDA from delaying action on a generic application unless there is a reason to protect public health. Nevertheless, the FTC and private plaintiffs have continued to challenge alleged improper petitioning activity harming generic competition.

Finally, both regulators and generic and biosimilar manufacturers have been exploring whether certain commercial practices unduly restrict the ability of generic or biosimilar products to launch successfully. One practice that has received significant scrutiny is the refusal of brand companies to provide product samples for bioequivalence testing required

---

166 id. at 219.
167 In re K-Dur Antitrust Litig, 686 F.3d 197, 214 (3d Cir. 2012).
169 See In re Lipitor Antitrust Litig. (Lipitor), 868 F.3d 231, 274 (3d Cir. 2017), In re Solodyn (Minocycline Hydrochloride) Antitrust Litig. (Solodyn), No. 14-md-02503, 2018 WL 563144, at *4–13 (D. Mass. 25 January 2018); In re Novartis and Par Antitrust Litig., 18 Civ. 4361(AKH), 2019 WL 3841711, at *4-5 (S.D.N.Y. 15 August 2019) (finding that whether a no-AG agreement is unjustified under Actavis should be subject to rule of reason); In re Zetia (Ezetimibe) Antitrust Litig., 400 F. Supp. 3d 418, 425 (E.D. Va. 2019) (holding that unreasonableness of no-AG agreement should be evaluated ‘in relation to the payor’s anticipated future litigation costs’).
170 21 USC, Section 355(q).
to complete an ANDA. Such refusals to provide samples have most often been challenged by generics for products that have regulatory restrictions on their distribution and thus cannot be obtained from normal wholesale channels.\textsuperscript{172} On 20 December 2019, Congress passed legislation providing eligible product developers a private right of action for the licence holder’s failure to timely sell samples on commercially reasonable, market-based terms, with the potential for injunctive and monetary relief.\textsuperscript{173} A second area that has resulted in recent lawsuits involves the use of contractual provisions that allegedly incentivise purchasers to forgo dealing with a generic or biosimilar product.\textsuperscript{174} US antitrust laws normally favour discounting and other competitive responses to competitive entry.

\section*{Transactional issues}

Although licence agreements, collaborations and other transactions in the life sciences industry in the United States have many elements in common with transactions in Europe, there are certain aspects that are unique. Perhaps the most noticeable difference is in the transactional documents themselves – US documents tend to be more detailed than their European counterparts, and persons not familiar with US practice are often surprised by the length and complexity of US agreements. The goal is to provide a comprehensive and precise road map, anticipating where possible significant actions and decision points that might arise to eliminate ambiguities as to the parties’ rights and obligations and reduce the likelihood of disputes. For this reason, drafting and negotiating these agreements requires input from a wide range of functional experts with knowledge of industry practice and legal requirements, including regulatory, intellectual property, tax, product liability, commercial and antitrust issues.

The intellectual property (IP) and regulatory regimes also differ from those in Europe in ways that must be expressly addressed in agreements for the United States. For example, joint patent owners have an equal and undivided interest in the joint patent, and in the absence of contract language to the contrary, each may exploit it freely without accounting to the other. Also, the royalty term under a patent licence typically may not extend beyond the life of the licensed patents. In addition, patent and regulatory regimes for drug products are linked, which requires special provisions dealing with patent listings, patent term restoration and the enforcement of patents against generic competitors. Similarly, the evolving biosimilar regime in the United States may require drafting attention depending on the interests of the parties.

Product liability is a more significant consideration in the United States than elsewhere, which requires attention to indemnification and insurance provisions, as well as dispute resolution mechanisms.

US bankruptcy law also affords special protection to licensees of patents and certain other IP rights. Generally, a party that declares bankruptcy in the United States has the right

\begin{footnotesize}
\begin{itemize}
\item\textsuperscript{173} Pub. L. No. 116-94, §610 (2019).
\item\textsuperscript{174} \textit{In re Remicade Antitrust Litig.}, 345 F. Supp. 3d 566, 580 (E.D. Pa. 2018).
\end{itemize}
\end{footnotesize}
to stop performing, or reject, its obligations under agreements to which it is a party. But the US bankruptcy statute provides that a licensee of IP rights under a licence agreement retains its licence in the event that the licensor rejects the agreement. The statutory provisions are, however, complex, and licensees must structure agreements carefully to take full advantage of them.

VIII CURRENT DEVELOPMENTS

In April 2019, Commissioner of Food and Drugs Scott Gottlieb resigned. Gottlieb had been an active Commissioner who focused on an array of topics, including streamlining and modernising drug development and increasing competition in the drug and biologics markets. The President nominated Dr Stephen Hahn, previously Chief Medical Executive, The University of Texas MD Anderson Cancer Center, as Gottlieb's replacement, and on 12 December 2019, the Senate confirmed the nomination.

The FDA continues to implement two statutes that became law during Gottlieb’s tenure: FDARA, which became law in August 2017,175 and the SUPPORT for Patients and Communities Act, legislation intended to stem the opioid crisis in America, signed in October 2018.176 With regard to FDARA, the law included provisions to require molecularly targeted paediatric cancer testing for certain adult oncology drugs, namely, a new active ingredient that is to be submitted on or after 18 August 2020 that is ‘directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a [paediatric] cancer’. The FDA recently issued mandated guidance to implement the Act.177 The FDA remains in the early stages of implementing the new authorities granted by the SUPPORT Act, including expanded REMS authorities that enable the agency to require packaging (such as unit dose packaging) or safe disposal technologies to render drugs ‘non-retrievable’ to mitigate serious risks of drug overdose or abuse. Congress also has considered legislation meant to work regulatory reforms that lower drug prices indirectly in the Lower Health Care Costs Act,178 but to date this bill has not become law. Legislation passed on 20 December 2019 instead makes targeted changes to the provisions addressing the transition of certain proteins from new drug applications to biologics licence applications.179

It remains to be seen whether Hahn will continue the agenda advanced by Gottlieb. For example, during Gottlieb's tenure, the FDA published guidance on many timely topics, including ‘suites’ of guidance documents on regenerative medicine regulatory issues.180 Gottlieb also emphasised the FDA's willingness to work with innovators to develop new stem cell therapies, but he also committed the agency to active enforcement programmes against fraudulent stem cell clinics. Recently, the FDA took enforcement action against a stem cell clinic selling an unapproved product, obtaining an injunction in June 2019, but it remains unclear whether such enforcement action will remain a priority in the post-Gottlieb

FDA. Similarly, during Commissioner Gottlieb’s tenure, the agency increased its focus on competition issues, launching the Drug Competition Action Plan and Biosimilars Action Plan, that were aimed at increasing access to generic and biosimilar drugs by streamlining and incentivising their development. It also is unclear whether these programmes will have the same level of priority within the agency in Hahn’s tenure.

Digital health and real-world evidence appear to remain agency priorities, with the recent release of agency frameworks on artificial intelligence and machine learning, real-world evidence, prescription drug use-related software, and draft guidance on clinical decision support software, among other things. During the Trump Administration, the FDA also has continued to advance plans for importation of drugs from Canada as a cost-saving measure. The agency published the Safe Importation Action Plan in July 2019 discussing two pathways for importation into the United States of lower cost drugs originally intended for foreign markets. To implement pathway 1, the agency has released a proposed rule implementing Section 804 of the FD&C Act to allow importation of drugs from Canada, and under pathway 2, the FDA released a draft guidance to enable sponsors to voluntarily import drugs sold in foreign countries with the potential for cost savings.

Finally, in the coming year, it is possible that Congress will enact legislation reforming the regulation of OTC drugs that are marketed without approved NDAs. The legislation may include procedures to facilitate the introduction of novel dosage forms and other improvements and give the FDA new authority to require updated safety information in the labelling of OTC drug products.

---

182 FDA, Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD), https://www.fda.gov/media/122535/download.
Chapter 34

VENEZUELA

Rosa Virginia Superlano and Victoria Montero¹

I INTRODUCTION

The life sciences sector has its own regulations and rules. The pharmaceutical and medical devices industries are regulated and supervised by the health authority. Compliance is paramount to obtain and maintain the licences and marketing authorisation required to do business. The main competent health authorities are the Ministry of Health (MPPS), the Rafael Rangel National Hygiene Institute (INHRR) and the Sanitary Comptroller Autonomous System (SACS). The main law is the Law on Medicaments.

II THE REGULATORY REGIME

i Classification

There are different regulations for medicines, foods and cosmetics. Each has their own rules, permits and authorisations. To know which requirements are applicable, definitions are given in the laws on medicine, food, medical devices and cosmetics.

Any substance and its associated substances or combinations thereof intended to prevent, diagnose, alleviate or cure diseases in human beings or animals, or to control or modify their physiological or physiopathological state is considered to be a medicine.

‘Food’ covers not only substances intended for the nutrition of the human body, but also those substances that are part of or brought together in the preparation, composition and conservation of food, drinks of all kinds and any other substances, with the exception of medicines, for the purpose of being ingested by human beings.

Cosmetic products are those made with natural or synthetic substances for external human use and local action, applicable on the skin for aesthetic and protective purposes. This definition also applies to products for use as or related to personal hygiene and perfumes.

ii Non-clinical studies

There is no regulation for non-clinical trials or the regulation of studies on animals.

The Venezuelan pharmaceutical industry is not well developed and therefore non-clinical trials are seldom carried out in the country.

There are also are no regulations on animal testing, only for clinical trials involving human beings.

¹ Rosa Virginia Superlano and Victoria Montero are junior partners at LEGA Abogados.
iii Clinical trials

Venezuelan law defines a clinical trial as any experimental evaluation of a drug by its administration or application in human beings, to highlight its pharmacodynamic effects or to collect data on its absorption, distribution, metabolism and excretion in the human body, to establish its efficacy for a specific therapeutic, prophylactic or diagnostic indication and to know the profile of its adverse reactions and interactions and establish its safety.

All clinical trials must be authorised by the MPPS. They must be carried out under conditions that respect the fundamental rights of the person, and for ethical and scientific reasons that advance biomedical research that affects human beings, in line with the Declaration of Helsinki on Human Research and all subsequent updates. All candidates who participate in research studies must be informed in advance about the scope and risks of the trial, and give their written consent, in which they state that they are fully aware of both the scope and the potential risk in taking part in the trial.

iv Named-patient and compassionate-use procedures

There are no named-patient or expanded-access programmes in Venezuela. The practice of supplying a doctor with unapproved medicine to treat a named patient or for compassionate use is not explicitly regulated in Venezuelan law. However, there are several provisions regarding medicine and pharmacy laws and regulations that may apply.

