ACKNOWLEDGEMENTS

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

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LATIN LEX
LEE AND LI, ATTORNEYS-AT-LAW
LEGA ABOGADOS
POLAK & PARTNER RECHTSANWÄLTE GMBH
PORTOLANO CAVALLO
Acknowledgements

RODRIGO, ELÍAS & MEDRANO ABOGADOS
SHUSAKU YAMAMOTO
SOŁTYSIŃSKI, KAWECZI & SZLĘZAK
VIEIRA DE ALMEIDA
WALDER WYSS LTD
WONGPARTNERSHIP LLP
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PREFACE

The seventh edition of The Life Sciences Law Review covers a total of 34 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. After many years of negotiations and false starts, the United States and EU have finally begun to implement a programme of mutual recognition of inspections of drug manufacturing establishments, thus simplifying the shipment of drug products between the jurisdictions and freeing resources to carry out more inspections in third countries. In the meantime, the United States continues to debate whether to repeal the comprehensive medical care legislation enacted during the Obama administration, and is now 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 planned 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
March 2019
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.

ICH

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.

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These included the European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Research and Manufacturers of America and the Japan Pharmaceutical Manufacturers Association.

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:

a development of the scientific consensus for a guideline;
b agreeing on the draft text of a guideline;
c consulting with regional regulatory agencies;
d adoption of harmonised guidelines; and
e 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.

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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.
iii 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,\textsuperscript{27} which also serves as the model for all major developed jurisdictions. Other topics are clinical safety (including pharmacovigilance),\textsuperscript{28} dose-response studies,\textsuperscript{29} ethnic factors,\textsuperscript{30} clinical trials generally (including statistical principles),\textsuperscript{31} clinical evaluation,\textsuperscript{32} clinical evaluation by therapeutic category\textsuperscript{33} and pharmacogenomics.\textsuperscript{34}

\textbf{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.\textsuperscript{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:

\begin{itemize}
\item \textit{a} Module 1 consists of regional administrative information, which varies by jurisdiction;
\item \textit{b} Module 2 contains summaries and overview documents;
\item \textit{c} 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);
\item \textit{d} Module 4 contains reports of non-clinical studies (safety); and
\item \textit{e} Module 5 contains reports of clinical studies (efficacy).
\end{itemize}

\textbf{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).

\textsuperscript{27} ICH E3.
\textsuperscript{28} ICH E1-E2F.
\textsuperscript{29} ICH E4.
\textsuperscript{30} ICH E5.
\textsuperscript{31} ICH E7-E11.
\textsuperscript{32} ICH E14.
\textsuperscript{33} ICH E12A.
\textsuperscript{34} ICH E15-E16.
\textsuperscript{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 organisations. 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

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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.
I 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 2019, there has been a change 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. With the exception of the registration of biological products, not many changes have occurred during 2018 regarding the issuance of regulations. Carlos A Chiale continues as head of the National Administration of Drugs, Food and Medical Devices (ANMAT).

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 former government issued the joint resolution Ministry of Industry 118/2012, Ministry of Health 546/2012 and Patent Office on 25 March 2013. Resolution 107/2012, which adds requirements to obtain the patentability of pharmaceutical products, triggered a lawsuit initiated by several companies, which has been ongoing since August 2013.

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

1 Emilio N Vogelius is a partner at Estudio Beccar Varela.
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.

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. In recent times, ANMAT has discouraged the qualification of companies only acting as sole importers and sellers of pharmaceutical products. 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.

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.

i 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;
c label information; and
d leaflet information for patients.

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 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. 840/1995 regarding 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.3

The import of such drugs has to be requested in each case by the patient or a civil association. 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.4 The total amount of drugs to be imported shall be for a treatment that does not exceed 60 days. If the treatment is longer, a new and different request shall be made in each case.

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3 Drugs for compassionate use must be for clinical situations, such as: diseases that compromise the life of the patient; diseases that evolve towards disability; diseases that cause a permanent disability; diseases that deteriorate the quality of life; and for eventual therapeutical situations, such as for treating patients who have illnesses for which there are no specific treatments in Argentina, for those who are intolerant to every available treatment, for those who would not correctly respond to the available treatment, for those whose bodies are incompatible with the available drugs, or for those who have been treated with that medicine in a foreign country and might suffer detrimental effects from changing to an authorised drug in Argentina, or when a drug has been discontinued in Argentina and a risk-benefit relationship exists that is reasonable.

4 This resolution makes a distinction that considers whether the drugs that will be imported have been previously authorised for commercialisation in other countries. Regarding drugs that have not been previously authorised for commercialisation, the requirements that have to be complied with in order to import them are: (1) even when the patient has a deadly disease, there must be scientific evidence to conclude that the drug might be effective and that there are not unreasonable risks for the patient; (2) the drug must be, at the time of the request, under investigation in at least one controlled clinical trial (unless all clinical trials have been concluded and the sponsor is actively seeking approval of the drug); (3) the drug must complete Phase II of investigation; (4) at least one clinical study must have been published in a prestigious publication; (5) the preclinical phase must be completed; and (6) the request must be accompanied by the manufacturer’s declaration, a medical report indicating the patient information and justification for the use of the drug signed by the physician, and a patient’s informed consent in writing, signed by him or her, which explains the reasons why the patient will use that drug. In cases where the patient is a minor or incapacitated, the consent must be signed by the responsible person in charge. With respect to the drugs that have been previously authorised for commercialisation by the health authority of a foreign country, the requirements that have to be complied with in order to import them...
According to Resolutions Nos. 942 and 426 of 2001, the import of these drugs is exempted from the payment of custom taxes and fees.

ANMAT specifically clarifies that its only intervention in this process is to issue a document that will provide the customs authority with evidence that the Board of Health endorses the request of the patient. The Board of Health also clarifies that it does not have competence with respect to aspects such as the authorisation for the acquisition of drugs by social security entities, or the provision of the drugs or the acts that need to be carried out to acquire the drug abroad.

Resolution No. 2324/97, also from ANMAT, specifically authorises non-profit civil associations that are legal entities to import drugs for compassionate use to sell to their members on a cost-price basis, and establishes that, to carry out that import, they must request authorisation from ANMAT (as described in Section II.iii). It is important to underline that in many cases, non-profit civil associations have made these requests.

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.

are: (1) the request must be accompanied by the manufacturer’s declaration, a medical report indicating the patient information and justification for the use of the drug signed by the physician, and a patient’s informed consent, in writing, signed by him or her and explaining the reasons why the patient will use that drug. In cases where the patient is a minor or incapacitated, the consent must be signed by the responsible person in charge; and (2) the request must be accompanied with preclinical investigation works, the clinical trials for the indication proposed and a certificate that authorises the use of the drug in that country.
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. 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.

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.

 ix Manufacturing control

Regulation No. 2819/2004, 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

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5 Article 4, Law No. 24,766.
6 Article 8, Law No. 24,766.
7 Regulation No. 13832/2016.
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.

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.
Nevertheless, the last government (which was in power until 10 December 2015) exercised
strict price controls despite the fact that no law existed that officially regulated prices, even
going so far as to initiate administrative actions against companies that it considered were
overpricing their products. Other actions that implied an indirect action were related to
continuous inspections from the health or tax authorities that did not impede work but
created a tense environment that occasionally lasted for weeks, thus affecting normal activities.
These inspections are mentioned as an example. The current government takes a more liberal
approach on the matter and it appears that no price control is being brought into effect.

It is relevant to offer an explanation regarding the supply of pharmaceutical products
to people affiliated to social security entities (affiliates), in particular those that are associated
with the public entity that deals with social security protection for retirees: the National
Institute of Social Services for Retirees and Pensioners.

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). The agreements
are usually 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 addition to this agreement, 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. 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,
onece 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 Kairos and Manual Farmacéutico, two 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 has been an 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. These kind of actions usually favour the claimant and are increasingly becoming a matter of common practice. 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.8

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.

8 Case included in AR/JUR/33790/2016.
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
Argentina is evolving away from being an administration that imposed very restrictive rules on commerce in general, and to pharmaceutical commerce in particular.

The previous administration enacted regulations that made difficult or impeded the possibility of patenting pharmaceutical products in Argentina. These are still in place. The pharmaceutical research industry reacted by filing administrative and judicial actions that have not been resolved.

The change in administration is relatively recent but, to date, similar attempts have not been noted. It appears that through the different social security organisations, the purpose of the current administration is to enter into agreements with the pharmaceutical industry, though it should be mentioned that, because of economic reasons, the incidence of local costs, including taxes and labour costs, puts pressure on the negotiations between the parties. It should be highlighted that pressure over the pricing of pharmaceutical products is a constant matter of discussion in these negotiations.

Although there is an agreement in place with the pharmaceutical industry as a whole (not one but several agreements), it should be noted that the intention of the authorities is to gradually cease in these kinds of agreements and move into a bidding scenario on a product-by-product basis. This was the trend in November and December 2018, and we imagine that this will continue. The major difficulty faced by the social security organisations is the administration and auditing of product consumption.

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.

Owing to the measures taken by the current administration, foreign trade has returned to normal, which allows for the import of products and active principles, as was the case in the past.
Although changes have been very recent, it appears that the trend is to return to a more liberal market, without abrogating the control to which the life sciences market is usually subject.
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

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1 Anthony Muratore is of counsel and Stephen Rohl is an associate at Jones Day.
are products whose principal intended action is not by pharmacological, immunological or 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 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

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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 2017 (No. 1), Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011 and Therapeutic Goods (Human Cells, Tissues and Organs) Determination 2018.


Sponsors must also ensure compliance with the relevant guidelines as to good clinical practice and safety monitoring and reporting, 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.

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:

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’.


Australia

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,\(^{11}\) biologicals\(^{12}\) and medical devices\(^{13}\) 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.

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(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$47,800 and A$191,800, respectively (or A$50,700 and A$202,800, respectively, for the priority pathway) and for a new biological are A$1,090 and A$72,200 to A$234,700, 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.

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.

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.
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.16

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).17 The Australian

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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 TGA 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.

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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).

xii 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 VI and VII).

III  PRICING AND REIMBURSEMENT

Under the Pharmaceutical Benefits Scheme (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

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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. 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.

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 FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

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:

a speaking at an education meeting or event;
b sponsorship to attend an educational event;
c the purpose of market research where the identity of the healthcare professional is
   known to the pharmaceutical company that contracted the market research; and

d 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.

VI 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.

VII 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.

VIII 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:

a. definitions of terms (including ‘health warning’ and ‘prominently displayed or communicated’);
b. the requirements for scientific or clinical claims and consistency with public health campaigns; and

c. 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.

Relatedly, the Therapeutic Goods Amendment (2017 Measures No. 1) Act 2017 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. a strict liability offence, which attracts a maximum penalty of A$21,000;
b. 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 the 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 developed a new approval pathway for prescription medicines whereby sponsors may apply for time-limited provisional registration on the ARTG (up to a maximum of six years) of a new prescription medicine or a new use of an already registered prescription
medicine. 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.

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’. 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:

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

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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.
AUSTRIA

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.
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

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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).13 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 2013.14 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

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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.\(^{15}\) 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.\(^ {17}\) 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

\(^{15}\) [www.basg.gv.at/azneimittel/vor-der-zulassung/klinische-pruefungen/].


\(^{17}\) [www.basg.gv.at].
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:

- according to the most up-to-date information and practical experience, the medicinal product must not be harmful when used;
- the ingredients (active substances as well as excipients) must be harmless and this must be proven scientifically;
- the product must be state of the art;
- any description of the medicinal product and the product *per se* must not be misleading; and
- 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:

- information on the name and marketing authorisation number of the product authorised in Austria;
- the state in which the parallel-imported product is authorised and marketed;
- the name and marketing authorisation number of the product to be parallel-imported;
- the name and address of the marketing authorisation holder established in the exporting country;
- a description of the packaging;
- the name and address of the person responsible for relabelling and repackaging; and
- a declaration that, for instance, the summary of product characteristics, packaging and labelling do not deviate from the product authorised in Austria.
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.\(^\text{18}\)

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.

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\(^\text{18}\) 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:

a the kinds of tasks envisaged, the production volume and the place where such activities will be conducted;

b the building’s condition, size of the facility, zoning classification, equipment and the exact location; and

c 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.\textsuperscript{21}

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

\section*{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.\textsuperscript{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 Act\textsuperscript{23} 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.

\section*{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.\textsuperscript{24} Substances can only be purchased:

\begin{enumerate}
  \item 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;
  \item by a scientific institution after the supervising authority has confirmed that the possession of such substances is needed for scientific purposes;
\end{enumerate}

\textsuperscript{22} Federal Law Gazette I No. 79/2010.
\textsuperscript{23} ErläutR 773 BlgNR XXIV.GP 6.
\textsuperscript{24} Federal Law Gazette I No. 112/1997, as amended.
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.

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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.

### V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

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.

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.

26 Federal Act of 3 July 1973 concerning compensation for vaccine damage, as amended.
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

Peter Bogaert and Charlotte Ryckman

I MATCHOONPTIOON

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 Peter Bogaert is a partner and Charlotte Ryckman 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.
The Royal Decree on Good Laboratory Practices\textsuperscript{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\textsuperscript{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 \textit{in vitro} embryos.\textsuperscript{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\textsuperscript{15} and 2005/28/EC.\textsuperscript{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

\textsuperscript{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.

\textsuperscript{13} The Law concerning Experiments on Human Beings of 7 May 2004, as amended. The act is implemented in a Royal Decree determining the Measures of Implementation of the Law of 7 May 2004 on the Experiments on Human Beings in Relation to Clinical Trials of Medicines for Human Use of 30 June 2004, as amended.

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


\textsuperscript{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.
A 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,\textsuperscript{17} 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 October 2018.\textsuperscript{18} 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.

\textit{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 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.


\textsuperscript{18} The amending act is the Law on Miscellaneous Provisions Regarding Health of 30 October 2018.
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:

a  

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;

b  

informed consent was obtained from the patient;

c  

the medicinal product is not being used in clinical trials;

d  

it does not concern a medicinal product that does not need a registration or marketing authorisation;

e  

there is no other available treatment on the market, under hospital exemption or as a magistral preparation;
there are no authorised products in other countries worldwide; and it is impossible to submit a request for a compassionate use programme.

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. 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.

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.

vi  Regulatory incentives

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 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.

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19 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.
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\textsuperscript{20} and Regulation (EC) No. 1901/2006\textsuperscript{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\textsuperscript{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.

**ix 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\textsuperscript{23} and a 1993 Royal Decree on samples,\textsuperscript{24} which implement the EU advertising rules into Belgian law. These include the general requirements that advertising must not be misleading.


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

\textsuperscript{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.
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.

**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. 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.

**xi 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).

**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. 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.

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25 Royal Decree of 18 March 1999, also cited above.
26 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.
28 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

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.

**i  Medicines**

Pricing and reimbursement 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 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

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29 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.

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

31 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.
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 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. 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

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32 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.
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.

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 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.33

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,

33 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.
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 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.\(^34\) 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.\(^35\) 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

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\(^34\) Article 38 Section 2 of the Coordinated Law of 10 May 2015 on the Practice of Healthcare Professions.

\(^35\) Under the Act on Compensation for Damage caused by Healthcare of 31 March 2010, as amended.
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.

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.36 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. However, there are elections in 2019, which could of course have an impact on the prioritisation of certain policy initiatives.

Changes are expected with regard to the distribution rules on medical devices (and those changes are, to some degree, related to the developments at EU level). Currently, 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. New legislation will change this and open up the distribution system. The new rules are expected to be published soon.37 The current notification requirement for distributors will reportedly continue to apply.

For several years now, there has been a strong emphasis on limiting the expenditure for healthcare coverage. This is indeed one of the central themes of 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

36 These are discussed in the EU chapter.
37 At the time of drafting of this contribution, the new rules had not been published yet.
provides a high-level overview of policy priorities in Belgium. It emphasises, 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). This is in line with the current trend of an increasingly frequent use of Article 81 agreements, which have become a central tool in the reimbursement policies. The Pact on the Future states that Article 81 agreements must be used more as ‘pay-for-performance’ tools instead of more traditional rebate mechanisms. In addition, several projects relating to healthcare expenditure are currently ongoing.

The Benelux countries and Austria 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. In the summer of 2017, a website was launched that contains some further information on the initiative and its procedures.38 In June 2018, Ireland joined the initiative, and various countries have reportedly expressed interest as well.

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. This builds on the price decreases that already applied to biologics in case of biosimilar market entry. In addition, there are discussions on launching product-specific projects to financially incentivise physicians to prescribe biosimilars instead of the originator biologics. The regulators are monitoring the uptake of biosimilars and if it does not sufficiently increase, further legislative measures (potentially including quota or other incentivising mechanism) cannot be excluded.

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. The use of the electronic patient file, for instance, is becoming increasingly important.

Finally, pursuant to the adoption of the EU General Data Protection Regulation, Belgium has revisited its privacy legislation, including privacy rules that apply specifically to scientific research. On 5 September 2018, the Belgian Law on the Protection of Individuals regarding the Processing of Personal Data of 30 July 2018 was published in the Official Gazette and therefore entered into force.39 Belgian law introduces specific requirements with regard to scientific research and the processing genetic data, biometric data and data concerning health.

38 See www.beneluxa.org/.
Chapter 6

BRAZIL

Alexandre Einsfeld, Joaquim Queiroz and Ivan Cunha

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 on 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 import products regulated by the law;
e issuing licences for the import and export of 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.

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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 (encompassing both medicines and medical devices) require authorisation by ANVISA and licensing by local sanitary authorities.

i Classification
According to Law 9,782/1999, the goods and 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, including 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 haemotherapy equipment and materials, as well as equipment and materials for laboratory and image diagnosis;
g immunobiologics 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 \textit{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, by other procedures or submitted to radiation sources.

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 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.

ii Non-clinical studies
Law 11,794/2008 establishes procedures for the scientific use of animals. 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 scientific use of animals.

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, issued by ANVISA and by the National Health Council (CNS), are Resolution CNS 466/2012, Resolution RDC 9/2015 and Resolution RDC 10/2015. No federal law has been enacted yet regarding this matter, but there is currently a bill of law pending in the Senate (PLS 200/2015), under scrutiny of the House of Representatives.

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, which focuses 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 203/2017 was released by ANVISA on 26 December 2017. It 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 are not authorised to apply directly, but 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 conservation 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 proposed instruction sheet to be included in the product package, a sample of the label’s layout, proof of payment of the sanitary fee and the intended price of the product must also must be submitted.

Issuance of marketing authorisation still takes a year or more. Law 13,411/2016 was enacted in order to rationalise the analysis and establish strict time limits based on transparent criteria of technical complexity and urgency in providing the drug to patients has been enacted.

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 157,414 euros 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 exclusive 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 two direct actions for alleged unconstitutionality, which are 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.

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 of 17 December 2008 and Normative Ruling 05 of 5 May 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.
ANVISA’s website has a comprehensive Q&A about drug advertisement, which can be found at: http://portal.anvisa.gov.br/documents/33864/284972/RDC96_COMENTADA.pdf/7092f0ca-f08a-43c4-ac7a-5d8ba208f2dd).

x 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.

xi Classification of products

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

a OTCs;

b drugs sold with medical prescription (without retention of the prescription);

c drugs sold with medical prescription, in which the prescription must be retained by the pharmacist or drugstore (no refill without another prescription);

d drugs subject to special control; and

e 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.

xii Imports and exports

The importation of medicines and medical devices is regulated by Resolution 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 20.16 per cent, according to CMED’s Rule 15, of 21 September 2018.
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 255/2018 that dictates the general rules concerning all administrative proceedings.

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 PAYERS
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

During 2018, ANVISA issued more than 50 new Resolutions. These new regulations concern several topics, such as importation of products, post-approval controls, outsourcing of production steps, analysis of quality control, transport and warehousing of medicines, and clinical trials.

A few of the most relevant regulatory changes are:

a. RDC 233/2018, which modified the definition of commercial transactions stated in the RDC 102/2016. The new concept is defined as a transaction between companies resulting in the transfer of assets or a group of assets, without the occurrence of any corporate transaction between them. The current concept of commercial transactions is broader than the previous one (limited to transactions involving the sale and purchase of assets).

b. RDC 234/2018, which updated regulation regarding outsourcing of drugs and biological products manufacturing stages, quality control, transportation and warehousing.

c. RDC 255/2018, which established ANVISA’s Internal Regulations.

d. RDC 257/2018, which modified the rules for analysis of quality control, transport and warehousing of medicines, and biological products by third parties.
INTRODUCTION

During 2018, China continued with its drug and device regulatory reform with respect to both streamlining the development and approval processes, and paying increased attention to the enforcement of good practice guidelines and post-market obligations, particularly in the wake of a scandal related to the manufacturing of vaccines that emerged during the summer. Otherwise, 2018 continued to see reform in the drug and device spaces in China, including a reorganisation of government agencies and further implementation of the blueprint for regulatory reform released in late 2017, 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 2017). The encouragement of innovation in the drug and device spaces continues to be a core goal of the 13th Five Year Plan and related policy plans that the government put in place thereafter.

These new reforms are not the first building block of this effort. They follow years of reforms that have accelerated during the past few years. For example, in 2013, the State Food and Drug Administration was reorganised into a more powerful ministry-level agency, referred to as the China Food and Drug Administration (CFDA). In 2018, the food function was removed from CFDA and it was reorganised into the National Medical Products Administration (NMPA), which is now the primary regulator of drugs, medical devices and cosmetics. The NMPA is subordinate to a new super-ministry, the State Administration for Market Regulation (SAMR).

China also continues to revise its framework laws and regulations for drugs and devices. In 2018, the NMPA worked with other agencies and branches of the government to release a new draft of the Drug Administration Law (DAL) for comment and a new draft of the Regulations on the Supervision and Administration of Medical Devices (RSAMD). These drafts build on many years of reform. For example, in 2014, the entire medical device regulatory regime was revised, and the State Council approved a subsequent amendment in 2017. In 2015, a new system of registration pathways for small molecule drugs was established, under which generic drugs must demonstrate therapeutic and quality equivalence with what should typically be a fully evaluated reference product, and new drugs or innovations (e.g., dosage forms) must now meet a high standard of being ‘new to the
China has also implemented a pilot marketing authorisation holder programme (MAH Pilot) in 10 cities, which is now being expanded nationwide for drugs and devices. The MAH Pilot permits domestic research-based companies to hold the rights to the product, while contracting out manufacturing, subject to a set of obligations.

These and other reforms continue to change the regulatory landscape in China. At the time of writing, the Innovation Opinion is final, and the laws and regulations that are meant to implement it are still emerging. Some reforms have already occurred via rule or fiat, but many are still in process. Therefore, this chapter describes the system for drug and device regulation as it exists at the time of writing, but also notes where and how some of the most innovative reforms may continue to affect different parts of this system.

II THE REGULATORY REGIME

i Regulatory agencies and their jurisdiction

As of the full government re-organisation in March 2018, the NMPA is now the primary pharmaceutical and medical devices regulatory agency in China. Many of the other agencies that had some hand in regulating drugs, including biologics, devices and combination products, have also changed names or merged with other agencies to become super-ministries. It 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 decisions for the departments to adopt and implement.

For drugs, the primary departments and centres include the Department for Drug Registration, which is subdivided into departments for research and development, chemically synthesised drugs and biological products, and the Department for Drug Supervision, which is subdivided by the type of manufacturing that each subdivision supervises (chemically synthesised, biologic) and a department in charge of pharmacovigilance activities. The affiliated centres are the Centre for Drug Evaluation (CDE) and the Centre for Drug Re-Evaluation (CDR). The CDE evaluates clinical trial and marketing authorisation applications. 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 department for supervising research and development. The supervision department 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.

With an official headcount of 216 at the national level (not counting contract personnel), the NMPA relies on provincial counterparts, which are merging with local administrations for industry and commerce to become ‘market supervision bureaus’, and

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3 See the Opinions of the State Council on Reform of the System of Evaluation, Review and Approval of Drugs and Medical Devices (State Council No. 44 2015), available at www.gov.cn/zhengce/content/2015-08/18/content_10101.htm.

similar device and drug regulatory authorities in the municipalities\(^5\) 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 review agencies (CDE and CMDE) with more reviewers. Real numbers are difficult to determine, but the NMPA’s announcement on the CDE’s hiring\(^6\) and the CDE’s annual reports indicate that it continues to add reviewers, and that the number has grown into the hundreds, from 60 to 70 a few years ago.\(^7\) The CMDE has similarly been adding reviewers but has fewer than the CDE.\(^8\) 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. 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 anti-monopoly 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 Ministry of Human Resources and Social Security also plays a part in setting the formularies for these insurance plans. For imported drugs, the China Customs Administration, which now includes parts of the former Administration of Quality Supervision, Inspection and Quarantine, 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

The NMPA administers laws, State Council regulations, rules and guidance documents related to drugs and devices. 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 2001.\(^9\) 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

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\(^5\) 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).

\(^6\) 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.


\(^8\) Statistics compiled by reviewing many hiring announcements on CMDE’s website, www.cmde.org.cn.

for the DAL, referred to as the DAL Implementing Regulations (DALIR), which were last amended in 2016. China released two proposed amendments to the DAL to implement the Innovation Opinion in October 2017 and November 2018, but they are not yet finalised.

The NMPA (and its predecessor agencies, the CFDA and SFDA) promulgated 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 regulation governing clinical trials and drug and biologic registration are the Drug Registration Regulations (DRR), for which the NMPA has not finalised a comprehensive amendment since 2007. An amendment in accordance with the Innovation Opinion has been planned for some time now but has not materialised.

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. 35,2017) (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 DAL or the DRR (or both) as the 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. Similarly, in 2018 it issued a document providing for implicit approvals (similar to notifications) for new drug clinical trials.10

China’s legislature has not enacted a law covering medical devices, but the State Council has enacted a framework regulation, namely the RSAMD.11 As with drugs, the NMPA has enacted a number of implementing rules covering registration, production and distribution.12 In 2014, the State Council revised the RSAMD, and the NMPA subsequently issued an entirely new set of substantially revised implementing regulations, governing device registration, manufacturing and distribution. In 2017, the State Council finalised a shorter amendment to the RSAMD to implement reforms to the approval of sites for medical device clinical trials and other issues, for example, related to the approval of a category of ‘large-scale medical devices’. At the time of writing, the NMPA has issued two other draft amendments to the RSAMD for public comment to implement device-related forms in the Innovation Opinion, such as the expansion of the MAH Pilot to medical devices, with the last being issued in June 2018. This amendment should make some progress in 2019.

Reform of the NMPA’s rules and guidelines on various aspects of medical devices and drugs continues on a regular basis. In August 2018, for example, the NMPA finalised a new and substantial rule on adverse event reporting of medical devices. Like the CDE, the CMDE issues its own rules and product-specific guidance documents.

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12 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.
### Classification

#### Drugs

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

*articles which are used in the prevention, treatment and diagnosis of human diseases and intended for the regulation of the physiological functions of human beings, for which indications, usage and dosage are established, including Chinese crude drugs, prepared tranches of Chinese crude drugs, traditional Chinese medicine preparations, chemical drugs substances and their preparations, antibiotics, biochemical drugs, radioactive pharmaceuticals, serum, vaccines, blood products and diagnostic agents.*

This definition should be read to include small molecule drugs, biologics, certain traditional Chinese medicine and certain *in vitro* diagnostics. In practice, the NMPA has significant discretion to determine whether a substance constitutes a drug or fits into another regulatory regime. 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.

Once determined to be a drug, the regulatory requirements applicable to a product will be determined by its pathway and its features. Even with the current reforms, the primary pathways remain those for domestically manufactured drugs or imported drugs, depending on whether the finished dosage form of the drug is manufactured inside or outside China. Among other differences, if the drug is to be manufactured in China, it must be made in a facility with the appropriate drug manufacturing licence and comply with China’s drug good manufacturing practice requirements.

Regardless of the place of manufacture, domestic drugs are then classified into three types: traditional Chinese medicines and natural drugs, chemical drugs and biological drugs. Within each classification, drugs are again placed into categories and subcategories. These classifications and sub-classifications determine the 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 CFDA 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.
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.

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.

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.\(^{15}\)

Biologics have not yet undergone a similar reform, although the CFDA proposed a new highly simplified classification system for biologics in October 2017. Currently, biologics are classified as either therapeutic or preventive (i.e., vaccines), then further classified into 15 subcategories under each heading.\(^{16}\) Classification depends on the drug’s marketing approval status in China and abroad, source material, composition and other factors. The subcategories are not necessarily mutually exclusive, which can lead to confusion and duplicative requirements. China does not have a pathway for biosimilars in its regulations. Rather, in 2015, it issued a guidance document on the development of 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. CDE has issued or proposed product-specific guidance documents for certain types of biosimilars since then.

As explained below, certain types of drugs may also be subject to separate and heightened requirements and require additional special permissions. Examples of this would be those that the NMPA classifies as ‘narcotic drugs’ and ‘psychotropic drugs’, which are discussed below.

**Devices**

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

> Medical devices means 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;


\(^{16}\) Appendix 3 of the DRR.
pregnancy control; and

provision of information for medical or diagnostic purposes by inspecting the samples of human bodies.\textsuperscript{17}

The RSAMD then defines three classes of medical devices:

\textit{Class I} medical devices means medical devices with low risks, and those for which safety and effectiveness can be ensured through routine administration; \textit{Class II} medical devices means medical devices with moderate risks, which must be strictly controlled and administered to ensure their safety and effectiveness; \textit{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.\textsuperscript{18}

As with drugs, the NMPA and its relevant divisions have significant discretion to determine what constitutes a medical device and what class it fits into. 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.\textsuperscript{19}

The NMPA oversees an electronic portal, run by the National Institutes for Food and Drug Control (NIFDC), that permits applications for a predetermination of device classification. The NMPA maintains and periodically updates a classification catalogue showing its medical device classification decisions. By reference to this catalogue, with the general classification rules, the applicant can make its own determination as to classification. In 2017, the CFDA finalised a new and extensive classification catalogue, offering a new system of organising different types of devices and more detail and examples of the types of devices that fit under the various entries. The new classification catalogue came into effect in August 2018.

As with drugs, the 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.\textsuperscript{20}

Some \textit{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 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:

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\textsuperscript{17} Article 76 of the RSAMD. This is an edited version of the translation available on www.chinalawinfo.com.