The Review Board of the INHRR may grant a special authorisation for the importation of non-registered pharmaceutical products for specific cases where there is no available medication or for the treatment of rare diseases. The Review Board will decide which cases merit authorisation, which may be granted for a maximum period of six months. (This procedure is considerably shorter than processing a sanitary registration certificate.) The following must be verified as part of the INHRR’s assessment: the pharmaceutical product to be imported under the above-mentioned circumstances is not available on the national market; the product is not intended for mass commercialisation; the specific health reasons for the importation; and any other fact that the Review Board may consider relevant.

Following authorisation by the Review Board, the MPPS will grant an importation permit for the pharmaceutical products without a sanitary registration certificate (or marketing authorisation). In the event that the importer’s intention is mass commercialisation of the product, a sanitary registration certificate must be obtained.

v Pre-market clearance

The registration procedure is initiated by filing an application form before the INHRR with the corresponding legal, technical, scientific and clinical documents, as well as samples of the product and the proposed container and labelling. The product name (or brand) must be specified and the following information, inter alia, must be provided: method of development, quali-quantitative formula, physicochemical properties of the active ingredients and excipients, clinical and preclinical studies, stability and bioequivalence protocols, package texts, labels and package insert with instructions (including dosage) and product samples.

After reviewing all the relevant documents and carrying out a pharmacological, physicochemical and microbiological analysis of the product, the Review Board of the INHRR issues a report stating the approved dosage, indications and contraindications of the product. This report is published in the Bulletin of the Review Board and then the INHRR issues an official communication containing the sanitary registration certificate (or marketing...
Venezuela

authorisation), which is later ratified by a resolution of the MPPS and published in the Official Gazette (in which all laws, regulations and main administrative authorisations are published).

vi Regulatory incentives
Medicines are not granted patents, in line with the Intellectual Property Law (1955). There are patents in existence that were granted during the period that Venezuela was part of the Andean Community of Nations (CAN); however, application of the Intellectual Property Law was resumed in 2008. There are no legal regulations that provide for extensions to patent terms.

There is also no special law that governs protection of the exclusivity of regulatory data; however, Venezuela is a signatory to the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which establishes the minimum data protection standards that each Member State must provide. Pharmaceutical companies do not have an exclusive right to market medicines. Likewise, medicines should not be prescribed under the name of a specific brand, but by the active principle ingredients or the International Common Denomination.

The Law on Medicaments establishes that public entities should acquire generic medicines in preference to brand-name products, and generic medicines must have a lower price than the equivalent brand-name medication.

vii Post-approval controls
Pharmaceutical companies must employ a qualified chemist to oversee the procedures for quality assurance of medications. The Rules of Good Distribution Practice of Medicines set out further regulations on personnel, facilities and documentation relating to pharmaceutical companies. These Rules also regulate the procedures required for the recall of medicines in the event that actual or suspected health risks are detected.

The MPPS has procedures in place to ensure the continuing protection of users against the adverse effects of drugs and all related complaints, and to take the necessary action to safeguard public health. The Standards of Good Manufacturing Practices for Pharmacovigilance (2010) set out the duties of the National Centre for Pharmacovigilance (CENAVIF), which aims to maintain a system for effective pharmacovigilance and the evaluation of adverse events caused by drugs. The Law on Medicaments sets out a notification procedure (based on a ‘spontaneous notification’ system), whereby manufacturers and representatives of medicines must designate a person to be responsible for pharmacovigilance. Health professionals and drug manufacturers are obliged to inform the agencies responsible for pharmacovigilance, and provide evidence of any detected side effects or harmful or secondary effects caused by medications.

viii Manufacturing controls
The regulatory authorities maintain prior control (through authorisations) and subsequent control (through audits) of the facilities used for the manufacture, conditioning, storage, transport and sale of medicines, cosmetics and food. There are standards that establish the minimum requirements that these facilities must have, with the aim of minimising the risk of error; allowing for proper cleaning and order; avoiding cross-contamination; and maintaining the high quality of the products. The presentation to the authorities of the physical description of the facilities (plans, construction materials, ventilation systems and others) and compliance
with rules of space distribution, separately by areas: storage, conditioning, raw materials, product is required finished, dispatch, waste, destruction, non-conforming, changing rooms and others. Depending on the type of product, there may be additional special requirements.

It is not necessary for the infrastructure to be owned by a manufacturer, distributor or marketer; the owner can be a third party. However, contracts must be signed prior to the use of any facilities by a third party, and the MPPS must be notified. All the installations, whether owned directly or by a third party, must have all the corresponding authorisations and uphold the required conditions.

ix Advertising and promotion
Advertising and promotion of medications are regulated by the Law on Medicaments (2000) and by the Venezuelan Standards for Advertisement and Promotion of Medications issued by the MPPS (2004).

Only medicines duly approved and registered for marketing purposes in Venezuela may be advertised. All advertising must be approved in advance by the MPPS. Advertising that targets the general public is limited to over-the-counter products. General advertising and promotion are forbidden for medicinal products that require a prescription from a physician or a pharmacist. Any advertising of medical products, whether verbal, audiovisual or written, must be informative, educative, true, up to date and testable; it must be in Spanish, and must contain the following warning: ‘If ailment does not get better with treatment, stop using and consult a doctor.’ Labels and containers must indicate the name of the product, the active substances, the concentration, the healthcare record number, the production and expiry dates, and the name and address of the representative or pharmacist of the medicinal product. Dosage instructions and contraindications must also be indicated clearly on the product.

Advertisements must not induce irrational self-medication or the abuse of medication, and it is prohibited for free samples of medication to be given out to the general public. The use of the words ‘harmless’ and ‘quality’ in the warning text is also prohibited. Comparing products and product prices is permitted, but mention must be made only of the generic denominations and not the brand names of the medications.

x Distributors and wholesalers
All pharmaceutical companies, distributors, representative offices and pharmacies must be authorised as sanitary authorities and must hold sanitary registration certificates.

The different processes involved in purchasing, importing, receiving, storing, dispensing and distributing medicines must be carried out in compliance with established procedures that guarantee the maintenance of quality of the medicines.

xi Classification of products
Medicines are classified as:

a those that must only be purchased in accordance with the provisions of the Organic Law on Narcotic and Psychotropic Substances;

b those that can only be purchased with a prescription or special permission from the MPPS;

c those that require a prescription prior to purchase. That prescription must be then retained by the chemist or pharmacy that supplies the medicine and be recorded in the log books kept for that purpose;
d those that require a prescription, but that prescription can be repeated as many times as stated therein; and
e those that can be purchased without a prescription.

Non-prescription medicines can be promoted and advertised on all forms of social media, but medicines that need a prescription must be promoted and advertised exclusively to doctors, dental surgeons, chemists or other health professionals. They can never be promoted or advertised to the general public.

xii Imports and exports

All medicines to be imported into Venezuela must be registered with the MPPS and importers must have the required sanitary registration certificate (or marketing authorisation) for each medicine to be imported and commercialised in Venezuela.

All imported medicines should have undergone clinical evaluation before being distributed, in the form of clinical trials carried out on patients in the country of origin by appropriate professionals linked to institutions that carry out research, such as universities and hospitals. An exception may apply if the appropriate technology for the clinical study does not exist in the country of origin. Medicines that do not comply with internal regulations cannot be imported. Certain kinds of medications (those that treat rare diseases, low-incidence pathologies in the country or those required for special sanitary circumstances or epidemics) may be imported and sold without a sanitary registration certificate (or marketing authorisation). However, these types of medications can only be imported by institutions, manufacturers or distributors that have been duly authorised, and may only be marketed by the authorised institutions.

In the case of exports, both pharmaceutical companies and their representative offices can export medicines that comply with all the statutory requirements.

xiii Controlled substances

Customs operations for importing and exporting narcotic and psychotropic substances shall be carried out by pharmaceutical and representative offices exclusively for raw materials, after obtaining the necessary licence and the corresponding authorisation, requested by the pharmaceutical agent and granted in his or her name.

xiv Enforcement

The MPPS and other regulatory authorities may carry out inspections at the facilities of importers and product marketers, including chemists, at any time at their discretion, or as a result of a third-party complaint, without prior notice. In the event that any irregularity or violation of the regulations is found, the authorities will initiate an administrative sanctioning procedure, during which the company can present its defence and supporting evidence; the time limit for this is four months, which can be extended for an additional two months. Offenders may be punished with a fine, partial or permanent closure of the establishment, revocation of the operating permits for the facilities, cancellation of the health records of any or all products, or confiscation or destruction of any or all products. During the procedure, precautionary measures can also be issued.
Any instance of advertising, offering or sale of adulterated, falsified, expired medicines, whose quantity, dose or composition has been altered, or substances that imitate medications or that endanger the health or life of users, will be sanctioned with imprisonment (of between six months and three years) and temporary disqualification from exercising one’s profession.

III PRICING AND REIMBURSEMENT

Before 22 November 2011, the market price of a medicinal product was subject to a dual regulation depending on its active ingredients. The prices of some products were regulated by the authorities, but other products were not price-regulated, and the authorities were given only 30 days’ notice of new market prices prior to the sale of products at those new prices. The Law on Fair Prices, as amended on 8 November 2015, applies to all individuals and corporations that, as a result of the performance of their activities within the territory of Venezuela, produce, import or commercialise goods or services for monetary reward. It establishes a maximum profit margin (of 30 per cent) for the determination of prices. Furthermore, as of November 2018, the National Superintendence for the Defence of Socioeconomic Rights, which is the agency that administers the Law on Fair Prices, issued a list of maximum prices for 54 essential medicines. These new prices were previously discussed with some pharmaceutical companies acting in the domestic market.

There is no public policy to reimburse the cost of medicines. The Venezuelan Social Security Office (IVSS) and public hospitals hand out medications free of charge. Private insurance companies do reimburse the cost of medicines, provided they are prescribed by a healthcare professional in connection with a condition covered by an insurance policy.

A programme entitled Pharmacy of High-Cost Medications was implemented in 2009. Under this programme, patients, whether affiliated to the IVSS or not, are given medication free of charge to treat the following diseases: cancer, multiple sclerosis, viral hepatitis, rheumatoid arthritis, haematological diseases, transplants, attention deficit hyperactivity disorder, osteoporosis, schizophrenia, Gaucher’s disease, Fabry disease, pulmonary hypertension and terminal chronic failure. To access these high-cost medications, the patient must file a medical certificate confirming the presence of the disease, his or her identity document and the prescription. This programme is managed by the IVSS and currently 46 pharmacies throughout Venezuela are used exclusively for this purpose.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

Administrative redress can be sought against administrative decisions imposed by the authorities. There is the recourse of reconsideration, whereby the public official is asked to reconsider his or her decision. There is also the recourse of hierarchy, whereby a change to the decision is sought before a public official in a higher position.