\textsuperscript{18} Article 4 of the RSAMD.

\textsuperscript{19} Article 16 of the RSAMD.

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
None of the aforementioned framework legislation has mentioned combination products. Instead, the NMPA issued a notice in 2009 to govern its review of drug and device combination products.\(^\text{21}\) 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.\(^\text{22}\)

iv  Non-clinical studies
Non-clinical studies for drugs must comply with the NMPA Drug Good Laboratory Practice Regulations,\(^\text{23}\) which may be similar to good laboratory practice requirements in other countries to some extent. Non-clinical studies for drugs must be conducted by institutions that have been certified by the NMPA to perform such studies to be accepted as part of a drug registration application. The NMPA also accredits laboratories that conduct pretrial testing for Class II and III devices. The Innovation Opinion may create more flexibility in this system by permitting both drug and device applicants to conduct testing outside this structure of state-accredited laboratories. Those implementing measures are still in progress.

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. For example, some devices are exempt from clinical trials based on existing data and the safety record of predicate devices. For both drugs and devices, the NMPA has adopted a more structured mechanism to accept foreign data to support marketing applications in China.

The Innovation Opinion also includes a conditional approval programme, under which a foreign-approved drug for an orphan indication or a drug for preventing or treating

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life-threatening diseases can be approved based on early-stage data. Various prior and subsequent documents have mentioned the conditional approval programme in different forms and levels of detail. Perhaps most significantly, in October 2018, the NMPA and NHC jointly issued procedures under which a drug designated by CDE and approved in the United States, EU or Japan, can receive approval in China on a special expedited basis.24

**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 CDE), which CDE must approve. As of July 2018, for a ‘new drug’ or a drug that has not yet been approved in China or outside, the applicant submits a dossier or materials and then may begin the trial according to its protocol if CDE has not objected within 60 days of the date of filing. This notification system – also referred to as ‘implicit approval’ – was also included in the proposed amendment of the DAL that the National People’s Congress issued for comment in late 2018. If it does not go through this system, the NMPA’s review of a CTA can take about one year or more.

Currently, for new drug trials, 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 for drugs that fit within the new drug pathway and those that are intended to treat certain illnesses or patient populations (e.g., children or elderly people) that the State Council or the NMPA considers to be clinically in demand. Priority review may also be possible for drugs that are in simultaneous development in the European Union and the United States. The NMPA is continually working to reduce this timeline for approval.25 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,26 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 recent legislative changes to the DALIR, this certification process has now changed from a pre-approval to a filing. Clinical trials in China are also governed by pharmaceutical good clinical practice (GCP) regulations,27 which

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

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, the information associated with it (including the protocol) can be difficult to amend, even for small changes. Although the agency is proposing to change current practice in this latest round of reforms, its regulations still do not include a clear procedure for protocol or other amendments to a CTA. 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. The NMPA has been revising the application requirements for chemically synthesised drugs, but the following requirements for biologics remain on the books.

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

As of 2017, if the drug has been approved abroad, China’s drug regulations generally require submission of proof of that prior to before 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.

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. 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.

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 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.

28 Appendixes 2 and 3 of the DRR.
30 Article 44 of the DRR.

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Devices

Clinical data are used to establish the safety and efficacy of medical devices that are registered for marketing in China. Clinical data are used to establish the safety and efficacy of medical devices that are registered for marketing in China.32 In general, manufacturers must submit clinical trial data to register Class II and Class III medical devices (including in vitro diagnostics).33 No clinical trial is required for Class I devices.34

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.35 To further define these categories, the NMPA issued multiple catalogues of exempt devices,36 ultimately issuing one unified catalogue in 2018, 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.37 In 2018, a proposed amendment to the RSAMD would remove the requirement for a clinical trial for Class II devices and potentially broaden the exemption for Class III devices to cover those that present a greater 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.

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.38 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.39 The NMPA issued procedures to implement this provincial notification requirement in July 2015.40 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 2016.41 These GCPs added to the provisions on informed consent (including those on consent from children and others who

32 Article 17 of the RSAMD.
33 id.
34 id.
35 id.
38 Article 18 of the RSAMD.
39 id.
40 See the Announcement on the Notification of Medical Device Clinical Trial (CFDA 2015), available at www.nmpa.gov.cn/WS04/CL2138/300025.html.
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.

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 to do so jointly with the Chinese clinical trial site (i.e., the hospital) from the Office of Human Genetic Resource Management within the Ministry of Science and Technology. This approval can also cover the exportation of the biospecimens and the data associated with them. This approval is required regardless of whether the foreign company is conducting genetic tests and covers any sample that contains human DNA.42 The regulations on human genetic resources also include controversial provisions on the sharing of intellectual property, including patent rights to any invention emerging out of the cooperation regarding collection of the samples. The Office of Human Genetic Resource Management 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.

**vi Named-patient and compassionate use procedures**

Under the Innovation Opinion, 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. The latest proposal would permit applicants to submit applications to the CDE. If the CDE determines that the application meets relevant requirements and the expanded access programme would not otherwise interfere with the trial, then it may approve an expanded access programme within 30 days.

Currently, the NMPA permits limited drug compounding for use on their own patients, sometimes without having to receive NMPA clinical trial approval or marketing authorisation.43 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.44

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. Medical institutions can assess patients for a treatment plan in the zone and apply for importation of unapproved medicines. Recently Bo’ao obtained approval to make those decisions for itself instead of obtaining NMPA approval. The drugs are then imported.

43 Article 25 of the DAL.
44 Article 36 of the DALIR.

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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. Bo’ao also permits fast-tracking of unapproved medical devices under similar circumstances.

vii Pre-market clearance

Drugs

As discussed, the NMPA review and approval is required for the domestic production or importation of drugs. The DRR provide five types of drug registration applications: (1) new drug; (2) generic drug; (3) imported drug; (4) supplemental applications; and (5) re-registration. With the exception of (4) and (5), the type of application depends on where the finished dosage form of the drug is manufactured.

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. More recent practice has shown that there may be some flexibility for other applicants to utilise another entity’s certificate of pharmaceutical product. 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 NIFDC for conformity with product specifications and quality standards. Under the Innovation Opinion, certain testing may be permitted at other third-party laboratories, which, if implemented in this manner, could significantly reduce some of the delays that have prolonged development in China.

The manufacturer must also appoint a local entity in China to act as the agent for the imported drug registration. Registration agents may be drug distribution entities that hold distribution licences, which allow them to book sales and promote the drug. The registration agents bear joint responsibility and liability for quality, safety and other regulatory obligations and related violations.

New drug application

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 and a separate GMP certification. Under a new plan, the manufacturing licence and the GMP certification will be merged. Depending on the existence of a manufacturing licence, the NMPA will issue a new drug certificate and, subsequently, an official drug approval number, which permits marketing of the drug.

As discussed above, the NMPA implemented an MAH Pilot for drugs manufactured in China. The MAH Pilot began in 2015 and was renewed in 2018. It was originally implemented

45 Article 11 of the DRR (2007).
46 Articles 84 to 95 of the DRR.
in 10 provinces, including Beijing and Shanghai. Individuals of Chinese citizenship and research institutions (which can include drug companies) working or established, respectively, in one of the pilot provinces are permitted to hold a licence for a domestically made product, including the rights to sell, distribute and receive profits from the drug. However, those individuals or entities could contract out the manufacturing and distribution or hold their own manufacturing and distribution licences. MAHs are also permitted to use more than one manufacturing site. Although on a limited scale, the MAH Pilot permits smaller research and development entities to hold product licences without developing costly facilities that they cannot afford. MAHs also have the ability to distribute their drugs directly without having to apply for a drug distribution licence.

Both the proposed DAL and RSAMD contain the structure for the MAH Pilot to become a regular feature of the regulatory landscape.

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.

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.

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. 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 NIFDC. 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.

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. However, the DRR require that

47 id. Notice for Issuing the Plan for the MAH Pilot (State Council General Office No. 41 2016), available at www.gov.cn/zhengce/content/2016-06/06/content_5079954.htm.
48 Opinion on Developing Therapeutic and Quality Equivalence Evaluation for Generic Drugs (State Council General Office No. 8 2016), available at www.gov.cn/zhengce/content/2016-03/05/content_5049364.htm.
51 Chapter 5 of the DRR.
all biologics go through the application pathway for new drugs, and do not provide for a separate biosimilar category. The application requirements may still be different depending on the subcategory of biologics. For example, 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.

In 2015, the CDE finalised a guidance document on biosimilars, 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 provisions on labelling and pharmacovigilance. Some biosimilars have been approved under this guidance.

**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, and by 2017, the NMPA touted reducing the backlog to only 4,000. 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.

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, and 160 business days for CDE review of generic drug applications. In practice, CDE review often takes longer. 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 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

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52 Article 12 of the DRR.
53 Appendix 3 of the DRR.
new drugs that treat unmet medical needs. The NMPA’s new priority categories over the past two 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 States and Europe. 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 NMPA renewed these priority review categories in late 2017 for the duration of 2018 and beyond.

As discussed, under the Innovation Opinion, the NMPA will permit conditional approval (permitting earlier approval of a drug that has showed promise in early trials and treats a life-threatening illness) provided that the drug meets post-marketing commitments. The NMPA permitted something like conditional approval before the Innovation Opinion (i.e., allowing foreign data to support orphan drugs with only a requirement that the applicant conduct a short study post-marketing), but this new system more officially permits early phase data to support expedited approval.

As discussed above, this measure permits drugs approved abroad that treat orphan indications and drugs marketed in the United States, the EU and Japan that the CDE has designated as fulfilling urgent clinical needs in China. The NHC and NMPA released a list of diseases qualifying as orphan diseases in 2018.

Re-registration application

The registration for an imported or domestic drug is valid for five years. Six months before expiry of the registration, the applicant must submit a re-registration application to the NMPA if it is an imported drug or to the local provincial drug regulatory authority if it is a domestic drug. Re-registration 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. The relevant regulatory authority must complete the review and either approve or deny the application within six months of accepting the filing. If the re-registration 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 re-registration applications for imported drugs to the CDE.58

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. While major post-approval changes require the NMPA review and approval, some minor changes can be notified to the agency and implemented without a full technical review. The proposal

59 Chapter 8 of the DRR.
described above relating to re-registration of imported drugs would also transfer final approval over supplemental applications for both imported and domestic drugs to the CDE to reduce delays.

**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, the innovation opinion could expand self-testing, and proposed drafts of the RSAMD have included provisions to this effect.

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 days of acceptance of the application, the materials are sent on to a technical review institution, which under normal circumstances has 60 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 days. Similarly, the technical review institution may make a one-time request for any supplementary materials required. It then has another 60 days from the time of receipt of those materials to make its decision. Once the technical review is complete, the NMPA has 20 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

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serve urgent clinical needs.61 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 re-registration 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 working days. Licensing items require another technical review before a modified registration certificate will be issued.62

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, post-approval regulatory incentives are weaker and their implementation is incomplete. China has established a system of patent protection for drugs and devices. China has not yet implemented regulatory data protection, and China has a kind of de facto market exclusivity implemented through a new-drug monitoring period (described below) for a product that has not been manufactured in China or is locally manufactured in China.

Under the Innovation Opinion, China committed to implement new incentive systems, including real 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.

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 2018, the NMPA released a draft regulatory data protection regulation in April,63 but the progress on the draft has stalled. Pursuant to this draft, 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 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. Technically there are 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 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 has approved the CTAs of other applicants for the same drug, those applications may proceed to registration. The Innovation Opinion leaves the fate of the monitoring period unclear.

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65 Article 18 of the DRR.

66 Article 19 of the DRR.
Proposed Regulatory Data Protection

Under a recently issued draft regulation, the Regulatory Data Protection (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.67

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).68 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.69

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;
g preliminary research must be complete, traceable and there must be a basic product model; and
h the data must be complete and traceable.70

68 Article 48 of the Measures on Medical Device Registration.
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 events and product complaints, and meet any conditions imposed as part of the product approval.71 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.72

For medical devices, the NMPA issued revised Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation in August 2018,73 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. 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., 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.74

71 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).
74 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.
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.

**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 MAH system makes it easier to transfer licences because the licences will be less linked to one manufacturing site.

Otherwise, for domestically manufactured drugs, licences are currently issued to the specific manufacturer for the specific manufacturing site. As a result, any transfer requires a transfer of ownership of the site because the two are bundled together. This is usually done via an equity acquisition of the holder of the two licences, because NMPA regulations have specifically prohibited any ‘purchase and sale, rental, or other loan of the licences’.

For imported licences, the situation is somewhat different because there is no manufacturing licence. Thus, the licence has been permitted to be transferred by a procedure to change the name of the holder, and the manufacturing site can 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.75

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75 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.
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.76

**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.

In any of the following circumstances, a drug shall not be re-registered [if]:

1. the application for re-registration is not made prior to the expiry date;
2. the relevant requirements set by the State Food and Drug Administration when approved for marketing are not met;
3. the Phase IV clinical trial is not completed as required;
4. the adverse drug reaction monitoring is not conducted in accordance with regulations;
5. there are uncertain therapeutic efficacy, serious adverse reaction or other factors harmful to human health upon re-evaluation by the State Food and Drug Administration;
6. the drug approval documents shall be withdrawn in accordance with the provisions of the Drug Administration Law;
7. the production conditions prescribed in the Drug Administration Law are not met;
8. the obligation of observation period is not fulfilled in accordance with regulations; or
9. there are other circumstances not in conformity with relevant regulations.

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.77

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

- production or sale of counterfeit or substandard drugs;78
- non-compliance with customs rules for imported drugs;79 or
- non-compliant labels.80

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

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76 Article 18 of the Measures for the Supervision and Administration of Medical Device Manufacturing (CFDA 2017).
77 Article 55 of the Measures on Medical Device Registration.
78 Articles 74 and 75 of the DAL.
79 Article 80 of the DAL.
80 Article 85 of the DAL.
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.\(^8\)

These grounds are echoed in the new adverse event reporting regulation for the devices discussed above. The revised RSAMD provide that obtaining a licence via fraudulent or corrupt means is grounds for revocation of the licence.\(^8\) 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 also interpreted certain provisions of the PRC criminal law to apply 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.

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 GMPs. Class I device facilities submit a notification to local food and drug regulatory authorities before proceeding with production.

For drugs, any proposed establishment of a facility must be approved by government agencies responsible for economic planning, and by the provincial regulatory authority for potential ability to meet GMP requirements. Upon completion of the facility construction, the facilities must pass GMP inspection and receive a GMP certificate 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.\(^8\) 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.\(^8\)

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.\(^8\)

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

\(^8\) Article 51 of the RSAMD.
\(^8\) Article 64 of the RSAMD.
\(^8\) Article 10 of the Measures for the Supervision and Administration of Medical Device Manufacturing.
\(^8\) Article 67 of the RSAMD; Article 67 of the Measures on the Supervision and Administration of Medical Devices Manufacturing.
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.

xi 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. 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 drug-specific advertisement requirements and prohibitions are 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 were promulgated jointly by the NMPA and the State Administration for Industry and Commerce (SAIC) in 2007. There have been various proposals to revise the agency-level drug advertising rules, but none have been finalised.

The provincial drug regulatory authority where the advertiser is located must review and approve all drug advertisement materials. Article 4 of the Advertisement Measures 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 advertisements. Advertisement approval is valid for one year only and no change is allowed to an approved advertisement. 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 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 label or package insert (off-label promotion). The prohibition against off-label advertising is set out in Article 6 of the Advertisement Standards:

The advertisement content relating to the indications or the primary therapeutic functions must be consistent with the drug instructions approved by the NMPA, must not expand or maliciously conceal, and must not contain any theories, viewpoints, or similar contents that are outside the drug instructions.

The Drug Administration Law of China 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), which, like the drug standards, are now also under revision as a result of the 2015 amendments to the
Advertisement Law. 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.

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 or device manufacturer to distribute the products that it manufactures for itself. Both drug and device distributors must meet respective sets of good supply practices.

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.

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.

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.

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


89 Articles 29 to 31 of the RSAMD.
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 may be required.\textsuperscript{92}

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.

\textbf{xv 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 Ministry of Health 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 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.

\textbf{xvi Enforcement}

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 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 In 2018, the NMPA also issued a notice 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 DAL, has included provisions against responsible individuals in addition to increased fines for entities.

The year 2018 was also a year in which a scandal with a vaccine manufacturer’s violation of drug GMP regulations shook up the policy environment. The discovery of the GMP violations led to the resignation and firing of certain key officials, and a renewed commitment to strict penalties in this area. Presumably as a result, the latest draft of the DAL had significant prohibitions and penalties generally and particularly related to vaccines and other biologics.

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

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97 Article 141 of the Criminal Law of the People’s Republic of China.
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.100

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 2,151 drugs in its most recent version, which the government revised in February 2017. Subsequently, in 2017 and 2018, the NRDL added approximately 53 drugs. This latest version includes a number of innovative drugs and increases the range of therapies available for paediatrics, cancer, hepatitis and cardiovascular diseases. 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.

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 State Medical Insurance Administration, as well as the Ministry of Human Resources and Social Security.

By contrast, the commercial insurance sector is smaller, but steadily developing.101 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.102

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.


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.

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. 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. 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. 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.\textsuperscript{106} The applicant can appeal an ARO or ARC decision to the State Council, whose decision is final, without the availability of judicial review.

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.\textsuperscript{107} 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:

\begin{itemize}
  \item $a$ the major evidence was inadequate;
  \item $b$ the administrative agency erroneously applied the law or regulations;
  \item $c$ the administrative act violated legal procedures;
  \item $d$ the administrative act exceeded authority;
  \item $e$ administrative power was abused; or
  \item $f$ the administrative act was obviously inappropriate.\textsuperscript{108}
\end{itemize}

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 DAL 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 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 two years since the government launched anti-bribery investigations of foreign drug manufacturers.

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:

\begin{itemize}
  \item $a$ no linkage between healthcare provider incomes and profits from drug sales or medical services;
  \item $b$ no rebates for prescribing medicine or referrals for services or drugs;
  \item $c$ no overcharging of patients;
\end{itemize}

\textsuperscript{106} Article 17-20 of the Administrative Reconsideration Measures of the CFDA.
\textsuperscript{107} Article 44 of the Administrative Litigation Law (NPC 2017), available at www.npc.gov.cn/npc/xinwen/2017-06/29/content_2024894.htm.
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, China revised the AUCL, which 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 2018, building upon the Innovation Opinion and other related policies, the NMPA issued proposed rules on medical representatives. These proposed rules were an effort to

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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.

VII CURRENT DEVELOPMENTS

The creation of the NMPA and continued work to implement the Innovation Opinion were at the centre of developments in 2018. 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 2018.¹¹² This sheds an encouraging light on the NMPA’s gradual harmonisation with international standards and regulatory systems, and the potential for continued regulatory reforms by the NMPA.

Although some of the reforms have slowed, the Innovation Opinion continues to drive reforms to review or approve applications efficiently through the use of good review practices and better communication with applicants through meetings throughout the development and approval processes to ensure that China approves drugs that meet the most pressing clinical needs. The NMPA is also implementing a stronger approach to pharmacovigilance and post-market surveillance through the MAH expansion and a ‘life-cycle’ approach to drug and device monitoring that takes into account a broader range of safe signals collected through more systematic and risk-based measures.

The key areas to watch in 2019 are the revisions of the RSAMD and the DAL and whether those will further cement some of the directions set in the Innovation Opinion. The IP reforms related to patent linkage and regulatory data protection will be a key area to watch in this respect.

I INTRODUCTION

The legal regulation of medicines and medical devices is to a great extent based on the applicable EU legislation. The national rules concerning medicines for both human and veterinary use are set forth in the Act on Pharmaceuticals, which specifies, inter alia, the requirements for obtaining marketing authorisation, manufacturing and distribution of medicines, clinical trials and pharmacovigilance. Furthermore, the Act on Pharmaceuticals regulates operation of the State Institute for Drug Control (the Institute), the main regulatory body responsible for human medicinal products, which is supervised by the Ministry of Health. The Institute oversees all the procedural matters (i.e., marketing authorisation process, applications for clinical trials, etc.) and is responsible for enforcement of the respective legislation relating to human medicines. As further explained below, rules for advertising of medicines are not laid down directly in the Act on Pharmaceuticals, but are subject to the Act on Advertising.

Medical devices are dealt with separately in the Act on Medical Devices, which, similarly to the Act on Pharmaceuticals, regulates areas such as clinical evaluation, registration and notification, distribution and sale of medical devices. The medical devices sector is also overseen by the Institute as the competent regulatory authority.

In addition, both of the aforementioned acts are accompanied by a number of ministerial decrees that lay down more specific rules in relation to particular issues, such as good laboratory practice, and specify the general requirements stipulated by the acts.

II THE REGULATORY REGIME

i Classification

As briefly outlined above, medicinal products are defined by the Act on Pharmaceuticals, which also provides for an exhaustive list of particular types of medicines, such as human medicines, veterinary medicines or human immunological medicines. Likewise, definition and classification of medical devices is subject to the Act on Medical Devices. The definitions

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1 Vojtěch Chloupek is a partner and Roman Norek is a junior associate at Bird & Bird.
3 Act No. 40/1995 Coll., on Regulation of Advertising, as amended.
4 Act No. 268/2014 Coll., on Medical Devices, as amended.
Czech Republic

reflect the respective EU directives; however, they have been slightly adjusted and the wording is thus not identical to the EU legislation. For example, the definition of a medicinal product under Czech law is a bit more specific and reads as follows:

A medicinal product shall mean:

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

b) a medicinal product shall also mean any substance or combination of substances which may be used or administered to human beings or used or administered to animals with a view to restoring, correcting or modifying the physiological functions by means of a pharmacological, immunological or metabolic effect or with a view to making a medical diagnosis.

In addition, the definition of medicinal products also includes medicines for veterinary use, as the two separate EU directives concerning human and veterinary medicinal products have been implemented by the Czech legislator into a common act. The statutory definitions provide a starting point for differentiating between strictly regulated medicinal products, and products such as dietary supplements or cosmetic products that do not fall within the scope of the Act on Pharmaceuticals. In the borderline issues, if the categorisation of a certain product is not clear, the Institute decides whether the product may qualify as a medicine or a medical device under the respective laws and, where relevant, under which category it falls. For the sake of completeness, dietary supplements are governed by the Act on Food and Tobacco Products and are assessed and approved by the Ministry of Health, not the Institute.

ii Non-clinical studies

Under the Act on Pharmaceuticals, operators conducting non-clinical safety studies are obliged to proceed in compliance with the principles of good laboratory practice. The procedures for non-clinical safety studies on medicinal products within laboratory tests, according to the principles of good laboratory practice, are laid down in the Ministerial Decree implementing the EU Directive on the inspection and verification of good laboratory practice. Furthermore, in the case of studies on animal models, the operators conducting non-clinical safety studies must observe the Act on the Protection of Animals against Cruelty.

iii Clinical trials

A clinical trial on medicines may only be commenced if (1) the Institute has issued an authorisation to commence the trial (or, in the case of clinical trials that are subject to the notification requirement only, the Institute has not rejected such a trial), and (2) the ethics...
committee has issued a positive opinion on the study. A mere notification is sufficient if the tested medicinal products are EU-authorised products or, if the products are not authorised in any EU Member State, where the products are not obtained by biotechnological processing or where the products containing substances of human or animal origin are not concerned. In addition, a clinical trial may only be undertaken in relation to trial subjects that have consented in writing to the trial after being informed of its nature, significance, implications and potential risks. The informed consent may be revoked by the trial subject at any time.

The ethics committee, consisting of healthcare professionals and non-medical members, shall protect the rights, safety and health of trial subjects and provide assurance of that protection by, for example, expressing an opinion on the clinical trial protocol. Furthermore, as a general rule, clinical trials on human medicines involving natural persons as trial subjects have to be governed by the rules of good clinical practice. Further guidelines as well as application forms for clinical trial authorisation and clinical trial notification are available in electronic form on the Institute’s website.

Recently, the Act on Pharmaceuticals has been amended to comply with the EU Clinical Trials Regulation. The amendment is not yet effective, however, and therefore the above procedure applies until the amendment legally comes into effect.

As regards the clinical trials on medical devices, the requirements for their commencement are to a certain extent similar to clinical trials on medicines. If the medical device is not CE-marked or if it is used for other than the original purpose within the scope of the clinical trial, the clinical trial requires a prior authorisation by the Institute, and the application should be submitted by the sponsor in electronic form via the Registry of Medical Devices. The ethics committee, which is an advisory body of the healthcare service provider, supervises the clinical trial and provides a written approval therewith. Subject to limited exceptions, a written informed consent by the trial subject must be obtained before the commencement of the clinical trial on medical devices.

iv  Named-patient and compassionate use procedures

As a general rule, only authorised medicinal products may be prescribed to patients, placed on the market and used in the delivery of healthcare services. However, an exception from this rule may apply in the delivery of healthcare services to individual patients. If the following statutory requirements are met, the attending doctor may prescribe or use a medicinal product that has not been authorised in accordance with the Act on Pharmaceuticals:

a  no medicinal product of adequate composition or similar therapeutic properties, for which a marketing authorisation exists, is distributed or marketed in the Czech Republic;

b  the medicinal product has been authorised abroad or it qualifies as a product for modern therapies, the manufacturer of which is a manufacturing authorisation holder in relation to the relevant pharmaceutical form;

c  use of the medicinal product is sufficiently justified by scientific findings; and

d  the medicinal product does not contain any genetically modified organisms.

v  Pre-market clearance

Under the Act on Pharmaceuticals, only medicinal products authorised by the Institute or medicinal products authorised in accordance with the EU Regulation laying down Community procedures for the authorisation and supervision of medicinal products for
human and veterinary use\textsuperscript{10} may be placed on the market in the Czech Republic. In the first case, the application for marketing authorisation shall be lodged with the Institute and the authorisation may only be granted to an applicant that resides or is established in the territory of any of the EU Member States. The Act on Pharmaceuticals sets out a list of documents and information that must accompany the application.

In respect of certain categories of medicinal products, such as human homeopathic products or traditional herbal medicinal products satisfying the statutory requirements, a simplified registration procedure may apply. If a homeopathic product has been authorised through the simplified procedure, that information must be clearly stated on the label as well as in the package leaflet. In the case of traditional herbal products, the labelling must state that use of the product is based exclusively on experience from long-standing use.

During the marketing authorisation procedure, the Institute should first assess the completeness of the application and, where it is found to be complete, the Institute must make a decision within 150 or 210 days of provision of the information about completeness of the application. The exact period depends on the type of medicine to be assessed. The marketing authorisation is valid for five years and may be subsequently renewed, based on a review of the risk-benefit ratio by the Institute. During the five-year term, the marketing authorisation may be changed, suspended or revoked if, for example, the medicinal product is harmful or the risk-benefit ratio of the product is not favourable.

Under the Act on Medical Devices, registration of persons intending to place medical devices on the market is required (in the form of a notification submitted electronically via the Registry of Medical Devices). Registration is completed once the Institute issues a certificate of compliance with the notification requirement and is subsequently valid for a period of five years, which may be repeatedly extended. The Act on Medical Devices also regulates the notification requirement in respect of medical devices that have been placed on the market. This notification is also valid for five years, and repeated extensions are possible.

\section*{vi Regulatory incentives}

Under the Act on Inventions,\textsuperscript{11} a supplementary protection certificate may be granted for substances protected in the territory of the Czech Republic by a valid patent, if they are the active substances of the medicinal products registered in accordance with the Act on Pharmaceuticals. An application for a certificate may be filed by the proprietor of the patent protecting the substance under the following requirements:

- the basic patent is valid in the territory of the Czech Republic;
- the product contains the active substance protected by the basic patent and has a valid marketing authorisation;
- the certificate has not yet been granted for the substance; and
- the marketing authorisation is the first authorisation to place the mass-produced medicinal product on the Czech market.

\textsuperscript{10} Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended.

\textsuperscript{11} Act No. 527/1990 Coll., on Inventions and Rationalisation Proposals, as amended.
The certificate takes effect for a period equal to the period that elapsed between the filing date of the basic patent application and the date of the first marketing authorisation enabling the medicinal product to be placed on the market in the Czech Republic, reduced by five years. That being said, the certificate may only be effective for a maximum period of five years.

There is no such supplementary protection in respect of medical devices.

vii Post-approval controls

The rules concerning staffing of the marketing authorisation holders, their risk management and safety reporting include a requirement to ensure that the sales representatives are qualified adequately to the nature of the medicinal product or, where a risk to the health of treated persons arises, a requirement to adopt all measures available to remedy the situation and limit the adverse effects of the medicinal product concerned. If a defect in the quality of the medicinal product is identified by the marketing authorisation holder or if a defect is found by a third person and notified to the Institute, the marketing authorisation holder must ensure that the patients can have the defective medicinal product exchanged by any pharmacy or, if that is not possible, ensure a complete recall of the product from the market.

The marketing authorisation holder is obliged to operate a pharmacovigilance system to collect information on the risks associated with the medicinal products, subject to the marketing authorisation, which will be subsequently evaluated by the marketing authorisation holder in terms of risk minimisation and prevention. Based on the evaluation, appropriate measures should be adopted to limit potential risks. Furthermore, the marketing authorisation holder must have permanently and continuously at their disposal a qualified person responsible for pharmacovigilance who ensures development and maintenance of the pharmacovigilance system; that person must be domiciled within the territory of the European Union. The Institute may request the marketing authorisation holder to appoint a contact person in the Czech Republic who would deal with pharmacovigilance issues and be subordinate to the qualified person domiciled in another EU Member State.

As regards variations to marketing authorisation, marketing authorisation holders must submit any change in an authorisation to the Institute for approval or, as the case may be, announce or notify the change. Variations to marketing authorisations are regulated by the directly applicable EU Regulation on assessment of variations to marketing authorisations for human and veterinary products.12 The marketing authorisation holder may also apply for transfer of the marketing authorisation to another natural or legal person. The Institute must decide about the application within 30 days of its delivery and specify, if the application is not rejected, the date on which the transfer is to be conducted.

As briefly discussed above, the Institute may change, suspend or revoke the marketing authorisation if, for example, the medicinal product is harmful or lacks therapeutic efficacy. Other reasons for revocation, suspension or change of the marketing authorisation of the medicinal product include findings that the risk-benefit balance is not favourable or that the qualitative and quantitative composition of the medicinal product is inconsistent with the documentation submitted.