It is also possible to go before the competent courts and bring an action to nullify the administrative decision. Natural and legal persons have the option of trying administrative recourses, as above, or going to court. If an administrative recourse has already been attempted, it is not possible to go to court until all the administrative recourses established by law have been exhausted.
FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The relationships between companies dedicated to the commercialisation of medicines and medical devices, including those who provide health services and insurers, are governed by the ordinary rules on common commercial relationships: the prohibition of constituting cartels, setting predatory prices, performing boycotts, exclusionary practices and unfair competition. The payment of bribes, the payment of or request for benefits to public officials, and individual bribes are also sanctioned. The public administration has the obligation to make bids for the acquisition of goods, including the purchase of medicines and health equipment.

The prohibited practices described above are sanctioned by the following regulations: Law Against Corruption, Antitrust Law, Organic Law of Fair Prices and Law of Insurance Activity. In the case of medicines, the provisions of the Rules of the Pharmaceutical Products Review Board of the INHRR and internal compliance code also apply and, for affiliated laboratories, the Code of Conduct of the Venezuelan Chamber of Medicine. The conduct of the health services is governed by the Law on the Exercise of Medicine and the Code of Medical Deontology.

SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There is no special liability regime for damage or injury caused by medicines. The ordinary civil liability established in the Civil Code requires pharmaceutical companies to pay material and non-material damages.

TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

The legislation governing anticompetitive practices is the Antitrust Law. Natural and legal persons, of public or private entities, national or foreign, for profit or non-profit, that carry out economic activities, or groups of the aforementioned who carry out these activities, in the national territory are subject to the provisions of the Law.

The anticompetitive practices designated in the Antitrust Law are: cartels; conduct, practices, agreements, contracts or decisions that prevent, restrict, distort or limit free economic competition; concerted practices; market concentration; and abuse of dominant position. Actions for unfair competition, infringement of patents, revocation or refusal to grant patents may be tried before ordinary courts; the procedure allows to agree precautionary measures.

ii  Transactional issues

Strategic collaborations, joint ventures, mergers and acquisitions are allowed by any corporation. However, they are regulated by the Antitrust Law, since they can cause anticompetitive effects. It is not mandatory to request approval or authorisation from the authorities prior to conducting a market concentration operation, nor is any approval or authorisation necessary for the operation to become effective. There is also no obligation to notify the regulatory bodies once the operation is concluded. The parties involved, at their discretion, after evaluating the possible risks of the operation, depending on the market
share of each of the participants in the operation, their location on the production scale, the total amount of the operation and the efficiencies to be generated, will decide whether it is expedient to request authorisation.

VIII  CURRENT DEVELOPMENTS

Venezuela continues to experience critical shortages of medicines and food. Foreign currency and price controls, hyperinflation and political instability remain some of the causes of this crisis. Requests continue to be made in some political quarters for a humanitarian channel to be opened to allow essential medicines to be brought into the country. The government has not yet agreed to this; however, it has maintained agreements with China, Russia and India for the importation of medicines, which may create more of an opening in the pharmaceutical market. As yet, this opening has not appeared. Notwithstanding this, the relaxation of the foreign exchange control regime that occurred during 2018, which became more flexible during 2019 and has allowed the pseudo-dollarisation of the economy, has been beneficial for importers of medicines. Also, during 2019, the government issued a provisional regulation (Resolution No. 075 issued by the MPPS) that temporarily allowed the importation of some medicines without a local marketing authorisation.
ABOUT THE AUTHORS

KARIN ABSALONSEN

Nyborg & Rørdam Law Firm P/S

Karin Absalonsen is a partner with Nyborg & Rørdam. Her main areas of practice are life sciences, corporate law and M&A. Karin has vast experience within the areas of biotech and life sciences through long-term and close client relations. She regularly advises clients with particular focus on research and development of biotechnological and medicinal products and contracts, including matters pertaining to research and development, clinical trials, material transfers and licences. Karin also has a particular focus on assisting founders and owners of biotech and life sciences businesses and their investors in respect of start-up, raising capital and new investments. She has been involved in a number of acquisitions and sales of biotech and life sciences businesses.

EVGENY ALEXANDROV

Gorodissky & Partners Law Firm

Evgeny Alexandrov graduated from the Russian State Academy of Intellectual Property (Moscow) as a lawyer, and in 2005 received his PhD degree in law. He joined Gorodissky & Partners in 2005.

He advises clients on intellectual property (IP) issues, including copyright, and associated rights, patent, trademark and other IP-related matters. He is one of the most experienced litigators in the firm and represents clients before the commercial courts and courts of general jurisdiction, as well as before administrative and law enforcement bodies.

Mr Alexandrov often participates in IP conferences as a speaker on IP issues and regularly publishes articles in Russian and foreign magazines and internet portals. He is a member of AIPPI and INTA, and speaks English.

MARÍA DEL CARMEN ALVARADO BAYO

Rodrigo, Elías & Medrano Abogados

María del Carmen Alvarado is a senior partner in the intellectual property department at Rodrigo, Elías & Medrano Abogados. She advises national and international investors on intellectual property, unfair competition, advertising, transfer of technology, franchising and life sciences. She is a former head of the Distinctive Signs Office at the National Institute
for the Defence of Competition and Protection of Intellectual Property. She was also an international lawyer with Frito-Lay Inc in Dallas and president of the Peruvian Association of Industrial Property and Copyrights.

**PRAVIN ANAND**

*Anand and Anand*

Pravin Anand is the managing partner at Anand and Anand. His practice areas and industry focus include intellectual property, litigation and dispute resolution. He completed his law studies in New Delhi in 1979 and since then has been practising as an intellectual property lawyer. He has been a counsel in several landmark IP cases involving the first *Anton Piller* Order (*HMV* cases), the first *Mareva* injunction order (*Philips* case), the first *Norwich Pharmacal* order (*Hollywood cigarettes* case), the moral rights of artists (*Amarnath Sehgal* case), the first order under the Hague Convention (*AstraZeneca* case), and several significant cases for pharma clients, such as Novartis, Pfizer and Roche. In recognition of pro bono work for rural innovators at grass-roots level, he received the National Innovation Foundation Award from the government of India.

Mr Anand is a co-author of the two volumes of *Halsbury's Laws of India* on intellectual property and serves on the editorial board of several international IP journals. He is the author of the India chapter in *Copyright Throughout the World* (Thomson Reuters). He is also on the editorial board of many leading journals on IP jurisprudence, international legal magazines such as *CTLR*, *Practical Law's Life Sciences Multi-jurisdictional Guide*, *India Business Law Journal*, *The Patent Lawyer*, *World Intellectual Property Review*, *Who's Who Legal: Patents*, the *LexisNexis Asia IP* guide and *ACCJ*. He has spoken extensively as a thought leader at various forums, including WIPO, AIPPI, INTA, LES, IBA, LAW ASIA and the UN Conference on LDCs in the Digital World.


**CAMILLA APPELGREN**

*Mannheimer Swartling Advokatbyrå*

Camilla Appelgren is a partner at Mannheimer Swartling. Her main areas of practice are life sciences, corporate, M&A and finance. She has been involved in domestic and cross-border transactions within the life sciences sector and a number of other industries, and regularly provides advice to publicly traded and privately held Swedish and international clients. Camilla has vast experience within the areas of healthcare, pharmaceuticals, food and medical devices, and regularly advises clients in contract negotiations and regulatory matters. Camilla is also engaged as a speaker at seminars and conferences, and has written a number of articles within the life sciences area. Camilla is ranked by *Chambers* as a leading individual within life sciences law in Sweden.
RAQUEL BALLESTEROS

_Bird & Bird (International) LLP_

Raquel Ballesteros holds a degree in law obtained with special distinction from the University of León in 1992 and has a master’s degree in health law from the Complutense University of Madrid. She is also a member of the Spanish Health Law Association. She has extensive knowledge of public law matters as a result of her preparation for joining the body of counsellors of the Spanish government. Raquel initiated her career as a lawyer in the private sector at Uría & Menéndez in 1995. From 1997 to 2005 she worked in the litigation department of Cuatrecasas, one of the best-known and highest-ranked legal firms in the Spanish litigation arena, joining Bird & Bird in November 2005 as one of the founding lawyers of the firm in Spain. Since then, she has headed the public law practice of the Bird & Bird Madrid office.

Both in contentious and non-contentious matters, Raquel has extensively counselled clients on different regulatory topics concerning medicinal products and medical devices, such as clinical trials and post-authorisation studies, clinical and biomedical research, prices, telemedicine, biotechnology and bioethics, information and clinical data protection, distribution and tracking, labelling, advertising and promotion.

She lectures on the International Master of Health Law course organised by the European University of Madrid as well as on other courses and at conferences relating to her areas of interest. She collaborates regularly with newspapers (Expansión) and specialised legal magazines.

JOHN BALZANO

_Covington & Burling LLP_

John Balzano is a partner in the New York office of Covington & Burling LLP. Mr Balzano’s practice focuses on advising drug, medical device, cosmetics, food and dietary supplement companies on issues of regulatory compliance, strategy and advocacy in China. His practice spans the life cycle of these products, from the research and development stage of development through to post-marketing and promotional issues. Prior to joining Covington, Mr Balzano taught Chinese law and regulation at both Yale Law School and Boston University Law School. He worked with the China Law Centre of Yale Law School to run administrative law and food and drug law projects with various scholars and government agencies in China. Mr Balzano has been a litigation attorney, and clerked for the Hon Joette Katz of the Supreme Court of Connecticut and the Hon Steven M Gold of the United States District Court for the Eastern District of New York. He received his JD and master’s in East Asian studies from Washington University in St Louis and his Bachelor of Arts degree in East Asian languages and cultures from Columbia University.

ROBIN BLANEY

_Covington & Burling LLP_

Robin Blaney is a partner in the life sciences practice of Covington & Burling LLP, dividing his time between the firm’s London and Brussels offices. He advises pharmaceutical, biotechnology, medical device and cosmetic manufacturers and trade associations on a wide range of regulatory, compliance, transactional and legislative matters, as well as the full range of commercial agreements that span the product life cycle in the life sciences sector.
His expertise includes clinical trial agreements, manufacturing and supply agreements, distribution and other marketing agreements, regulatory services agreements and tenders. He has particular experience of structuring and documenting transitional arrangements relating to product acquisitions and EU distribution structures. Mr Blaney writes and speaks regularly on subjects such as medical device regulation, pharmacovigilance and clinical trials.