Reporting and evaluation of adverse incidents and safety corrective actions regarding medical devices is carried out through a vigilance system. Generally speaking, an adverse

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12 Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, as amended.
incident is defined under the Act on Medical Devices as any failure or deterioration of characteristics or efficacy of a medical device which resulted or could have resulted in the death or serious deterioration of health of the medical device’s user or another individual. Accordingly, a field corrective action is defined as an action determined by the manufacturer with the aim of reducing the risks associated with the adverse incident. The Act on Medical Devices also stipulates a number of obligations for healthcare service providers at whose premises a suspected adverse incident has occurred.

In the event of discrepancies regarding inclusion of the CE mark (e.g., the medical device that has been placed on the market is CE-marked without authorisation), the Institute is entitled to issue a decision for withdrawal of a medical device from the market.

viii Manufacturing controls

Manufacturing of medicinal products is subject to an authorisation from the Institute. An application for the authorisation must contain, among other things, specification of the site where the medicinal products are to be manufactured and evidence that the applicant has at their disposal suitable and sufficient premises, technical equipment and control facilities for the required activity. Based on the information provided, the manufacturing authorisation must specify the premises in which the manufacture may be carried out. Furthermore, within the inspection activities, the Institute may conduct ad hoc inspections of the designated premises.

Contrary to legal regulation of medicinal products, the Act on Medical Devices does not contain any specific provisions concerning manufacturing facilities.

ix Advertising and promotion

Advertising and promotion of medicines is specifically addressed by the Act on Advertising. As a general rule, only medicines authorised under the Act on Pharmaceuticals may be advertised. The Act on Advertising distinguishes between two categories of advertising of medicines – advertising aimed at the general public and advertising aimed at healthcare professionals. As regards advertising aimed at the general public, it cannot promote, inter alia, prescription-only medicines. Such products may only be the subject of advertising aimed at healthcare professionals. This form of advertising may be carried only through information channels targeting healthcare experts, such as professional magazines, and must include accurate, current and verifiable information, basic information according to the summary of product characteristics, information about the manner of dispensing the product according to the registration, and information about the reimbursement status of the product under the public health insurance system. Furthermore, it is prohibited for advertising aimed at healthcare professionals to offer, promise or provide them with any gifts or other benefits, unless they are of insignificant value and relate to the activities of the professional.

Any advertising of over-the-counter medicines aimed at the general public must clearly state that the product being advertised is a human medicine and include the brand name of the product as stated in the marketing authorisation. In addition, potential customers must be provided with the information necessary for the proper use of the medicine and be given a clear instruction to read the package leaflet. The Act on Advertising also provides for a list of prohibited actions (e.g., the advertising must not suggest that the human medicine is a food or cosmetic product or that consultation with a healthcare professional is not necessary).

As the advertising of medical devices it not subject to any specific rules, the general provisions of the Act on Advertising apply.
Distributors and wholesalers

Medicinal products may be distributed in the territory of the Czech Republic either by (1) persons authorised directly by the Institute to conduct this activity or (2) a holder of a distribution authorisation granted by a competent authority of another EU Member State. In the latter case, the EU-based distributor is, however, obliged to give prior notice to the Institute to show evidence of the distribution authorisation and provide information regarding the scope of distribution and the location of distribution stores.

To obtain the authorisation, the applicant must:

a. have suitable and adequate premises, installations and equipment, so as to ensure proper storage and distribution of the medicinal products;

b. have ensured the services of persons who are eligible under the Act on Pharmaceuticals to handle the medicinal products, and the services of a qualified person designated as being responsible for compliance with the statutory requirements; and

c. show evidence of the prerequisites to fulfil the obligations imposed on distributors by the Act on Pharmaceuticals.

Distribution of medical devices may only be conducted by distributors who are registered with the Institute. To be registered, a distributor must notify the Institute of its operation prior to the commencement of the distribution service. The Act on Medical Devices does not stipulate any additional requirements regarding the registration of distributors of medicinal products.

Classification of products

Medicinal products are classified under the Act on Pharmaceuticals into the following categories; the classification of a particular medicinal product is carried out by the Institute as part of the marketing authorisation procedure:

a. medicinal products that are subject to medical prescription;

b. medicinal products that are subject to restricted medical prescription;

c. medicinal products that may be dispensed without the (restricted) medical prescription (i.e., over-the-counter medicines);

d. medicinal products that may be dispensed without the (restricted) medical prescription with restrictions; and

e. selected medicinal products (i.e., medicines that may be dispensed without a medical prescription outside pharmacies).

Generally speaking, a medicinal product must be dispensed with a medical prescription if it might jeopardise, whether directly or indirectly, the health of the patient. When classifying a medicinal product as prescription-only, the Institute should consider, for example, whether it contains a substance classified as a narcotic or psychotropic or whether it may lead to addiction or be misused for illegal purposes. In certain cases, the Institute can stipulate in the marketing authorisation that the medicinal product concerned is to be dispensed on a restricted medical prescription, which means that the product may only be prescribed by a specialist or a doctor with a professional qualification under supervision of the specialist based on his or her written authorisation. Medicinal products will usually fall within the restricted-prescription-only category where the supervision of a specialist is required during treatment or where the medicinal product is intended for treatment that may only be conducted at an inpatient healthcare facility. Similarly, in the case of over-the-counter
medicines, the Institute can stipulate in the marketing authorisation that the medicinal product concerned is to be dispensed with restrictions. In this case, a medicinal product may only be dispensed to persons for whom it is intended and, therefore, the provider authorised to dispense the product is obliged to maintain records of who it has been dispensed to. The restriction may represent, in particular, specification of the dose for individual administration or specification of an age limit in relation to persons asking to be given the medicinal product.

As regards ‘selected medicinal products’, these may be used without expert consultation and are mainly used to cover the acute needs of the patient (e.g., medical products intended for treatment of mild pain). Rules of good practice for the retailers of selected medicinal products are laid down in Ministerial Decree No. 106/2008 Coll.\textsuperscript{13}

As of 1 January 2018, medicinal products should be prescribed on a medical prescription in electronic form (making a medical prescription in paper form is allowed only in limited cases).

The Act on Medical Devices provides in respect of medical devices classification a non-exhaustive list of medical devices, including, for example, an active implantable medical device, an \textit{in vitro} diagnostic medical device or a custom-made medical device. However, this classification does not affect prescription or sale of the medical devices. In addition, medical devices may be classified into risk classes I, IIa, IIb or III in ascending order by the degree of risk corresponding to the use of the medical device concerned.

\textbf{xii Imports and exports}

Under the Act on Pharmaceuticals, a manufacturing authorisation is required for importation of medicinal products from third countries. The person who oversees the import from a third country must have at his or her disposal a certificate of quality control drawn up in compliance with the marketing authorisation for each batch of the medicinal product.

Importation of medical devices is to be conducted by an importer registered with the Institute, and the imported medical devices may only be supplied to a distributor, a healthcare service provider, a dispenser or a seller. As regards custom-made medical devices, only those medical devices in respect of which a declaration of conformity has been issued and which has been CE-marked may be imported. For the purposes of exporting a medical device outside the EU Member States, the manufacturer of a notified medical device established in the Czech Republic has to apply for a free-sale certificate, which is a public document certifying that the medical device has met the conditions for being placed on the market.

\textbf{xiii Controlled substances}

Controlled substances, such as narcotics and psychotropics, are governed by the Act on Addictive Substances,\textsuperscript{14} which regulates, \textit{inter alia}, the handling of addictive substances (i.e., narcotics and psychotropics as defined by the Governmental Regulation on Lists of Addictive Substances),\textsuperscript{15} their import and export, and transition operations therewith. Every individual export operation of an addictive substance is subject to an authorisation by the Ministry of Health, except for the exporting of mass-produced medicinal products containing certain categories of addictive substances. The export authorisation may only be issued after

\textsuperscript{13} Ministerial Decree No. 106/2008 Coll., on Good Practice for the Retailers of Selected Medicinal Products and on a Specialist Course for the Retailers of Selected Medicinal Products.

\textsuperscript{14} Act No. 167/1998 Coll., on Addictive Substances, as amended.

\textsuperscript{15} Governmental Regulation No. 463/2013 Coll., on Lists of Addictive Substances, as amended.
submission of an import authorisation issued by the country where the export is to take place or, if an import authorisation is not required, the approval of a relevant authority in the importing country. Similarly, imports of addictive substances to the Czech Republic must be authorised by the Ministry of Health.

xiv Enforcement

As stated above, the Institute is responsible for enforcement of medicinal products and medical devices legislation. The aim of an inspection is to check compliance with statutory requirements. The Institute is authorised, in particular, to suspend the validity of marketing or manufacturing authorisations that have been issued pursuant to the Act on Pharmaceuticals. In the event of an administrative offence, a fine of up to 20 million Czech koruna or a ban on operations for a period of up to two years may be imposed.

As regards inspections relating to medical devices, the Institute is entitled to require the suspension or termination of use of a medical device if it decides that use of the device may result in imminent danger of harm to the health of patients. All costs associated with the Institute’s decision are to be borne by the healthcare service provider. As regards administrative offences, the level of fines that may be imposed for non-compliance with the Act on Medical Devices are significantly lower than those stipulated in the Act on Pharmaceuticals; the maximum fine is 2 million Czech koruna.

III PRICING AND REIMBURSEMENT

Regulation of pricing and reimbursement of medicinal products is governed by the Act on Public Health Insurance,16 which stipulates (1) how the maximum prices of mass-produced medicinal products are to be determined and (2) the principles for determining the amount of reimbursement and conditions thereof. In both cases, the Institute is the ruling authority.

The maximum price of medicinal products as stipulated by the Act on Public Health Insurance shall mean the maximum price for which a medicinal product is sold by the manufacturer to other members of the distribution chain. The maximum price is determined as an average of the three lowest prices of the medicinal product concerned in the countries of the ‘reference basket’, which currently includes 18 EU Member States.17 As regards reimbursement, it is key whether the medical product concerned falls within any of the ‘reference groups’ or not. Every reference group18 includes medicinal products that have comparable indications and positions for the type of treatment (in other words, the medicinal products are interchangeable). In respect of medicinal substances or medicinal products included in a particular reference group, the Institute stipulate the usual daily therapeutic dose in relation to which the reimbursement is to be determined. The amount of reimbursement is always the same for all medicinal products in one reference group. The Institute determines the exact amount of the reimbursement on the basis of the lowest manufacturing price of a daily therapeutic dose of the medicinal product concerned, as ascertained in any of the EU Member States.

16 Act No. 48/1997, on Public Health Insurance, as amended.
17 The following Member States are excluded: Bulgaria, Czech Republic, Estonia, Luxembourg, Germany, Austria, Romania, Greece, Cyprus and Malta.
18 Particular reference groups are laid down in the Ministerial Decree No. 384/2007, on List of Reference Groups, as amended.

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The Act on Public Health Insurance also pertains to reimbursement of medical devices. However, the Constitutional Court judged that certain provisions of the Act on Public Health Insurance relating to the mechanism for determining the reimbursement of medical devices violate the right to free medical care and to medical aids on the basis of public insurance and, therefore, repealed those provisions. Consequently, the Act on Public Health Insurance has been amended to set out new rules for reimbursement of medical devices. The new mechanism applies in respect of the individually manufactured medical devices (custom-made medical devices) as of 1 January 2019. Newly notified medical devices will be reimbursed in accordance with the amended rules as of 1 October 2019 and the currently reimbursed medical devices will be reimbursed in accordance with the new rules as of 1 December 2019. The Act on Public Health Insurance provides for a new categorisation of medical devices, extends the range of medical devices that will be fully covered by the health insurance and stipulates reimbursement limits. New medical devices will now be added to the reimbursement scheme on a monthly basis (not just once every six months as per the old rules).

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

As a general rule, decisions made by the Institute, the main regulatory body responsible for both medicinal products and medical devices, may be challenged within administrative proceedings before the Ministry of Health, which oversees the activities of the Institute. As regards judicial review of decisions made by administrative bodies, a review may be initiated within two months of a decision by the Ministry of Health being delivered to the claimant. Subject to limited statutory exceptions, the judicial review may not be initiated if the claimant has not appealed against the first-instance decision of the Institute. Providing the statutory requirements are met, the first-instance court decision may be further reviewed by the Supreme Administrative Court. The area of administrative and judicial remedies is governed by the Code of Administrative Procedure19 and the Code of Administrative Justice, 20 respectively.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Legal regulation of the interaction between marketing authorisation holders and healthcare professionals is subject to the Act on Advertising. As discussed above, in connection with advertising of medicinal products aimed at healthcare professionals, it is prohibited to provide the professionals with any gifts or other benefits, unless they are of insignificant value and relate to the activities of the professional. Samples of medicinal products may exceptionally be provided in limited amounts to persons entitled to prescribe them. Every sample provided must correspond to the smallest package of the medicinal product that has been placed on the market and must be designated as ‘not for sale’ or ‘free sample’. In addition, samples may only be provided on the basis of a written request by the person who is entitled to prescribe the medicinal product concerned. As regards the participation of healthcare professionals in conferences and meetings, for example, held for the purpose of promoting medicinal products, the extent of accommodation and refreshment that is

provided by the pharmaceutical companies free of charge must be appropriate, ancillary in respect of the main purpose of the conference or meeting and cannot pertain to any persons other than the healthcare professionals themselves.

The Act on Advertising does not provide for any similar rules in relation to the promotion of medical devices. Therefore, general rules concerning advertising and anti-corruption and bribery laws apply.

VI  SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Liability for injuries caused by medicines or medical devices may be assessed either from a general civil law perspective or on the basis of special provisions of the Act on Pharmaceuticals and the Act on Medical Devices. In the context of the Act on Pharmaceuticals, the liability of particular entities or individuals involved in the process of manufacturing, marketing, distributing or prescribing depends on the statutory regime in which the medicinal product is used. For example, if a registered medicinal product causes adverse effects, it is the marketing authorisation holder who is liable for the potential injuries. It is also key whether the adverse effects caused by the medicinal product are specified in its summary of product characteristics. If not, the marketing authorisation holder may not be released from his or her liability. If a non-registered medicinal product is used under the conditions specified in Section I, the liability lies with the healthcare service provider.

As regards the use of a medicinal product within a clinical trial, under the Act on Pharmaceuticals, the sponsor is required to hold a liability insurance covering the death and injuries of the trial subjects. The insurance should pertain not only to the liability of the sponsor but also to the liability of the investigators.

The requirement concerning liability insurance for the purposes of clinical trials is also embodied in the Act on Medical Devices. In other cases, the Act on Medical Devices does not provide any specific rules concerning liability.