INÊS CALDAS DE ALMEIDA

Vieira de Almeida

Inês Caldas de Almeida is a senior associate at VdA with extensive experience in the life sciences sector. She works on a daily basis with a number of pharmaceutical companies, and with companies in the medical devices sector, in matters related to compliance, marketing and promotional activities, pricing and reimbursement, clinical trials and authorisation procedures.

JOSÉ ALBERTO CAMPOS-VARGAS

Sánchez Devanny

José Alberto is a partner at Sánchez Devanny, who heads the life sciences practice group that deals with diverse legal issues regarding products such as medicines, medical devices, food and beverages, cosmetics, cannabis, tobacco and health services, among others. He has more than 23 years of experience advising clients in connection with their operations in Mexico with highly regulated products either by the Ministry of Health or the Ministry of Agriculture and other related authorities in such products’ processes regarding importation, warehousing, manufacturing, marketing, transportation, etc.

He has advised clients in industries highly regulated by the Mexican health and agricultural authorities in connection with strategic planning of Mexican operations, including obtaining licences, authorisations and permits of diverse kinds, planning for mergers, acquisitions and spin-offs of entities that carry out highly regulated activities or that involve the use of these kinds of products, as well as those rendering services related to health.

Likewise, he has advised a considerable number of legal entities in connection with the publicity and marketing strategies for regulated products and services, in connection with the planning and development of labelling, as well as with the planning, review and authorisation of marketing materials all the way to litigious procedures before authorities such as COFEPRIS, SENASICA and PROFECO.

IRENE CARLET

Studio Professionale Associato a Baker & McKenzie

Irene Carlet joined Baker McKenzie in June 2019. She focuses her practice on healthcare and administrative law matters advising national and international companies on regulatory, compliance and public procurement issues.

Irene graduated cum laude from Trento University in 2019 with a final dissertation on constitutional and healthcare law.

During her studies, Irene took part in the Erasmus Programme spending a semester at Newcastle University Law School in England. She is also the author of several contributions on bio and healthcare law matters.
KRISTA HESSLER CARVER
*Covington & Burling LLP*

Krista Carver is a partner in the firm of Covington & Burling LLP. She focuses on FDA regulatory and legislative matters for companies in the biotechnology and pharmaceutical industries and related transactional matters. Ms Carver counsels clients on an array of issues, including biosimilars and Hatch-Waxman regulatory issues; regulatory exclusivities and life-cycle management strategies; regenerative medicine; digital health; priority review vouchers; risk evaluation and mitigation strategies (REMS); the FDA’s expedited programmes; and clinical trial data confidentiality and transparency. Ms Carver also assists clients with advocacy before the FDA, including formal dispute resolution requests and citizen petitions, and with legislative issues surrounding amendments to the Federal Food, Drug, and Cosmetic Act and related laws, including the 21st Century Cures Act, FDA Reauthorization Act of 2017 and the SUPPORT Act. With respect to biosimilars, she assisted biotechnology innovators in legislative matters leading up to the enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and now represents clients in connection with FDA interpretation and implementation of the BPCIA. She received her law degree, magna cum laude, from Harvard Law School in 2006.

GRANT CASTLE
*Covington & Burling LLP*

Grant Castle is a partner in the London office of Covington & Burling LLP, practising in the areas of life sciences regulatory law, with an emphasis on pharmaceutical and medical device regulation and associated compliance issues. He has assisted clients with a wide range of regulatory and compliance issues, with a focus on GxP compliance matters, and has participated in formal and informal good manufacturing practices, good clinical practices, drug safety and pharmacovigilance proceedings before the European Medicines Agency, national authorities, courts and self-regulatory bodies. He also advises extensively on advertising and commercial practices matters, including advertising disputes.

He speaks and lectures frequently on compliance issues in both the pharmaceutical and medical device areas at the University of Surrey, the University of Wales and Cranfield University. He received a BSc in chemistry with first-class honours from Imperial College of Science, Technology and Medicine in London in 1991 and a PhD in organic chemistry from Trinity College, University of Cambridge in 1994.

CHANG MAN PHING
*WongPartnership LLP*

Chang Man Phing’s main areas of practice encompass civil and commercial litigation, including disputes relating to companies, shareholders and directors, insurance, contracts and employment contracts. She regularly advises companies on potentially litigious matters involving breach of fiduciary duties, breach of confidentiality obligations and breach of non-compete and non-solicitation clauses. She specialises in medical law and healthcare matters and regularly acts for patients seeking redress against hospitals and medical practitioners through medical negligence claims. She has acted for US pharmaceutical company Merck
Sharp & Dohme in proceedings in Singapore involving worldwide litigation. She has also acted for Cordlife Group Limited, a major player in Singapore’s cord blood banking services industry, in both litigation and licensing advisory matters.

Man Phing is also a prosecuting counsel for the Singapore Medical Council, Singapore Dental Council, Allied Health Professions Council and Council of Estate Agencies in disciplinary proceedings against errant members. With her extensive experience, she undertakes advisory works for healthcare institutions, statutory boards and multinational corporations. She has advised the Singapore Medical Council in the review of amendments to the legislative framework and was also part of the team of lawyers in the review and drafting of the statutory framework governing Dubai Healthcare City’s healthcare professionals and operators. Separately, she provides legal advice to various institutions, including the Health Promotion Board, the National University of Singapore and the National Council of Social Services.

**YONG HOON CHO**
*Kim & Chang*

Yong Hoon Cho is an attorney in the firm’s healthcare practice, antitrust and competition practice, mergers and acquisitions practice, anti-corruption and corporate compliance practice, and foreign direct investment practice. He also has extensive experience advising clients in the automotive industry across a wide range of corporate and securities transactions.

Mr Cho has over 15 years of experience in advising clients on competition law issues arising out of daily operations of healthcare company clients. A key focus of his practice deals with Korea Fair Trade Commission investigations into competition law violations and global merger filings for inbound and outbound transactions in the healthcare industry.

Mr Cho has also defended pharmaceutical and medical device clients in investigations by competition authorities with respect to marketing and promotional practices. He has also advised on establishing company compliance programmes, and on implementing global mergers in Korea.

He received an LLM from Columbia Law School in 2011 and graduated from the Judicial Research and Training Institute of the Supreme Court of Korea in 2002. Mr Cho received an LLB from Seoul National University in 1999.

**SUPHAKORN CHUEABUNCHAI**
*Chandler MHM Limited*

Suphakorn is an associate at Chandler MHM and has been with the firm since 2013. He is a specialist in corporate law and has advised clients on mergers and acquisitions as well as due diligence on Thai target companies. His experience ranges across multiple sectors, including e-commerce, automotive, tourism, transportation business, life sciences and the import of hazardous substances. He also provides legal advice on foreign investment laws and taxation.

**MYUNG SOON CHUNG**
*Kim & Chang*

Myung Soon Chung is a foreign attorney practising in the firm’s healthcare as well as antitrust and competition practice groups.
Ms Chung has advised numerous multinational pharmaceutical and medical device companies on compliance with laws and regulations governing interactions with healthcare professionals, regulatory requirements as well as in connection to disputes with business partners including distributors.

Ms Chung has also represented numerous multinational companies in Korea Fair Trade Commission investigations into cartel activities including in the pharmaceutical industry, paper industry, air carrier industry and commercial vehicle industry.

She has also advised numerous multinational companies on various competition law issues including abuse of market dominance and unfair trade practices. Her practice also includes advising clients during disputes raised before the Korea Fair Trade Mediation Agency.

Ms Chung received her JD, magna cum laude, from Syracuse University College of Law in 2005, MBA from Colorado State University in 2001 and BA from Yonsei University in 1993.

FELIPE CORONEL C

Latin Lex

Dr Felipe Coronel is the founding partner of Latin Lex Consulting. He has over 15 years of solid experience in the life science sector in Latin America. He studied law at Pontificia Universidad Católica de Chile between 1997 and 2003 (magna cum laude), and in 2005 he received his jurisprudence doctorate (magna cum laude), becoming authorised to practise law in Chile and Ecuador. He is a former general counsel and chief compliance officer and former board member of Grünenthal (German pharmaceutical multinational company) in Latin America, and has professional experience in different countries of Latin America. Between 2005 and 2009 he taught civil law, and since 2013 he has taught corporate law and compliance at Inidem Business Law School. He is fluent in Spanish, English and French.

SARAH COWLISHAW

Covington & Burling LLP

Sarah Cowlishaw is a partner in the life sciences group in the London office of Covington & Burling LLP. Her practice focuses on life sciences regulatory and commercial law for pharmaceutical, medical device, food and consumer products. She has a particular focus on digital health matters, including medical device regulation and associated commercial matters. Her advice on general regulatory matters includes borderline determinations, food classifications, adverse event and other reporting obligations, manufacturing controls, and labelling and promotion. On the commercial side, she advises on the full range of agreements that span the product life cycle in the life sciences sector. Her expertise includes clinical trial agreements, manufacturing and supply agreements, distribution and other marketing agreements and regulatory services agreements. She also advises on regulatory aspects of corporate and commercial deals, particularly regulatory due diligence.

IVAN CUNHA

Fialdini Einsfeld Advogados

Ivan Cunha is a senior associate at the São Paulo office. The bulk of his workload is comprised of complex litigation cases involving public contracts and biddings, consumer law and IP as well as regulatory matters.
ROBERTO CURSANO

*Studio Professionale Associato a Baker & McKenzie*

Roberto Cursano is a partner at Baker McKenzie and co-leads the Italian pharmaceutical and healthcare law department. He focuses on healthcare law and compliance, and assists in tender procedures, the negotiation of public contracts and litigation before administrative courts. Roberto is a former administrative officer in the Italian Ministry of Health and helps clients working closely with the Italian Public Administration.

He earned a PhD in Italian and EU constitutional law from the University of Teramo in 2010 and is admitted to the bar before the Italian Supreme Court and the Council of State.

Roberto advises primarily on pharmaceutical and healthcare matters. These include product licensing and marketing, clinical trials, pricing and reimbursement, promotions, interactions with healthcare professionals, distribution of products, and public procurement issues.

Additionally, he assists in anti-bribery matters and related investigations, and helps set up internal compliance models preventing corruption-related crimes, money laundering and corporate crimes.

As well as training and tutoring in the master’s degree programme on clinical trials of pharmaceutical products at La Sapienza University of Rome, Roberto regularly publishes articles and scientific contributions. He also frequently hosts and participates in seminars and presentations on pharmaceutical and administrative law matters.

RICARDO DE VETTOR PINILLOS

*Rodrigo, Elias & Medrano Abogados*

Mr De Vettor is a senior associate in the intellectual property department at Rodrigo, Elias & Medrano Abogados. He provides advice on intellectual property law, focusing in particular on the legal enforcement of trademark rights through administrative proceedings and judicial cases, including injunctions and seizures. Mr De Vettor also provides advice on regulatory issues in respect of medicines, medical devices, cosmetics, sanitary products and clinical trials. He is the current secretary of the Peruvian Association of Industrial Property and Copyrights (APPI).

ALEXANDRE EINSFELD

*Faldini Einsfeld Advogados*

Alexandre Einsfeld is the partner in charge of the office in Rio de Janeiro. He works throughout the country in complex litigation related to regulatory law, intellectual property and contractual disputes. Besides litigation, he provides advice in these areas to national and foreign companies.

ILYA GORYACHEV

*Gorodissky & Partners Law Firm*

Ilya Goryachev graduated from Moscow State Linguistic University in 2012 as an international lawyer and joined Gorodissky & Partners in 2013.

He focuses on providing legal support on intellectual property (IP) and general commercial matters, including trademarks, patents and copyright enforcement; unfair
About the Authors

competition; domain disputes; licensing, assignments, franchising and other IP-related transactions; advertising and marketing regulations; launching joint ventures; IP issues in M&A transactions; IP due diligence; personal data protection; and industry-related regulatory affairs, including advising life science companies.

Mr Goryachev is the author of several articles on IP and commercial law matters. He speaks English and French.

AARON GU
Covington & Burling LLP

Aaron Gu is an associate in the Shanghai office of Covington & Burling LLP. Mr Gu advises multinational and Chinese companies on a range of corporate, regulatory compliance and advocacy issues, particularly those in the healthcare and life science industries, as well as cross-border transactions, including clinical trial matters, licence and collaboration, mergers and acquisitions, foreign direct investments, and outbound investments. Prior to joining Covington, Mr Gu worked in the Shanghai office of a leading international law firm and the New York office of a leading Chinese law firm. He received his LLM from New York University School of Law and his Bachelor of Law from East China University of Political Science and Law.

KARINA HELLBERT
Polak & Partner Rechtsanwälte GmbH

Karina Hellbert joined Polak Attorneys-at-Law in 2004; she is head of the life sciences department. She holds degrees in law and natural sciences, and specialises in pharmaceutical law, medical devices, intellectual property law, patent litigation, licensing, unfair competition law, commercial issues, customs matters, IT, product liability and food law.

Ms Hellbert is an associate professor at the Danube University Krems and has written numerous articles in the fields of, inter alia, regulatory issues, product liability and pharmaceutical advertising.

In recent years, Ms Hellbert has been involved in running various major patent and supplementary protection certificate cases for multinational companies, not only before the civil courts, but also before the criminal courts. In addition, she regularly represents clients in product liability cases before the civil courts. Her work in the life sciences field includes advice on regulatory issues such as data protection, labelling, borderline issues, clinical trial agreements, reimbursement and compliance with anti-bribery provisions in the health field.

MELANIE HO
WongPartnership LLP

Melanie Ho is a leading lawyer in medical law in Singapore. Her depth of experience includes advising and acting for the Singapore Medical Council and Singapore Dental Council in disciplinary actions taken against doctors, and representing plaintiffs against medical practitioners and hospitals.

In 2017, she succeeded in an appeal against insurer AIA for claims involving at least S$1.2 million and acted for the Singapore Medical Council in highly publicised disciplinary proceedings against a Singaporean oncologist for professional misconduct. Melanie has been actively involved in setting up internal standard operating protocols and reviewing numerous
directives issued by regulatory bodies. Melanie is the first and only Singaporean lawyer invited by the Dubai Healthcare City Authority to sit on its Appeals Board, which hears appeals relating to professional misconduct cases.

She was the lead partner in the review and drafting of the statutory framework governing Dubai Healthcare City’s healthcare professionals. She was lauded as one of the three pillars in the firm’s investigations team by *Global Investigations Review 100 2019* – a guide to the world’s top 100 leading firms for corporate investigations. Melanie is a recommended disputes resolution lawyer in *The Legal 500 Asia Pacific* 2015, and a highly regarded legal practitioner in the area of life sciences, having been selected by her peers in *Best Lawyers* 2017 and 2018 for her work in litigation and medical malpractice litigation. She is also recognised as a leading lawyer in *Who’s Who Legal: Life Sciences 2017* for product liability.

**KATHERINE JUANG**

*Lee and Li, Attorneys-at-Law*

Katherine Juang is an associate partner at Lee and Li, Attorneys-at-Law and has been a member of the Taipei Bar Association since 2002. Ms Juang obtained a master’s degree in law in Taiwan and her master’s thesis dealt with the protection of medical information. She specialises in pharmaceutical regulatory compliance, data protection compliance, IP law and competition law. She advises various local and foreign clients on pharmaceutical regulatory matters, relevant patent litigation and compliance structure.

**RICHARD KINGHAM**

*Covington & Burling LLP*

Richard Kingham is a senior counsel at Covington & Burling LLP, where he serves as co-head of the life sciences industry group. He previously served as the managing partner of the firm’s London office and as a member of the firm-wide management committee. Since joining the firm in 1973, he has concentrated on regulation of pharmaceuticals and related products. He has acted for most of the major pharmaceutical and biotechnology companies in the United States and Europe, as well as the principal trade associations of the pharmaceutical industry. He has served on committees of the World Health Organization, the Center for Global Development, the Institute of Medicine of the US National Academy of Sciences and the National Institutes of Health. He is currently an adjunct professor at the Georgetown University Law Center, and has lectured at the University of Virginia School of Law and the graduate programme in pharmaceutical medicine at Cardiff University. He received his law degree in 1973 from the University of Virginia, where he served as articles editor of the law review and was elected to the Order of the Coif (the law school honour society).

**TAKESHI S KOMATANI**

*Shusaku Yamamoto*

Takeshi S Komatani is currently principal of the chemical/pharma and bio/life sciences groups at Shusaku Yamamoto, and has a number of counsels including in academia, start-ups, and big pharma in Japanese and non-Japanese entities.

Takeshi received his PhD from the University of Tokyo, Japan, with Professor K Inoue, and qualified as a Japanese licensed, registered pharmacist (chemist) with a certificate of *Kampo* and natural medicines specialist qualification. He was a researcher at F Hoffmann-La
Roche in Basle, Switzerland. Thereafter, he joined Shusaku Yamamoto, a patent and law firm in Osaka, Japan, in 1998, and was registered to practise before the Japanese Patent Office and appear as patent and trademark counsel before the Japanese courts, admitted in 2000. He was registered as an IP litigation certified attorney before the Japanese courts in 2004. He has completed the EU-recognised PharmaTrain course on implementing reliable standards for high-quality postgraduate education and training in medicines development, at Osaka University in 2017. He also received an LLB from Keio University in 2019. In 2019, he also qualified as a Board Certified Member of the Japanese Association of Pharmaceutical Medicine, which is equivalent to having completed the Certified Physician Investigator accredited by the Association of Clinical Research Professionals.

He has been chosen as an intellectual property (IP) mentor as a part of the IP Mentoring Team through a project called IPAS run by the Japan Patent Office in 2019, and thus also is assisting a number of start-ups in addition to his regular clients.

He is a member of the International Association for the Protection of Intellectual Property and vice chair of TRIPS standing committee since 2018, and a member of the editorial board of the Pharmaceutical Patent Analyst (UK) since 2012. He is also a member of the Japan Patent Attorneys Association, the Asian Patent Attorneys Association, the Intellectual Property Association of Japan, the Japan Pharmaceutical Association, and the American Association for the Advancement of Science and the Certified Specialist Association of Intellectual Property Management. He has lectured, and contributed a number of articles, extensively on Japanese and international/trilateral IP and pharma law/practice.

PRANAT LAOHAPAIROJ
Chandler MHM Limited
Pranat is a counsel at Chandler MHM and has been with the firm since 2012. He has worked with Thai and international clients on merger and acquisitions, antitrust, corporate, anti-corruption, compliance, and data protection, providing advice and services including due diligence, deal structuring, negotiation, contract drafting, deal execution, in-house training and public seminars (on anti-bribery, antitrust and data protection), and translation. He regularly works on domestic Thai deals as well as on cross-border investments, and his experience spans multiple sectors, including oil and gas, mining, automotive, wholesale and retail, chemical, electronics, real estate, gaming and information technology, metal, leasing, life sciences, and the food and beverage industries. He is admitted to the Bar of the State of New York.

HILMA-KAROLIINA MARKKANEN
Castrén & Snellman Attorneys Ltd
Hilma-Karoliina Markkanen specialises in intellectual property law and advises clients in various industrial property rights and copyright-related matters. Her main practice areas also include life sciences, consumer protection and advertising law and technology.
ARLIN MERCHANT

*Kabraji & Talibuddin*

Arlin Merchant works on various corporate and commercial matters focusing on project finance transactions in the power sector, and acts as counsel for various financial institutions including International Finance Corporation, Asian Development Bank, Export-Import Bank of Korea, Industrial and Commercial Bank of China and China Development Bank. Arlin regularly advises in relation to debt and equity financing and other financial market transactions. She possesses experience in drafting, negotiating and advising clients on all aspects of a transaction. She handles queries relating to company law, securities law, labour law, foreign exchange regulations, regulatory and compliance matters including competition and takeover laws and other contentious and non-contentious contractual matters.

VICTORIA MONTERO

*LEGÁ Abogados*

Victoria Montero joined LEGÁ Abogados in 2013 as a member of the corporate and M&A practice group. Victoria has extensive experience in the pharmaceutical sector and has led the M&A transactions the firm has handled recently in the life sciences sector. She also has extensive experience in advising clients in the life sciences and healthcare industries, in general contractual matters and regulatory issues, including distribution agreements, joint venture agreements, the processes for acquisition, transfer and withdrawal of marketing authorisations, the legal framework applicable in the promotion and advertisement of pharmaceutical products and for licences to operate as a pharmaceutical wholesaler and marketing company. She also advises companies in a number of sectors, including food and beverages, agro-industry, oil and gas, banking and finance, digital media and telecommunications.

Victoria holds an LLM in global health law with a certificate in food and drug law from Georgetown University Law Center (2018), and during her studies served as a research assistant at the O’Neill Institute for National and Global Health Law in Washington, DC.

ANTHONY MURATORE

*Jones Day*

Anthony Muratore has more than 35 years of experience in the area of intellectual property law and is consistently recognised as one of Australia’s leading patent litigators. During this time, he has acted in some of the most significant patent disputes in Australia, a number of which have involved testing important aspects of patent law. These include the High Court’s rulings on whether isolated nucleic acids and methods of treatment of human beings are patentable subject matter.