VII  TRANSACTIONAL AND COMPETITION ISSUES

i  Competition law

Generally speaking, Czech competition law corresponds to a large extent to EU competition rules. At the national level, the authority responsible for enforcement of competition legislation is the Office for the Protection of Competition. In respect of medicinal products, concerns about the adverse effects on competition were raised recently in connection with an amendment to the Act on Pharmaceuticals under which the distributors of medicinal products may require supplies of the medicinal products from the marketing authorisation holders to an extent corresponding to their market share. According to some opinions, this measure has the potential to freeze the market and may result in preventing other undertakings from entering the medicinal products market. Despite the concerns that were raised, the amendment came into force as of 1 December 2017.

ii  Transactional issues

The conclusions in the European Union chapter also apply in respect of the Czech jurisdiction.
VIII CURRENT DEVELOPMENTS

Since 2018, healthcare professionals have been obliged to prescribe medicinal products in electronic form only. The electronic prescriptions are subsequently to be stored in the ‘central storage of electronic prescriptions’ maintained by the Institute, where they can be accessed, for example, by the pharmacists.

As regards planned legislative changes, a new amendment to the Act on Pharmaceuticals that regulates ‘patient’s pharmaceuticals records’ is currently in the legislative process and, if passed, it should come into force around the middle of 2019. This amendment should allow physicians and pharmacists to view a patient’s full pharmaceuticals records so as to avoid adverse interactions of different medicinal products. Also, the Act on Pharmaceuticals should be amended as of 9 February 2019 to implement the EU legislation laying down the rules for the safety features appearing on the packaging of medicinal products for human use.
I INTRODUCTION

Medicines for human use are regulated in Denmark by EU Regulation (EC) No. 726/2004\(^2\) and Directive 2001/83/EC,\(^3\) which have been implemented in national law primarily in the Health Act,\(^4\) the Medicines Act,\(^5\) the Pharmacy Act\(^6\) and the Committee Act.\(^7\) The legislation lays down the harmonised EU requirements for regulation of medicines in Denmark. Advertising and promotion of medicines are partly covered by EU law, whereas pricing and reimbursement are regulated by national law. The Danish Medicines Agency (DMA) is the competent authority. Other relevant competent authorities are primarily the Danish Ministry of Health, the Danish Health Authority and the Danish Patient Safety Authority. Several statutory advisory bodies have been established to advise the DMA in its decision-making with respect to regulation of medicines, namely the Medical Products Committee, the Pharmacovigilance Council and the Reimbursement Committee.

II THE REGULATORY REGIME

i Classification

Medicines for human use are defined as:

\[
\text{any product that (a) is presented as a suitable product for the treatment or prevention of diseases in human beings, or (b) may be used in or administered to human beings to restore, change or modify physiological functions by a pharmacological, immunological or metabolic effect or to make a medical diagnosis.} \text{\footnote{Medicines Act. Consolidated Act No. 99 of 16 January 2018, Section 2(1).}}
\]
The decision as to whether a product will be deemed a medicine, a medical device or another regulated product depends largely on the presentation and the product’s demonstrated mode of action. The DMA determines whether medicines should be classified as over-the-counter medicines (OTCs) or prescription medicines. The decision as to whether approved medicines should be restricted for use in specific patient groups and prescribing status is also decided by the DMA. Medicines approved by the European Medicines Agency (EMA) will maintain their classification status in Denmark. Natural medicines, traditional herbal medicines and homeopathic products are also regulated by the DMA, whereas complementary medicines and vitamins are regulated by the Danish Veterinary and Food Administration. Prescription medicines may be dispensed only by pharmacies, but it is permitted for some OTCs to be sold elsewhere. As of 1 January 2018, some OTCs are placed freely in pharmacies, shops and retail stores, and are no longer be placed behind a counter or locked in a cabinet. A list of these OTCs can be found on the DMA website.

ii Non-clinical studies

Non-clinical studies of compounds must be conducted in compliance with the principles of good laboratory practice (GLP). GLP defines the standards for the planning, conducting, monitoring, recording and reporting of in vitro and in vivo studies. All animal studies must be carried out in accordance with the principles of Directive 2010/63/EU. Permissions to conduct animal studies on vertebrate animals and foetuses of mammals must be granted by the Animal Experiments Inspectorate (AEI). The AEI approves all animal experiments in Denmark and undertakes inspections of all facilities where animal experiments are carried out.

iii Clinical trials

Clinical trials on human beings are regulated by Directive 2001/20/EC and Regulation (EU) No. 536/2014 as implemented into Danish law. All clinical trials must be conducted in accordance with the principles of good clinical practice (GCP) and the verification of their applications for tests on chemical substances.
in accordance with the principles of good clinical practice (GCP).\textsuperscript{20,21} Before initiation of the study, the protocol may be subject to approval by the DMA and an ethics committee.\textsuperscript{22} Trial subjects must receive proper written and oral information about the trial before consenting to participate. Informed consent forms must be signed by the trial subjects and stored by the primary investigator.\textsuperscript{23} As clinical trials may be subject to inspection by the DMA, participants must be informed about this before consenting to participate. The informed consent form must contain a section describing the DMA’s unconditional access to all trial and patient data.\textsuperscript{24} Injuries occurring in clinical trial subjects are covered by a publicly funded compensation scheme (see Section VI).\textsuperscript{25}

**Sponsor**

In Danish law, the clinical trial sponsor is defined as the individual, company, institution or company that takes the overall responsibility for the initiation, management and, in some cases, financing of the clinical trial.\textsuperscript{26} The trial sponsor has several legal obligations, such as registration of the trial in EudraCT, reporting of trial results to EudraCT and reporting of adverse events occurring during the trial to the DMA. The definition of the term ‘sponsor’ in Danish law (as stated above) is not the same as in Directive 2001/20/EC, which defines a sponsor as an individual, company, institution or organisation that takes responsibility for the initiation, management or financing of a clinical trial.\textsuperscript{27}

**iv** **Named-patient and compassionate use procedures**

In special cases, the DMA may authorise the prescribing of unlicensed medicines, such as those approved but not marketed in Denmark or pharmacy compounds.\textsuperscript{28} Hence compassionate use permissions are only granted in situations where the unlicensed medicine cannot be substituted by a medicine already marketed in Denmark. Physicians, dentists and veterinary surgeons may apply for a single permission for use of unlicensed medicines in specific patients or apply for a general permission that allows use of an unlicensed product for all patients affiliated with a specific hospital department or general practice. When applying for compassionate use permissions, the DMA usually requires information about the name of the medicine, active ingredients, medical form, strength, producer, distributor, indication for use and medical justifications for the application. Medicines prescribed for compassionate use are also subject to the rules for reporting adverse events to the DMA.\textsuperscript{29}

\begin{itemize}
\item \textsuperscript{20} 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.
\item \textsuperscript{21} Executive Order No. 695 of 12 June 2013 on good clinical practice in clinical human trials.
\item \textsuperscript{22} Medicines Act. Consolidated Act No. No. 99 of 16 January 2018, Section 88.
\item \textsuperscript{23} Executive Order No. 498 of 13 May 2018, Section 7 and 8 on informed consent of participating in clinical trials.
\item \textsuperscript{24} Executive Order No. 498 of 13 May 2018, Section 12(1).
\item \textsuperscript{25} Consolidated Act No. 995 of 14 June 2018, Section 19(3) on complaints and compensation.
\item \textsuperscript{26} Executive Order No. 695 of 6 December 2013, Section 2(1), no. 6 on good clinical practice.
\item \textsuperscript{27} Directive 2001/20/EC, Article 2(e).
\item \textsuperscript{28} Medicines Act. Consolidated Act No. No. 99 of 16 January 2018, Section 29.
\item \textsuperscript{29} Executive Order No. 1823 of 15 December 2015 on reporting of adverse events for medicinal products.
\end{itemize}
v  Pre-market clearance

Medicines must be approved by the EMA or DMA and included on the medical register (www.medicinpriser.dk) before they can be marketed in Denmark. The applicant for and holder of a marketing authorisation must be established in an EEA country, or represented in Denmark by another EEA company. Generic medicines may be authorised according to the abridged application procedure, in which applicants may omit some or all of the preclinical and clinical trial data if bioequivalence can be documented with a reference product and regulatory data exclusivity for the reference product has expired.

vi  Regulatory incentives

Patents may be granted for medicines for 20 years from the date of filing as provided in the Patent Act, Section 40. When granted a marketing authorisation for a medicine, the marketing authorisation holder may benefit from a data protection period of eight years from the first marketing in the EEA. If new indications are approved later, the data protection period may be extended to 11 years. Danish law concerning supplementary protection certificates (SPCs) is harmonised with EU Directives. The duration of an SPC is limited to a maximum of five years without the possibility of extension. Supplementary protection for medicines may in turn be extended by an additional six months if the patentee has tested the suitability of the medicines for children in accordance with Regulation (EC) No. 1901/2006 and Regulation (EC) No. 1902/2006. Article 36 of Regulation (EC) No. 1991/2006 allows for a further six-month extension of the SPC if a paediatric indication is approved by the regulatory authorities. An application for a paediatric extension should also be filed with the Danish Patent and Trademark Office (DKPTO).

Patented indications

When dispensing medicines, pharmacies are legally obliged to substitute the cheapest medicine within the relevant substitution group. If a medicine has a patented indication, it may have an effect on how the DMA establishes the substitution group to which the

35 Section 9 of the Executive Order on Marketing Authorisation No. 1239 of 12 December 2005.
40 Medicines Act. Consolidated Act No. 99 of 16 January 2018, Section 60(1) and Executive Order No. 1654 of 18 December 2018 on the prescription and dose dispensing of medicines, Section 62(1).
medicine belongs. Consequently, the marketing authorisation holder of a medicine with a patented indication must inform the DMA about the patent or SPC and its expiry date, and the DMA will subsequently 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. This means in practice that the pharmacy should dispense the medicine with the patent protected indication.41

vii Post-approval controls
Marketing authorisation holders of medicines are legally obligated to establish and maintain a pharmacovigilance system, have access to a qualified person situated in the EEA and to comply with national rules on reporting suspected adverse reactions.42 The reporting requirements of adverse events from medicine use are described in Executive Order No. 1823 of 15 September 2015. According to Section 4(1) thereof, physicians, dentists, midwives, veterinary surgeons and pharmaceutical companies are legally obliged to report all suspected adverse events and exposure reactions in patients or animals they are treating.43 It is not mandatory to report adverse events caused by medication errors to the DMA.44 Pharmacists, consumers, patient relatives and lawyers may all report adverse events directly to the DMA. All serious adverse events must be reported to the DMA no later than 15 days after a physician, dentist, midwife or veterinary surgeon becomes aware of the event.45 During the first two years of marketing, all adverse events must be reported. After the two-year period, reporting obligations cover serious or unexpected adverse events only.46 For generic medicines, only serious or unexpected adverse events and exposing reactions must be reported; the reporting requirements apply from the time when marketing of the medicines has begun.47 Additionally, 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.48

viii Manufacturing controls
Manufacturers of medicines must have a manufacturing authorisation, under Section 39 of the Medicines Act. Medicines are to be manufactured in accordance with Good Manufacturing Practice (GMP)49 guidelines and the European Commission’s guidelines listed in Volume 4

41 Executive Order No. 1654 of 18 December 2018 on the prescription and dose dispensing of medicines, Section 62(7-8).
43 Executive Order No. 1823 of 15 September 2015 on reporting of adverse events from medicine use.
44 id., Section 4(6).
45 id., Section 4(5).
46 id., Section 4(3).
47 id., Section 4(4).
48 https://laegemiddelstyrelsen.dk/da/hivirkninger/supplerende-overvaegning/.
of the Rules governing medicinal products in the European Union.\textsuperscript{50} Manufacturers must have at least one qualified GMP person permanently and continuously at their disposal.\textsuperscript{51} Permissions will be granted by the DMA, and the DMA will regularly inspect the companies.

Distributors and wholesalers must also be authorised by the DMA, under Section 39 of the Medicines Act, and may also be inspected by the DMA. Information about authorised distributors and wholesalers may 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.\textsuperscript{52} Distributors and wholesalers must approve and review their suppliers regularly to monitor the suppliers’ compliance with the GDP rules.

\textbf{ix  Advertising and promotion}

Advertising of medicines is regulated in Part 7 of the Medicines Act and Executive Order No. 1153 of 22 October 2014 on advertising rules for medicines.\textsuperscript{53} The main purpose of the legislation is to protect the public against misleading and prohibited advertising of medicines and to ensure that the public have access to objective and adequate information about medicines. Advertising for prescription medicine to the general public is not allowed,\textsuperscript{54} but direct advertising to healthcare professionals (HCPs) is permitted.\textsuperscript{55}

\textbf{x  Controlled substances}

Manufacturers, wholesalers and others who handle medicines classified as euphoriants (e.g., narcotics or psychotropic substances) need a manufacturing, import or wholesale licence that specifically includes those substances.\textsuperscript{56} Authorisation of narcotics or psychotropic substances may be granted if the substances are prescribed to drug addicts for medical purposes. Dispensing of the medicines may be made by physicians, pharmacists and institutions involved in treatment of drug addicts.\textsuperscript{57} A list of euphoriants subject to control by the Danish authorities is available on the DMA website.\textsuperscript{58}

\textbf{III PRICING AND REIMBURSEMENT}

\textbf{i  Pricing}

The pricing of medicines is in general fixed and no approval by the authorities is required. Prices are fixed for 14-day periods, and therefore pharmaceutical companies must, every 14 days, provide to the DMA a price list with information about medicines for sale during the subsequent two-week period, under Section 77 of the Medicines Act. Price registration

\textsuperscript{50} European Commission. EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines.
\textsuperscript{51} Executive Order No. 1358 of 18 December 2012 on the manufacturing and import of medicines and pharmaceutical intermediates.
\textsuperscript{52} Executive Order No. 1359 of 18 December 2012 on good distribution practice of pharmaceuticals.
\textsuperscript{53} Executive Order No. 1153 of 22 October 2014 on advertising rules for medicines.
\textsuperscript{55} Executive Order No. 1153 of 22 October 2014 on marketing of pharmaceuticals, Section 11.
\textsuperscript{56} Executive Order No. 557 of 31 May 2011 on euphoriants.
\textsuperscript{57} id., Section 4(1)(4).
\textsuperscript{58} https://laegemiddelstyrelsen.dk/da/godkendelse/virksomhedstilladelse-og-registrering/euforiserende-stoffer/\newline liste-over-stoffer/.
is mandatory if pharmaceutical companies intend to market medicines in Denmark. The national substitution rules determine that pharmacies are legally obliged to substitute a prescribed medicine to the cheapest generic or parallel-imported medicine when dispensing. Only rebates strictly related to cost-savings activities by the distributor can be given to private pharmacies. In the secondary healthcare sector, discounts in the form of reduced medicine prices are achieved through price tenders conducted by Amgros, the Danish regions’ joint procurement service.

ii Reimbursement
Reimbursement of medicines is determined by the DMA based on recommendations made by the Medicines Reimbursement Committee. Several types of reimbursement may be granted, under Section 152 of the Medicines Act. Pre-approved reimbursement means that the medicine has achieved general reimbursement at the time of marketing in Denmark and therefore the physician may prescribe medicines at reimbursed prices directly to the patient.

For medicines not generally reimbursed, the physician may apply for individual reimbursement, of which there are three types: single, increased and reimbursement for the terminally ill. Single reimbursement is for special cases where the patient can obtain reimbursement for a medicine that does not have general reimbursement. To obtain single reimbursement, the physician must apply to the DMA and document why the patient concerned needs treatment with a particular medicine. The physician may apply for increased reimbursement if a patient needs a more expensive generic medicine, even if there is a less expensive alternative 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. Terminally ill patients who choose to spend their last time in their own home or in a hospice can have their medicine expenses covered if prescribed by a physician. The physician or the hospital can apply for a licence for reimbursement of the terminally ill patient.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES
The DMA is the national administrative body 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 tried by the courts if challenged by a party with a legal interest in the case.