Anthony has established a reputation acting as the Australian member of global teams representing clients in complex, multi-jurisdictional patent disputes. He has acted in a range of matters involving biotechnology, pharmaceuticals, mechanical engineering, chemistry and information technology. In the biotechnology and healthcare fields, he has acted in matters involving patents relating to drug formulation, transdermal drug devices, synthetic nucleotides, sterility assurance, gene silencing, photodynamic therapy, contact lenses and CPAP for the treatment of sleep apnoea.
Anthony is on the WIPO list of arbitrators and is a member and past chairman of the Intellectual Property Law Committee of the Law Council of Australia.

**MELISSA MURRAY**  
*Bird & Bird (MEA) LLP*

Melissa Murray is an experienced commercial lawyer based in Dubai. She has practised in the United Arab Emirates for over 14 years and has a deep understanding of the regulatory framework surrounding the healthcare industry in the Middle East. In addition to providing commercial advice to healthcare clients, Melissa also advises other industries and international businesses on commercial and corporate matters relating to their operations in the United Arab Emirates and the wider Middle East region. Her experience includes advising on hospitality, IT, IP, franchising, media, data protection, privacy, consumer protection, food, sports and regulatory matters.

**JACEK MYSZKO**  
*Sołtysiński, Kawecki & Slezak*

Jacek Myszko joined SK&S in 2003 and became a partner in 2020. He focuses his practice on IP-related issues, pharmaceutical law and food law in its various aspects.

Mr Myszko graduated with a law degree from the Nicolaus Copernicus University in Torun, Poland and with a diploma in EU studies from the J Monnet European Studies Centre. He also completed an IP law programme at the Jagiellonian University in Cracow, Poland and various international courses organised by, inter alia, the University of Cambridge (English and EU law), the Catholic University of America and Columbus School of Law (business and trade law). He has advised Polish and foreign clients in many cases on all aspects of trademark and biotechnical patent protection; various aspects of medicinal products distributions schemes, including direct distribution, distribution via public tenders and application of reimbursement procedures; restructuring and acquisition (including audits) of pharmaceutical companies and pharmacies; and issues related to contacts of pharmaceutical companies and medical devices companies with healthcare professionals (training, scientific conferences, etc.).

**JILL NIU**  
*Lee and Li, Attorneys-at-Law*

Jill Niu is a partner at Lee and Li, Attorneys-at-Law. Her practice focuses on medical and healthcare laws (including compliance of privacy and data protection in conducting clinical studies and marketing programmes), employment and labour laws, corporate governance and compliance, and tax litigation. Ms Niu also acts as counsel to a local association of multinational pharmaceutical firms and has been advising the association on the code of marketing practices, including privacy and data protection issues, from the perspective of clinical trial laws and regulations. She has been a member of the Taipei Bar Association since 1992.
NORASETH OHPANAYIKOOL

Chandler MHM Limited

Noraseth is an associate at Chandler MHM. He advises on general Thai commercial and business laws including company law, regulatory oversight and laws regarding corporate matters.

RICCARDO OVIDI

Studio Professionale Associato a Baker & McKenzie

Riccardo Ovidi has been a lawyer at Baker McKenzie since September 2014. He focuses his practice on pharmaceutical and healthcare law issues, advising on regulatory and compliance matters concerning the manufacturing, marketing, distribution and import of medicinal products and medical devices.

Riccardo was awarded his law degree from LUISS Guido Carli of Rome in 2005, subsequently earning a Master of Laws in international business and trade law from Fordham University School of New York in 2011. He is admitted to the Italian and the New York State Bar.

Riccardo regularly advises pharmaceutical and medical device companies on complex matters related to the advertising and promotion of medicines and medical devices, interactions with HCPs and HCOs and the payback system. His expertise includes the drafting and negotiation of warehousing, distribution and logistics agreements, professional services agreements, clinical trial and sponsorship agreements.

Riccardo has also an extensive experience in corporate compliance matters assisting companies operating in the healthcare sector with the setting up and updating of compliance models aimed at preventing corruption-related crimes and corporate crimes, and with the construction of internal policies and procedures and codes of conduct.

ROSA OYARZABAL

Covington & Burling LLP

Rosa Oyarzabal is an associate in Covington & Burling LLP’s Brussels office. She assists clients across a range of regulatory, legal and procedural matters in the pharmaceutical and food sectors. Her practice focuses on the EU rules and on the laws in key EU Member States, including Belgium, France, Italy and Spain.

HANNA PALOHEIMO

Castrén & Snellman Attorneys Ltd

Hanna Paloheimo is head of the life sciences practice at Castrén & Snellman. She specialises in life sciences, intellectual property and technology, and dispute resolution, including patent litigation. She advises life science companies in various matters, including transactions and regulatory matters. Besides her law degree, she holds a master of sciences degree in genetics, and this combination provides useful insight in meeting the special needs of life science, pharmaceutical and biotechnology companies. Chambers Europe, Chambers Global, Best Lawyers and Intellectual Asset Management rank Hanna Paloheimo among Finland’s leading legal experts.
FRANCISCA PAULOOURO
Vieira de Almeida

Francisca Paulouro is an of counsel at VdA and head of the firm’s life sciences practice area. She has worked in the firm’s life sciences practice group for more than 15 years, having significant expertise in regulatory matters related to pharmaceuticals, biotechnology, medical devices and cosmetics, under both EU and national law, and has been involved in several cross-border projects. She is fully dedicated to life sciences, assisting, on a day-to-day basis, several major innovative pharmaceutical companies operating in Portugal, and the Portuguese Pharmaceutical Industry Association. Her expertise and work with clients cover a wide range of matters, including, among others, licensing requirements, data exclusivity, pricing, reimbursement, market access, compliance, marketing and promotional activities, clinical trials and distribution. She is ranked by *Who’s Who Legal* as a recommended lawyer for life sciences.

JOAQUIM AUGUSTO MELO DE QUEIROZ
Fialdini Einsfeld Advogados

Joaquim Augusto Melo de Queiroz is a partner at the São Paulo office, serving clients in the pharmaceutical, consumer goods and energy industries. Joaquim routinely tackles highly complex matters involving strategic litigation in regulatory, civil, contractual and administrative law matters.

JESSADA SAWATDIPONG
Chandler MHM Limited

Jessada is a managing partner at Chandler MHM. He specialises in banking and finance, particularly project finance, with a focus on major cross-border energy and natural resources, infrastructure, regulatory, life sciences and real estate projects. He has consistently been ranked as a top legal practitioner for over a decade by leading commentators. As a legal adviser with broad expertise, he has assisted many domestic and multinational clients with diverse operations in Thailand. His expertise includes working on a wide range of M&A transactions, joint ventures, structuring foreign investments, and on project finance transactions. He has advised investors on development and operation of projects within the power, alternative energy, mining, and petroleum industries in Thailand, in addition to broader corporate and regulatory matters.

KAMILA SEBEROVÁ
Wolf Theiss

In the course of her career, Kamila Seberová has advised a number of major companies from the life sciences sector on regulatory matters related to pharmaceuticals, medical devices and food supplements, clinical trials, price regulation or marketing and advertising of pharmaceuticals as well as assessment of compliance with legal regulations and ethical codes. Moreover, she often assists her clients in patent and unfair competition disputes or proceedings before the State Institute for Drug Control, Ministry of Health and administrative courts. Kamila is a
About the Authors

KAMILA VELIOVA

Kamila Veliova is a partner at Anand and Anand, and heads the firm’s corporate practice. A graduate of the faculty of law at Charles University, Prague, she has over 20 years of experience in the law firm sector. She has advised clients throughout her career in various fields, including corporate and M&A matters, employment, and real estate. Kamila has represented clients in the Czech Republic and abroad in major corporate transactions. She has also represented clients in regulatory and judicial matters, including in the area of M&A and employment. Kamila has successfully represented clients in several high-profile cases and has been involved in various court proceedings. Her expertise includes corporate law, M&A, employment, and real estate. She is ranked as a Leading Lawyer in AsiaLaw Leading Lawyers (2014–2016); acknowledged as a recommended leading lawyer in intellectual property for 2014 in Chambers Asia-Pacific; nominated as the Managing Intellectual Property IP Star (2014 and 2016) India for patents; and features as a leading lawyer in Asia IP Experts 2016.

ARCHANA SHANKER

Archana Shanker is a senior partner at Anand and Anand, and heads the firm’s patent practice. A graduate of the faculty of law at Delhi University, North Campus, she completed her postgraduate diploma in bioinformatics and pharmaceutical regulatory affairs. She is an active contributing member of various international bodies, such as the Asian Patent Attorneys Association, Association Internationale pour la Protection de la Propriété Intellectuelle and the Fédération Internationale des Conseils en Propriété Industrielle. Archana’s comprehensive repertoire enables her not only to represent clients in contentious matters in the pharmaceutical industry, but also to advise on protection and prosecution across a number of business sectors, including bioinformatics, pharmaceuticals, biotechnology and chemicals, not only in India but also in the United States, Europe, Japan and other key jurisdictions.

Her unique and innovative approach has led to her clients winning important claims of significant commercial value in the areas of software, mechanics and electronics. She is leading the firm’s efforts in nascent legislation of geographical indications and plant variety. Archana handles complex patent litigation issues before various judicial and quasi-judicial forums in India, such as the High Court and Intellectual Property Appellate Board, and has been involved in advising her clients on patent strategies and regulatory affairs. Client mandates repeatedly favour her as a counsel of choice. Her practice blends the legal acumen with the business know-how required in this complex area of practice.

She is a regular speaker and panellist at various national and international forums; author of articles in various publications such as Managing Intellectual Property, Asia IP, IAM Magazine and Lexology Getting The Deal Through: Patents. She also features on the editorial panel of Life Sciences Intellectual Property Law Review and regularly has articles published in various leading industry-focused specialised journals.


SURABHI SINGHI

Surabhi Singhi is a corporate lawyer based in the UAE. She has been practising in the UAE for around six years. She has worked across industries, and advised clients in the healthcare industry, particularly on M&As, joint ventures, spin-offs, restructurings, IPOs, business establishments, and tax and regulatory matters in the UAE and in India. She has worked as
a lead counsel in several M&A transactions and advised on corporate, civil commercial and agency laws of the UAE. She has acted for governmental organisations, institutional investors and global and regional corporates based in the United States, Europe, the Middle East and Asia.

EW A SKRZYDŁO-TEFELSKA

Sołtysiński, Kawecki & Szeląg

Ewa Skrzydło-Tefelska joined SK&S in 1999 and became a partner in 2006. She combines practice with academic work as a lecturer of EU law at the university in Lublin, where she received her PhD in 1987 and title of habilitated doctor in 2013. She studied for several years in France, the United States and at The Hague Academy of International Law. Dr Skrzydło-Tefelska’s practice focuses on advice and litigation in patent and trademark protection matters, including unfair competition and advertising.