60 Executive Order No. 1654 of 18 December 2018 on prescriptions and dose dispensing of medicines, Section 62.
61 Executive Order No. 1153 of 22 October 2014 on advertising of pharmaceuticals, Part 9.
63 Executive Order No. 671 of 3 June 2016 on the medicines compensation system.
65 Executive Order No. 671 of 3 June 2016 on the medicines compensation system, Section 6.
66 id., Section 11.
67 id., Section 9.
FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

HCPs’ professional interactions with the pharmaceutical industry are highly regulated to ensure that cooperation takes place in an ethically responsible manner. The interaction is primarily regulated by national rules and an ethical code issued by the Ethical Committee for the Pharmaceutical Industry (ENLI). Only members of ENLI are covered by its special regulations and subject to its sanctions.68 The Danish Health Act, Chapter 61a provides the legal framework for pharmaceutical companies’ relationship with HCPs. The specific rules are set out in Danish Executive Order No. 1154 of 22 October 2014 on healthcare professionals’ relationships with pharmaceutical companies as amended by Danish Executive Order No. 1685 of 16 December 2016. An overall description of the rules follows hereafter.

i  Financial benefits for healthcare professionals

Pharmaceutical companies’ financial support to HCPs is regulated in Sections 26 and 28 of the advertising rules for medicines.69 According to these rules, when attending educational and promotional activities with a scientific or professional purpose, HCPs may receive financial support in the form of payment of the reasonable costs in relation to dining, travelling and accommodation.70 Pharmaceutical companies’ financial support to HCPs’ activities outside Denmark is subject to notification by HCPs registered by the DMA. Information about financial support will be published on the Agency’s website for a period of two years. The following information will appear on the website: unambiguous identification of the HCP (name and possibly an authorisation number), profession, pharmaceutical company, information about activity and date of termination of the activity.

ii  Healthcare professionals’ affiliation with pharmaceutical companies

Physicians and dentists undertaking clinical duties and proprietary pharmacists must notify the DMA of any relationship with pharmaceutical companies or apply for permission before they establish a relationship with a pharmaceutical company.71 The rules apply to pharmaceutical companies that have marketed medicines in Denmark (Section 7(1) of the Medicines Act) or companies with permission to produce, import and distribute medicines (Section 39 of the Medicines Act). Affiliations between HCPs and public hospitals do not need to be reported to the DMA.

A relationship includes any professional or financial relations with a pharmaceutical company. A professional relationship may cover individual tasks (e.g., research, teaching or the writing of articles), or full-time or part-time employment. Generally, all types of relationships are covered by the rules, as well as activities for which the HCP does not receive payment. Financial relations also cover HCPs who own or hold shares in a pharmaceutical company.72 Scientific advice, ownership, positions of trust and ownership of shares in the

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68 Ethical Committee for the Pharmaceutical Industry. Available at: www.enli.dk.
69 Executive Order No. 1154 of 22 October 2014 on healthcare professionals’ affiliation with pharmaceutical companies.
70 Danish Pharmaceutical Marketing Authorisation Act (Executive Order No. 1153 of 22 October 2014, Section 28.
71 The rules also apply to medical device companies established in Denmark. Further restrictions apply.
72 Executive Order No. 1154 of 22 October 2014 on advertising of pharmaceuticals.
pharmaceutical company to a value of more than 200,000 Danish kroner require approval by
the DMA. Information about teaching and research activities, as well as ownership of shares
in pharmaceutical companies to a value up to 200,000 kroner are only to be notified to the
DMA. When establishing a relationship with a physician, dentist or proprietary pharmacist,
a pharmaceutical company must inform the person of his or her notification duty, as well as
the company’s reporting requirements, and publish the information on the DMA website.73
Pharmaceutical companies’ notification to the DMA must be repeated once a year and no
later than on 31 January each year by using a specific template on the DMA website.74 The
information will be deleted from the DMA website after a two-year period.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Patients, trial subject and donors are covered by a publicly funded compensation scheme,
which covers injuries occurring in connection with medical treatments in the public and private
healthcare system; injuries that result from adverse events from medicine use, and personal
injuries occurring during clinical trials.75 The basic conditions for obtaining compensation
are that the person must have been injured by a treatment made by an HCP or from the use
of medicines. Time and causal relationship must be documented. Compensation can only be
awarded for damage caused by the treatment or medicine and not injuries that may be related
to the patient’s basic condition. If the personal injury is covered by the compensation scheme,
the patient or relatives are prevented from claiming compensation pursuant to other laws.76
Assessment of claims is made by the Patient Compensation Association and decisions may be
appealed to an independent board. If the decision is upheld by the board, a legal complaint
may be filed. In cases where compensation has been awarded and the patient injury was
caused by a defect or flawed dangerous characteristic of the medicine, the government might
file a recourse claim against the producer.77 The opportunities for filing for recourse are
limited, as producers are only legally responsible for injuries caused by a defective medicine,
and not developmental injuries or already-known adverse events.78

VII TRANSACTIONAL AND COMPETITION ISSUES

Transactions within the Danish life science sector are not considerably different from those
in other European jurisdictions. General European competition law principles and legislation
are applicable in Denmark.79 Sanctions for entering into cartel agreements under Danish
competition law may include imprisonment for up to 18 months if the infringement is
intentional and of a grave nature, whereas the sanctions under EU competition law are

73 id., Section 16(1-4).
74 id., Section 17.
77 Product liability covers the EU rules listed in Directive 85/374/1985/EE, the product liability rules
based on case law. And the Danish Product Liability rules specified in the Consolidated Act No. 261 of
limited to fines.\textsuperscript{80} On 31 January 2018, the Danish Competition Council ruled that a pharmaceutical distributor had abused its dominant position by charging Amgros unfair prices (a 2,000 per cent price increase over a six-month period) for a certain medicinal product for which the distributor held an exclusive distribution contract. The decision was upheld by the Competition Appeals Tribunal on 29 November 2018. The case has been submitted to the Danish State Prosecutor for Serious Economic and International Crime.

\section*{VIII CURRENT DEVELOPMENTS}

The second half of 2019 is expected to see the Danish government propose a bill for an external reference pricing (ERP) system. The ERP system will work as a price regulation measure to reduce list prices on medicinal products in Denmark. The ERP system will apply to both hospital medicines and medicines eligible for subsidy that are not covered by the voluntary price-cap agreement concluded between the Danish government and the Danish Association of the Pharmaceutical Industry (LIF). Pharmaceutical companies that have not joined the voluntary price-cap agreement must report their prices on medicinal products in nine selected ‘comparable’ countries, which are Finland, Sweden, Norway, the United Kingdom, Ireland, Austria, the Netherlands, Belgium and Germany. The Danish list price on the specific medicinal product will be calculated as an average based on the reported nine prices. The ERP system could enter into force as early as 2020; however, uncertainty exists because of the Danish parliamentary election that will take place in the first half of 2019.

In February 2018, the Danish regions adopted joint regional policies for continuity training and skills development in collaboration with the industry. By now, three out of the five regions have transposed the principles by entering separate agreements with LIF. The three regions are the Capital Region, the Region of Southern Denmark and the Region of Zealand. The agreements govern the sponsoring of healthcare professionals by pharmaceutical companies. The purpose of the principles is to facilitate a sound industry collaboration without risking the impartiality of the hospital staff. Though the agreements differ, they generally provide that invitations must be sent to the hospital management instead of the individual staff member. The companies may not, directly or indirectly, put names on the staff members they wish to attend training events. The hospital management decides at its discretion who shall be able to attend the events. The invitation cannot be subject to other obligations. Pharmaceutical companies organising or backing specific continuity training and skills development events targeted at the regions’ hospitals must report such events to ENLI, which will verify that the rules are complied with. Consequently, pharmaceutical companies that have not joined ENLI will be unable to continue their training activities, since ENLI will not take and verify invitations received from companies that are not its members. Since the adoption of regional policies in the beginning of 2018, ENLI has more than doubled its number of member companies that are not part of either LIF, IGL (the Danish Generic and Biosimilars Medicines Industry Association) or FPM (the association for parallel imports of medicines).

Finally, there has been some deliberation with respect to the scope of tasks for the recently established Danish Medicines Council. The issue concerned the Council’s possible recommendation for off-label use of medicinal products. Among its responsibilities,

the Council must provide the five regions with recommendations to ensure fast and homogeneous use of new and existing medicines. To achieve this, the Council issues joint regional treatment guidelines. Expert committees assist in the medical assessment in relevant therapeutic areas and produce drafts for such guidelines. In early 2018, a protocol for such assessment revealed that the Council intended to include comparators that were not licensed for the therapeutic indications of the medicines that they were compared to (off-label). This prompted pharmaceutical companies and LIF to address the issue to the Council, arguing that such comparison could be perceived as an (indirect) recommendation for off-label use, ignoring the rationale for the marketing authorisation system and jeopardising patient safety by encouraging treatment with unlicensed medicines. It was argued that such comparison could consequently be considered illegal advertisement. Following some debate in the media, the Council informed that it had added to the protocol that the comparator in question will not be included in the recommendation.
I INTRODUCTION

Medicines for human use are regulated primarily by Directive 2001/83/EC and Regulation (EC) No. 726/2004. 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) 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.

Medical devices are regulated by a series of EU directives: Active Implantable Medical Devices Directive 90/385/EEC, Medical Devices Directive 93/42/EEC and In

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1 Grant Castle and Robin Blaney are partners at Covington & Burling LLP.
4 The EEA comprises the 28 EU Member States plus Iceland, Liechtenstein and Norway.

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. Article 2(2) of Directive 2001/83/EC formally incorporates this principle into EU law. It provides that:

*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, Directive 93/42/EC contains 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 of application of the Cosmetics Regulation (EC) No 1223/2009’ and a ‘Manual on borderline and classification in the community regulatory framework for medical devices’. The Commission has also published concrete guidance on the borderline between medicines and medical devices in MEDDEV 2.1/3.

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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). 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 (pharmacotoxicological) 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. 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, at least until Clinical Trial Regulation (EU) No. 536/2014 becomes applicable, which is now likely to be in 2020. 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 (1996 version). 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.

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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.


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**

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 EU rules do not contain specific requirements for compensation and insurance for injuries to study subjects. There are no special rules for investigator-initiated studies.

Medical Devices Regulation (EU) 2017/745 contains detailed new clinical trial rules for medical devices, modelled on those applicable to clinical trials of medicines, which will apply from 26 May 2020. Among other things, the new rules impose obligations on the sponsor of the investigation, and contain specific requirements for compensation and insurance for injuries to study subjects. The IVD 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 European Union without a marketing authorisation. However, this is subject to a number of exemptions, including the ‘named-patient’ exception. 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:

- in response to a *bona fide* unsolicited order;

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15 Article 5(1) of Directive 2001/83/EC.
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
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 can not 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. 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 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.
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 European Union 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 European Union 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 European Union.

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 European Union unless the device also contains a medicine or a blood derivative. However, all medical devices placed on the market in the EEA 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 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 the new Medical Devices Regulation (EU) 2017/745 and the new IVD 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.

vi Regulatory incentives

Medicines

A supplementary patent 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:

a. the product is protected by a basic patent in force;

b. a valid marketing authorisation has been granted for the product;

c. the product has not already been the subject of a certificate; and

d. 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’,16 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.

vi) 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.

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.

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18 Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, as amended.
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 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. 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.

Manufacturing controls

Medicines

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.


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 13485:2012 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.

ix 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 code
of practice on interactions with healthcare professionals, a code of practice on interactions with patient organisations and a code of practice on 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**

**Medicines**

Any company engaged in wholesale distribution of medicinal products in the European Union 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 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’.

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

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20 EFPIA Code of Practice on the promotion of prescription-only medicines to, and interactions with, healthcare professionals.
21 EFPIA Code of Practice on relationships between the pharmaceutical industry and patient organisations.
22 EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations.

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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 European Union, 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**

There are currently no EU-harmonised rules that govern the distribution of medical devices, although some Member States do regulate the activity.

**xi 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.

xii 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, Regulation (EU) 2017/745 and 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.

xiii 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.

xiv 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.24 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 European Union, 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 European Union 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


27 The Queen, on the application of Association the British Pharmaceutical Industry v. Medicines and Health-care Products Regulatory Agency (Case C-62/09) [2010] ECR I-3603 (ABPI v. MHRA).
Treaty on the Functioning of the European Union (TFEU) permits direct challenges to the legality of EU acts and allows the EU courts\(^{28}\) 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.

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.\(^ {29}\) 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\(^ {30}\) 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.

### ii 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.

\(^{28}\) 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.

\(^{29}\) TWD Textilwerke Deggendorf GmbH v. Germany (Case C-188/92) [1994] ECR I-833.

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,31 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 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.32

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

31 See Section II.ix.
32 EFPIA HCP Code, updated June 2014.
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.

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.33

Directive 85/374/EEC34 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 European Union against whom they can bring a claim. The term includes any manufacturer of finished products, raw materials or parts within the European Union; importers of products from outside the European Union; 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

33 Directive 2001/20/EC; see Section II.iii on clinical trials.
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.35

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 TFEU.36 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).37 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).38 Lundbeck and the generic companies have appealed the General Court’s judgment to the European Court of Justice. Conversely, the General Court ruled in *Servier* 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.39

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.40 The decision has been appealed to the UK Competition Appeal Tribunal, which has made a referral to the CJ.

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).41 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

35 Article 5(4) of Directive 2001/83/EC.
37 Commission Decision of 9 July 2014 in Case COMP/AT.39612 – *Perindopril (Servier)*.
38 Case T-472/13 *Lundbeck v. Commission* [2016].
39 Case T-691/14 *Servier v Commission* [2018]
40 Case CE/9531-11, Paroxetine investigation: anticompetitive agreements and conduct.
41 Case A480, Antitrust’s investigation on the price increase for Aspen’s anticancer drugs.
Kingdom. An appeal was brought to the UK Competition Appeal Tribunal, which ruled against the CMA’s decision. The CMA has received permission to appeal the UK Competition Appeal Tribunal’s decision to the UK Court of Appeal. At least two other investigations relating to excessive and unfair prices charged are under way in the United Kingdom. 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. Market sharing has remained on the agenda, with the Italian Lucentis/Avastin case having been referred by the Italian Council of State to the ECJ in March 2016. 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 European Union. 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 CE/9742-13, Phenytoin sodium capsules: suspected unfair pricing.
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 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. 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. However, at the time of writing, only one notified body has been designated under Regulation (EU) 2017/745. We are not aware of any notified body that has yet been designated under Regulation (EU) 2017/746, meaning in practice it is not yet possible to bring an in vitro medical device to market, and 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 2014.45 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 expected to come into effect in 2020, 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.

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There is a clear drive towards greater transparency in medicines regulation. This is particularly true of the EMA, which has begun releasing significant parts of marketing authorisation dossiers in response to requests for access under Regulation (EC) No. 1049/2001.\(^4\) This practice continues to be the subject of legal challenges by a number of pharmaceutical companies before the European courts. An EMA policy on the proactive publication of clinical trial data took effect on 1 January 2015, which provides for the EMA to make public the data submitted in support of marketing authorisation applications once a product has been approved, subject to the deletion of personal data. The EMA has recently placed online clinical trial data for the first products subjected to its proactive release policy.