As a co-head of the intellectual property department at SKS, with a strong emphasis on life sciences, she advises numerous clients from the pharmaceutical and medical devices sector, foodstuff producers and manufacturers of cosmetics both in regulatory matters and in the litigations involving their IP rights.

She is the author of books and articles on various aspects of EU and Polish law, especially involving issues of industrial property protection, pharmaceutical law and advertising. She is a frequent speaker at national and international conferences in the area of industrial property law, advertising law and pharmaceutical law.

ROSA VIRGINIA SUPERLANO

LEGA Abogados

Rosa Virginia Superlano joined LEGAME Abogados in 1999 and advises companies in the areas of telecommunications, information technology, competition, compliance, insurance, digital media, e-commerce and the pharmaceutical sector. Rosa Virginia is an attorney with extensive knowledge and expertise in the regulations applicable to different sectors. She has provided assistance to national and multinational corporations in processing, obtaining and transferring sanitary registrations and regulatory permits, as well as assisting in regulatory and authorisation proceedings before most public administration agencies. Rosa Virginia has extensive expertise in negotiation, preparation and implementation of logistic services and exclusive distribution agreements, and was seconded as legal counsel in the local subsidiary of a major international pharmaceutical company.

Rosa Virginia holds a specialisation in competition law from Monteávila University in Venezuela (2006); and a law degree (1986) and a commercial law specialist LLM from Andrés Bello Catholic University in Venezuela (1991).

She is recognised as a ‘leading individual’ by Chambers Latin America for life sciences and as a ‘recommended individual’ by The Legal 500 for competition and antitrust.

ODD SWARTING

Cirio Advokatbyrå

Odd Swarting is a senior counsel at Cirio. He works as legal adviser to public and privately held clients in various branches of industry and has more than 25 years of experience and focus in the healthcare, pharmaceutical, medical devices and food sectors. In addition to
transactions, collaborations and other commercial contracts, his practice largely involves research and development projects, pricing, substitution and other regulatory matters, and various issues pertaining to the public sector. Odd also has substantial experience in counselling clients during financial crises. Odd has been engaged as a speaker at various seminars and conferences and has written many articles within, inter alia, the life sciences area. Odd is ranked by Chambers as a leading individual within life sciences law in Sweden.

CÉCILE THÉARD-JALLU
De Gaulle Fleurance & Associés

With a profile in IT, commercial contracts, innovation technologies, data privacy and intellectual property law, Cécile Théard-Jallu has developed a strong experience for international players in the private and public sectors, including major American and European structures, particularly in the fields of health, life sciences, insurance, energy, the environment, telecommunications, mobility and more generally digital technology.

She helps clients design and implement their digital strategy and technological innovation (connected devices, artificial intelligence, Big and Smart Data, blockchain, robotics, etc.).

She focuses on complex contractual transactions, including R&D and consortium, technology transfers, licensing deals or technology change related projects, with or without public funding. In addition, she advises clients on the engineering, design, negotiation and implementation of their commercial, IT, technological and industrial contracts.

She has carried out numerous missions related to the protection of personal data, including with the GDPR’s arrival.

She worked for approximately one year in Washington, DC as a seconded lawyer within Covington & Burling LLP and as a seconded lawyer with one of the world’s leading medical equipment companies. As a member of the ‘Health/Life Sciences’ and ‘Technology’ groups of the International Bar Association, she has been included for several years in the Best Lawyers ranking published in partnership with Les Echos, in the ‘Biotechnologies’ and ‘Information Technologies’ categories for France.

BART VAN VOOREN
Covington & Burling LLP

Bart Van Vooren, PhD is a senior associate in Covington & Burling LLP’s Brussels office. He has a broad regulatory practice under EU and national laws, handles legislative and other policy assignments and provides strategic advice. Significant experience includes orphan medicines, ATMPs, advertising, regulatory exclusivities and transparency issues. He has handled more than two dozen cases before the EU Court of Justice. He is a leading global expert on life science companies’ compliance with the Biodiversity Convention and the Nagoya Protocol.

EMILIO N VOGELIUS
Estudio Beccar Varela

Emilio N Vogelius is a senior corporate law partner of Estudio Beccar Varela. He started his professional career as a clerk to a national commercial court and later moved to the private practice of Estudio Beccar Varela. He is fluent in Spanish and English.
He is currently head of the firm’s arbitration team and the life sciences team, and is the partner who initiated these practices within the firm.

The principal focus of his practice within the life sciences team is legal assistance to pharmaceutical companies. He is also the legal adviser for the Argentine Chamber of Medical Specialities, the chamber that includes most local subsidiaries of research laboratories.

He led the drafting of several publications, including the Argentina chapter of Practical Law’s *Life Sciences* multi-jurisdictional guide in 2012 and several annual editions of *The Life Sciences Law Review*.

Mr Vogelius has participated in several meetings and congresses as a lecturer, including the 2017 Healthcare Compliance Certification Program organised by Seton Hall Law School, Newark, New Jersey, and has published several works, including co-authoring *World Intellectual Property Rights and Remedies*, published by Oceana Publications Inc (2001), and the chapter on Argentina in *International Arbitration in Latin America*, published by Kluwer Law International (2003).

**XAVIER VUITTON**
*De Gaulle Fleurance & Associés*

Xavier Vuitton, PhD, is an expert in litigation. Former barrister to the French Supreme Courts (Council of State and Court of Cassation), he is a member of the Paris Bar and Quebec Bar. He acts frequently as an expert witness before Canadian and American courts in various disputes. He is also an associate professor at the University of Paris-Est.

**DAISY WANG**
*Lee and Li, Attorneys-at-Law*

Daisy Wang is a senior counsellor at Lee and Li, Attorneys-at-Law. After receiving an LLB from the National Taiwan University, Ms Wang pursued and received her LLM from the University of Illinois. She served with the National Bureau of Standards (the former IPO) for more than two years and joined Lee and Li in 1979 to handle patent and IP-related matters. Ms Wang is experienced in handling patent procurement and strategy consultation, patent dispute resolution, technology licensing, etc. and, since the 1990s, has handled various leading patent and IP cases, including for Intel, Philips, ABB, Sony and Celanese. Since 2000, Ms Wang has also helped clients with their Greater China patent and IP matters, including both prosecution and enforcement aspects of these issues. Since 1999, Ms Wang has continually been nominated as a reputable IP professional in surveys carried out by various international organisations and publications, such as *Asia IP*, MIP, *Who’s Who Legal*, Chambers and Partners (*Chambers Asia*), IAM, the American Biographical Institute, Euromoney (*Expert Guides*) and *Intercontinental Finance Magazine*.

**CELINE WEBER**
*Walder Wyss Ltd*

Celine Weber completed her law studies at the universities of Zurich, Geneva, Paris X Nanterre and New South Wales in Sydney (BLaw 2010, Master in Life Sciences Law 2012). She was admitted to the Bar in 2017. Before joining Walder Wyss, Celine Weber worked as a court clerk at the District Court in Meilen, Zurich, and as a trainee lawyer at a major corporate law firm in Zurich.
ANDREAS WILDI
Walder Wyss Ltd

Andreas Wildi studied medicine at the University of Zurich and graduated as medical doctor (MD). Working part-time in hospital, GP practice and on international rescue missions, he completed his law degree at the University of St Gallen HSG (MLaw). Before passing the bar exam, he gained his first professional legal experience as clerk with the Cantonal Court of Schaffhausen and with a recognised business law firm in Zurich. From his first position as an attorney at law in a large Zurich business law firm, Andreas Wildi was asked to work for the Swiss government, where he led the pharmaceutical reimbursement and pricing unit in the Federal Office of Public Health. Thereafter, Andreas Wildi broadened his market access expertise internationally, as EMEA market access law director for Janssen Pharmaceuticals (Johnson & Johnson). Since 2012, he has built up his legal practice in a large, renowned Zurich business law firm. In 2015, Walder Wyss elected Andreas Wildi as their partner.

JENNY WONG
Jones Day

Jenny Wong is an associate who practises in intellectual property law, focusing on patent litigation. Jenny has represented clients in complex patent infringement and revocation proceedings in the life sciences and technology sectors in multi-jurisdictional patent disputes in the Federal Court of Australia. Her experience includes matters relating to human vaccines, small molecules, biosimilar monoclonal antibodies, and solar cell technology. Jenny also advises clients on issues relating to freedom to operate and pricing and reimbursement of prescription pharmaceutical products in Australia. She holds a PhD in biochemistry and has extensive research experience in molecular biology.

ANTHIA A ZAMMIT
Anthia Zammit Legal

Anthia A Zammit LLB, LLD is an advocate admitted to practise law in Malta (EU) and is a licensed legal consultant in the State of New York (US). Anthia advises multinational mega-cap, private and publicly listed companies and institutions in the healthcare, life sciences, biotechnology, and pharmaceutical industries. Anthia drafts, reviews and negotiates contracts related to regulated products. She provides advice on market access, EU and national licensing and marketing authorisations, including EU regulatory data protection, EU risk management plans, pricing and reimbursement, compliance matters, advertising and labelling, R&D, clinical trials, and pharmacovigilance agreements. Anthia drafted the commercial agreements and terms introducing and implementing anti-corruption and anti-bribery provisions and procedures for leading pharmaceutical companies. Anthia has extensive experience in European regulatory law and compliance of medicinal products, pharmaceuticals, biologics, biosimilars and medical devices. She worked in-house and on a consultancy basis with and for the Medicines Authority (Malta’s national competent authority responsible for the regulation of medicinal products and the pharmaceutical industry), and was recently engaged to draft Malta’s medical cannabis regulations, general guidelines, and licence application. She served as legal counsel to the Malta Chamber of Commerce’s Healthcare Business section and was a member of the Policy Advisory Group of the European Patients Forum, a not-for-profit, non-government organisation that represents the interests
of an estimated 150 million patients in public health and health advocacy across Europe. She has participated as a keynote speaker in high-level healthcare conferences on invitation of the European Commission. Anthia earned her LLB (Bachelor of Laws) and LLD (Doctor of Laws) from the University of Malta.
### Appendix 2

#### CONTRIBUTORS’ CONTACT DETAILS

<table>
<thead>
<tr>
<th>Name</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANAND AND ANAND</strong></td>
<td>First Channel Building&lt;br&gt;Plot No. 17A&lt;br&gt;Sector 16A&lt;br&gt;Film City, Noida&lt;br&gt;Uttar Pradesh 201301&lt;br&gt;India&lt;br&gt;Tel: +91 120 4059 300&lt;br&gt;Fax: +91 120 4243 056/058&lt;br&gt;<a href="mailto:pravin@anandandanand.com">pravin@anandandanand.com</a>&lt;br&gt;<a href="mailto:archana@anandandanand.com">archana@anandandanand.com</a>&lt;br&gt;www.anandandanand.com</td>
</tr>
<tr>
<td><strong>BIRD &amp; BIRD</strong></td>
<td>Bird &amp; Bird (International) LLP&lt;br&gt;Paseo de la Castellana 7, 7th floor&lt;br&gt;28046 Madrid&lt;br&gt;Spain&lt;br&gt;Tel: +34 91 790 6000&lt;br&gt;Fax: +34 91 790 6011&lt;br&gt;<a href="mailto:raquel.ballesteros@twobirds.com">raquel.ballesteros@twobirds.com</a>&lt;br&gt;Bird &amp; Bird (MEA) LLP&lt;br&gt;Level 14, Burj Daman&lt;br&gt;Dubai International Financial Centre&lt;br&gt;PO Box 507110&lt;br&gt;Dubai&lt;br&gt;United Arab Emirates&lt;br&gt;Tel: +971 4 309 3222&lt;br&gt;Fax: +971 4 309 3223&lt;br&gt;<a href="mailto:melissa.murray@twobirds.com">melissa.murray@twobirds.com</a>&lt;br&gt;<a href="mailto:surabhi.singhi@twobirds.com">surabhi.singhi@twobirds.com</a>&lt;br&gt;www.twobirds.com</td>
</tr>
<tr>
<td><strong>ANTHIAZAMMIT LEGAL</strong></td>
<td>Victory Court, Apt 8A, Wileg Street&lt;br&gt;St Paul’s Bay, SPB 1922&lt;br&gt;Malta&lt;br&gt;Tel: +356 9921 2212&lt;br&gt;<a href="mailto:az@anthiazammit.com">az@anthiazammit.com</a>&lt;br&gt;www.anthiazammit.com</td>
</tr>
<tr>
<td><strong>CASTRÉN &amp; SNELLMAN ATTORNEYS LTD</strong></td>
<td>PO Box 233&lt;br&gt;(Eteläesplanadi 14)&lt;br&gt;00131 Helsinki&lt;br&gt;Finland&lt;br&gt;Tel: +358 20 7765 214&lt;br&gt;<a href="mailto:hanna.paloheimo@castren.fi">hanna.paloheimo@castren.fi</a>&lt;br&gt;<a href="mailto:hilma-karoliina.markkanen@castren.fi">hilma-karoliina.markkanen@castren.fi</a>&lt;br&gt;www.castren.fi</td>
</tr>
</tbody>
</table>
CHANDLER MHM LIMITED
36th Floor, Sathorn Square Office Tower
98 North Sathorn Road
Silom, Bangrak, Bangkok 10500
Thailand
Tel: +66 2009 5000
Fax: +66 2009 5080
jessada.s@mhm-global.com
pranat.l@mhm-global.com
suphakorn.c@mhm-global.com
noraseth.o@mhm-global.com
www.chandlermhm.com

CIRIO ADVOKATBYRÅ
Mäster Samuelsgatan 20
Box 3294
103 65 Stockholm
Sweden
Tel: +46 8 527 916 00
odd.swarting@cirio.se
https://cirio.se

COVINGTON & BURLING LLP
Kunstlaan 44 Avenue des Arts
1040 Brussels
Belgium
Tel: +32 2 549 5230
Fax: +32 2 502 1598
royarzabal@cov.com
rblaney@cov.com
bvanvooren@cov.com

2701 Two ifc, Shanghai ifc
No. 8 Century Avenue
Pudong New District
Shanghai 200120
China
Tel: +86 21 6036 2500
agu@cov.com

265 Strand
London WC2R 1BH
United Kingdom
Tel: +44 20 7067 2000
Fax: +44 20 7067 2222
gcastle@cov.com
scowlishaw@cov.com

The New York Times Building
620 Eighth Avenue
New York, NY 10018-1405
United States
Tel: +1 212 841 1000
jbalzano@cov.com

www.cov.com

DE GAULLE FLEURANCE & ASSOCIÉS
9 rue Boissy d’Anglas
75008 Paris
France
Tel: +33 1 56 64 00 00
Fax: +33 1 56 64 00 01
ctheardjallu@dgfla.com
xvuitton@dgfla.com
www.degaullefleurance.com
ESTUDIO BECCAR VARELA
Tucumán 1, 3rd floor
1049AAA
Buenos Aires
Argentina
Tel: +54 11 4379 6800
Fax: +54 11 4379 6860
evogelius@beccarvarela.com.ar
www.beccarvarela.com

JONES DAY
Aurora Place
Level 41, 88 Phillip Street
Sydney NSW 2000
Australia
Tel: +61 2 8272 0500
Fax: +61 2 8272 0599
amuratore@jonesday.com
jennywong@jonesday.com
www.jonesday.com

FIALDINI EINSFELD ADVOGADOS
Av. Presidente Juscelino Kubitscheck
1700/14th floor
04543-000 São Paulo, SP
Brazil
Tel: +55 11 3848 2240
alexandre.einsfeld@feadv.com.br
joaquim.queiroz@feadv.com.br
ivan.cunha@feadv.com.br
www.feadv.com.br

KIM & CHANG
39, Sajik-ro 8-gil
Jongno-gu
Seoul 03170
Korea
Tel: +82 2 3703 1114
Fax: +82 2 737 9091/9092
yhcho1@kimchang.com
myungsoon.chung@kimchang.com
www.kimchang.com

KABRAJI & TALIBUDDIN
406-407, 4th Floor, The Plaza at Do
Talwar
Clifton, Block 9
Karachi 75600
Pakistan
Tel: +92 21 3583 8871-6
Fax: +92 21 3583 8879
arlin.merchant@kandtlaw.com
www.kandtlaw.com

GORODISSKY & PARTNERS LAW
FIRM
B Spasskaya Str, 25, bldg 3
129090 Moscow
Russia
Tel: +7 495 937 6116
Fax: +7 495 937 6104
alexandrove@gorodissky.ru
goryachevi@gorodissky.ru
www.gorodissky.com

LEE AND LI, ATTORNEYS-AT-LAW
8F, No. 555, Sec. 4, Zhongxiao E. Rd.
Taipei 11072
Taiwan
Tel: +886 2 2763 8000
Fax: +886 2 2766 5566
katherinejuang@leeandli.com
jillniu@leeandli.com
daisywang@leeandli.com
www.leeandli.com

LATIN LEX
Tower Financial Center (Edificio Tower
Bank) Piso 17, Of. 17C
Calle 50 y Beatriz M de Cabal
Panama
Tel: +507 388 2655
Fax: +507 388 2655
fcoronel@latinlex.net
www.latinlex.net

© 2020 Law Business Research Ltd
Contributors' Contact Details

LEĞA ABOGADOS
Av. Eugenio Mendoza, Urb. La Castellana
Torre La Castellana, Piso 7
Caracas 1060-A
Venezuela
Tel: +58 212 277 2200
rsuperlano@lega.law
vmontero@lega.law
www.lega.law

RODRIGO, ELÍAS & MEDRANO ABOGADOS
Av. San Felipe 758
Jesús María
Lima 15702
Peru
Tel: +511 619 1900
Fax: +511 460 6306
mcalvarado@estudiorodrigo.com
rdevettor@estudiorodrigo.com
www.estudiorodrigo.com

MANNHEIMER SWARTLING ADVOKATBYRÅ
Norrlandsgatan 21
Box 1711
111 87 Stockholm
Sweden
Tel: +46 8 595 060 00
camilla.appelgren@msa.se
www.mannheimerswartling.se

SÁNCHEZ DEVANNY
Av. Paseo de las Palmas #525 Piso 6
Col. Lomas de Chapultepec
Miguel Hidalgo
Mexico City 11000
Mexico
Tel: +52 55 5029 8500
Fax: +52 55 5029 8571
jacampos@sanchezdevanny.com
www.sanchezdevanny.com

NYBORG & RØRDAM LAW FIRM P/S
Store Kongensgade 77
1264 Copenhagen K
Denmark
Tel: +45 33 12 45 40
kab@nrlaw.dk
www.nrlaw.dk

SHUSAKU YAMAMOTO
17th floor, Grand Front Osaka Tower C
3-1 Ofuka-cho
Kita-ku
Osaka 530-0011
Japan
Tel: +81 6 6372 3910
Fax: +81 6 6372 3919
tskomatani@shupat.gr.jp
www.shupat.gr.jp

SŁOTYSIŃSKI, Kawecki & Szlęzak
Jasna 26
00-054 Warsaw
Poland
Tel: +48 22 608 7000
Fax: +48 22 608 7070
ewa.skrydlo-tefelska@skslaw.pl
jacek.myszko@skslaw.pl
www.skslaw.pl

POLAK & PARTNER RECHTSANWÄLTE GMBH
Am Getreidemarkt 1
1060 Vienna
Austria
Tel: +43 1 582 58 0
Fax: +43 1 582 58 2
k.hellbert@fplp.at
www.fplp.at

© 2020 Law Business Research Ltd
STUDIO PROFESSIONALE
ASSOCIATO A BAKER & McKENZIE
Viale di Villa Massimo, 57
00161 Rome
Italy
Tel: +39 06 44 06 31
Fax: +39 06 4406 3306

Piazza Meda, 3
20121 Milan
Italy
Tel: +39 02 76231 1
Fax: +39 02 7623 1620

roberto.cursano@bakermckenzie.com
riccardo.ovid@bakermckenzie.com
irene.carlet@bakermckenzie.com
www.bakermckenzie.com/en

VIEIRA DE ALMEIDA
Rua Dom Luís I, 28
1200-151 Lisbon
Portugal
Tel: +351 21 311 3451
Fax: +351 21 311 3406
fp@vda.pt
ica@vda.pt
www.vda.pt

WALDER WYSS LTD
Seefeldstrasse 123
PO Box
8034 Zurich
Switzerland
Tel +41 58 658 58 58
Fax: +41 58 658 59 59
andreas.wildi@walderwyss.com
celine.weber@walderwyss.com
www.walderwyss.com

WOLF THEISS
Pobřežní 12
Prague 8
Karlin, 186 00
Czech Republic
Tel: +420 234 765 111
Fax: +420 234 765 110
kamila.seberova@wolftheiss.com
www.wolftheiss.com

WONGPARTNERSHIP LLP
12 Marina Boulevard
Level 28
Marina Bay Financial Centre
Tower 3
Singapore 018982
Tel: +65 6416 8000
Fax: +65 6532 5722
melanie.ho@wongpartnership.com
manphing.chang@wongpartnership.com
www.wongpartnership.com