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. The National Supervisory Authority for Welfare and Health (Valvira) supervises medical devices and 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 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 2018. Sailab – MedTech Finland, a registered association of health technology suppliers, has issued its own code of ethics, which is based on the MedTech Europe Code of Business and governs, inter alia, the marketing of medical devices. This code entered into force on 1 January 2018, but it contains a transitional period which will end on 1 January 2019.

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Generally, the marketing of medicines and medical devices to consumers is also regulated by the Finnish Consumer Protection Act (38/1978) and Regulation 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.
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, Valvira and the National Committee on Medical Research Ethics. Fimea has issued a regulation regarding clinical trials.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.

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.

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.

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² Fimea's Regulation 2/2012 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.
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 Valvira. 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 Valvira before the device is placed on the Finnish market or at most within one week after the sale of the device has begun. Valvira must also be informed of all adverse incidents relating to medical devices as soon as possible. Valvira has issued several regulations regarding medical devices concerning, for example, conformity assessment and the CE marking.

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.

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

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4 Conformity Assessment of Medical Devices 1/2011 and CE marking of Medical Devices 2/2011.
5 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.
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 a 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. 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
Finland

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 Valvira 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.

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.\(^6\)

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.

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.

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\(^6\) Fimea’s Regulation 5/2013 on Good Distribution Practices.
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).

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:

- manufacturing, importing, storing, carrying for sale or supplying medicinal products;
- neglecting to make a notification, provide information or keep records concerning medicinal products; or
- failing to comply with a prohibition issued by Fimea.
A medicinal product offence may also be punished under the Finnish Criminal Code, 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 and Valvira 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 is still a topic of conversation. 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 competition-restricting aspects. The Finnish Competition Authority (FCA) drafted a report in 2012 regarding the functionality and competition aspects of the system, but no measures have been taken so far. A recently published report by a working group for the Ministry of Social Affairs and Health states, however, that the current pharmacy licence system should be retained. At the same time, releasing prescription-free medicines to the retail trade has been discussed.

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. Responsibility for organising social welfare and healthcare services will be moved from municipalities to social welfare and healthcare regions. This will have a significant effect on the life sciences sector.

The pharmacy system has been a topic of conversation, and there are 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 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 will be applicable to members not complying with the Code. A similar system for the pharmaceutical sector has been in existence for a long time through Pharma Industry Finland, but now the medical devices sector has introduced a similar binding self-regulatory system of its own.
Chapter 12

FRANCE

Sophie Pelé

I INTRODUCTION

The French regulatory framework for life sciences products is regarded as highly sophisticated and was one of the pillars for the creation of the EU regulatory framework. However, the EU framework has developed significantly and now the French and EU regulations do not always correspond to each other. An example of this is the French concept of exploitant (a licensed company authorised to market pharmaceutical products, which may differ from the marketing authorisation holder), which has no equivalent in the EU regulations.

Despite these discrepancies, the French regulations broadly reflect the EU regulations regarding the manufacture and marketing of pharmaceutical products and medical devices, with the exception of the pricing and reimbursement schemes, which remain national in nature. Manufacture and marketing matters are governed by the French Public Health Code. Pricing and reimbursement matters are covered by the Social Security Code. In addition, ‘soft law regulation’ tends to play an important role, not only through good practices harmonised across Europe, but also from a medico-economic standpoint.

This dual system is also reflected in the organisation of competent national authorities. The French National Agency for the Safety of Medicines and Health Products (ANSM) is in charge of the health and safety aspects of both medicines and medical devices, including:

a the approval of clinical trials;
b the granting of marketing authorisations;
c the issuance of ‘dear healthcare professional’ letters;
d the authorisation of advertising; and
e inspections of manufacturing premises.

The National Authority for Health (HAS) is responsible for medico-economic aspects, notably the publication of guidelines recommending therapeutic strategies for the treatment of certain diseases and the assessment of the therapeutic and medico-economic benefit for reimbursement purposes through its Transparency Committee (for medicines) and its National Commission for Medical Devices and Health Technologies Assessment (for medical devices). Finally, the Ministry of Health, which includes the Pricing Committee (CEPS), oversees the pricing of reimbursed products.

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II THE REGULATORY REGIME

Despite their supervision by the same national health agencies, medicines and medical devices are subject to two separate legal regimes. Medicines are governed by the provisions transposing the EU code relating to medicinal products for human use and cannot be tested, marketed or promoted without prior approval. Medical devices are subject to the provisions transposing into French law the CE marking requirement regime applicable throughout Europe, and harmonisation will be fostered by the direct application of Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices, and Regulation (EU) 2017/746 on in vitro diagnostic medical devices, both adopted on 5 April 2017, which will apply as from 26 May 2020 and 22 May 2022 respectively.

The adoption of these Regulations reinforces the trend towards increased similarity between both categories of products. In France, for instance, advertising material for medical devices has been mostly aligned with the prior-approval regime applicable to medicines. In addition, medicines and medical devices are subject to very similar processes in terms of pricing and reimbursement.

i Classification

Rules and principles governing the classification of health products are broadly based on EU case law. For instance, the Administrative Supreme Court referred to the European Court of Justice the regulatory status of software assisting in the prescription of pharmaceutical products, which have been qualified as medical devices because of their aim. At the same time, French case law continues to broaden the scope of products falling within the definition of pharmaceutical products. This is the case for various food supplements claiming to have therapeutic effects or containing substances with therapeutic properties, and tiger balsam, the status of which is still not settled.

More recently, the Finance Bill for 2019 introduced the new category of hybrid medicines into the French regime. Like generics, hybrid medicines may be substituted for a reference medicine, but they are not similar to the originator product in terms of indications, dosage, pharmaceutical form or route of administration. The applicable conditions for substitution are therefore still pending, and these will be determined by a ministerial order. Hybrid status might notably concern medicinal products with a different form or packaging from the originator product.

ii Non-clinical studies

The status of non-interventional studies conducted on human beings has been aligned with rules applicable to clinical trials, with some specificities. For instance, the ethics committee can give its opinion with only four members present, and the approval from the ANSM is not required.

4 Administrative Supreme Court, 8 June 2016, No. 387156.
5 CJEU, 7 December 2017, C-329/16, Preliminary ruling from France about the qualification of prescription assistance software.
6 Criminal Supreme Court, 12 July 2016, No. 15-82873, unpublished; Criminal Supreme Court, 30 January 2018, No. 16-86.702, unpublished; Criminal Supreme Court, 23 October 2018, No. 17-84.098, unpublished.
7 Criminal Supreme Court, 8 July 2015, No. 14-83.624.
iii Clinical trials

Clinical trials for medicines and medical devices conducted in France must receive a prior opinion from an ethics committee and prior approval by the ANSM. In some cases, the ANSM can refuse to grant the approval. In a judgment dated 3 April 2015, an administrative court upheld one such refusal.8

Decree No. 2016-1537 of 16 November 2016 significantly amended the regime applicable to clinical trials. Private sponsors must supply all the tested products free of charge to the healthcare centres hosting the healthcare professionals (HCPs) appointed as investigators and compensate for the costs and extra costs incurred in conducting the trial. For transparency reasons (particularly to avoid conflicts of interest that could arise between the ethics committees (ECs) and healthcare institutions) and to allow an appropriate assessment of the projects, the competent ECs are now designated on a lottery basis, from among those available and whose members have necessary skills in the project field under consideration. In addition, the requirements regarding reporting of adverse or unexpected events have been significantly strengthened, and can lead to the provisional suspension of the administration of the tested product in Phase I.

The ANSM initiated a pilot phase during which, on a voluntary basis, ECs, subject to the sponsor’s acceptance, can implement EU Regulation No. 536/2014 on clinical trials. Following two years of implementation, the time frame for the review of applications is, on average, 68.9 days. In addition, to improve access to innovative therapies, and in anticipation of upcoming EU regulation of clinical trials, the ANSM set up, on an experimental basis, fast-track authorisations of clinical trials, which are likely to apply to both advanced therapies and new trial on known substances. Starting from 15 October 2018, this new experiment applies to all phases of clinical trials and aims to reduce the application review period from 60 to 25 days for clinical trials on known substances, and to 40 days for innovative treatments.

In 2014, the French government issued harmonised template agreements with the aim of accelerating the implementation of trials within French public hospitals.9 Decree No. 2016-1538 of 16 November 2016 broadens their application to any type of privately sponsored trial. The harmonised agreement is exclusive of any other agreement entered into in the framework of the same trial. It must therefore include the negotiations with the investigators, associations participating in the trial, etc. Moreover, when a trial involves several centres, the negotiation of financial aspects takes place between a single hospital and the sponsor; other centres will be bound by the same financial provisions. The aim is to be able to negotiate with the coordinating centre within a 45-day period. Hospitals receive financial incentives from public funds if they successfully implement the template. Moreover, sponsors might also provide for counterparts in return for the quality of the data collected, which correspond to former financial incentives related to the inclusion of patients. In 2015, 2,135 agreements had been entered into through this route with 91 healthcare institutions, whereas there were 3,117 agreements with 112 establishments in 2016.

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8 Paris Administrative Tribunal, 3 March 2015, No. 1401975/6-1, AB Science.
9 Instruction No. DGOS/PF4/2014/195 of 17 June 2014 relating to the implementation of a template agreement for biomedical research with a private sponsor in public hospitals.
Named-patient and compassionate-use procedures

Named-patient and compassionate use procedures were significantly updated and strengthened by the Bertrand Law of 29 December 2011. A temporary authorisation for use (ATU) may be granted to treat severe or rare diseases for which no treatment has been authorised, if and when the treatment cannot be delayed.

When requested by the pharmaceutical company intending to market the product, an ATU will be granted if safety and efficacy are presumed and if a marketing authorisation has or will be applied for within a given time frame. When requested by a physician on a named-patient basis, an ATU will be granted if safety and efficacy are presumed, if the patient cannot be treated through a clinical trial, and if the product is either subject to a clinical trial or an application for marketing authorisation (even temporary), at least in a request form. The last of these conditions may be bypassed in a few specific cases, such as where there is a high probability of severe consequences for the patient without treatment. The Finance Bill for 2019 has opened up the possibility of obtaining an ATU for medicines that are already authorised for another indication where previously only medicines that had not been authorised were likely to be granted an ATU, for their first indication. Moreover, the Bill also provides that medicinal products authorised without a previous ATU but meeting the ATU criteria may be subject to a temporary reimbursement on that basis until final agreement on their reimbursement price, under conditions including the obligation to keep the product on the market for a certain length of time and at a price that may be set unilaterally by the CEPS.

Alongside these ATUs, the Bertrand Law has created a regulated scheme for off-label use, called temporary recommendation for use (RTU). A product may be prescribed off-label without any marketing authorisation or ATU, either because it is indispensable to the treatment of a patient, in light of the existing state of the art, or because it is permitted by an RTU issued by the ANSM. The conditions for granting RTUs are similar to those for ATUs, except that they are imposed on pharmaceutical companies by the authorities. In addition, the law amending social security funding for 2014 broadened the RTU regime to include cases where therapeutic alternatives might be available but not with the same active substance, dosage or pharmaceutical form. On 29 June 2016, the Administrative Supreme Court upheld this broadening of the RTU regime to cases where therapeutic alternatives are available, which had been challenged on the basis of, among other things, violation of Article 5 of Directive 2001/83/EC.

RTUs tend to get closer to standard marketing authorisations in several ways: first, they are issued for up to three years but can be indefinitely renewed (for example, an RTU was adopted for the medicinal product Avastin in 2015 and this was renewed for a new three-year period in September 2018); second, the Social Security Bill for 2018 has mirrored the pricing negotiation regime for the indications covered by an RTU, for which a distinct price can be agreed with the Pricing Committee (CEPS). The objective is clearly to encourage the use of the RTUs, despite the fact that they are deemed to cover exceptional circumstances.

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10 Law No. 2011-2012 of 29 December 2011 relating to Increasing the Safety of Medicines and Health Products.
v Pre-market clearance

The procedures for the approval of commercial distribution of medicines and medical devices stem from EU regulations. There is a peculiarity in France arising from the concept of an *exploitant* of medicines. In addition to the requirement of a marketing authorisation, a medicine may only be marketed by an authorised marketing company, whose premises and operation have been inspected and authorised by the ANSM. The *exploitant* must either be the marketing authorisation holder, a third party appointed by the latter, or both. He or she must carry out the pharmaceutical activities connected with the sale, promotion and monitoring of the products, and only pharmacovigilance activities can be subcontracted as such. A head pharmacist is responsible for the control of all the pharmaceutical activities, such as pharmacovigilance processes and the compliance of promotional material with relevant laws.

Medical devices can be marketed in France provided they carry a CE marking. However, in addition, manufacturers located in France must notify the ANSM of the first marketing of their devices, as well as any commercialisation in France of implantable and Class III medical devices on French territory (pursuant to the classification of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices), and provide a copy of the instruction leaflet.

vi Regulatory incentives

Data and market exclusivity rules in France follow EU regulations. However, there are some national peculiarities concerning the preservation of originators’ intellectual property rights. First, originator companies must notify their rights to the ANSM for publication purposes. Second, such rights can also be notified to the CEPS, which undertakes, in principle, not to issue any reimbursement decision for generic products more than six months before the expiration of the originator’s intellectual property rights. The CEPS cannot, however, prevent an at-risk launch scenario.

Increasingly, regulatory incentives tend to be developed at the pricing and reimbursement stage. Indeed, framework agreements entered into by the CEPS and the pharmaceutical and medical devices companies provide for pricing incentives or conditional pricing, subject to the conduct of additional studies to monitor the safety and efficacy of their products.12 The framework agreement between the CEPS and the pharmaceutical companies covering the period 2016–2019 also confirms the ability to agree on pay-for-performance schemes, but only in situations where the application of the usual pricing provision is not adequate. Moreover, the ministries supervising the CEPS stated that they intended pay-for-performance agreements to be limited to cases where the social security would not bear any risk, which *de facto* reduces the number of such innovative agreements.13

In addition, the framework agreement speeds up the process for the determination of the price for the most innovative products, and provides for the discharge of mandatory rebates to innovative, orphan and paediatric drugs. Also, various provisions favour innovative

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13 Ministerial Orientation, 17 August 2016.
paediatric indications, which are granted a one-year extension of guaranteed pricing (six years instead of five), as well as a guaranteed daily treatment cost not lower than for the adult dosage or the possibility of agreeing on a capped total turnover.

On another front, prescription of biosimilar medicines delivered in community pharmacies is incentivised by various means. First, healthcare institutions that have entered into an agreement with a Regional Health Agency will get an incentive corresponding to 20 per cent of the price difference between the biosimilar and the reference medicine in proportion to the biosimilar prescription rate. Moreover, since October 2018, certain healthcare institutions have been selected to trial alternative means of increasing the use of biosimilars alongside an increased incentive of up to 30 per cent.

vii Post-approval controls

Following the French scandal concerning Poly Implant Prothèse (a company that produced breast prostheses), post-approval controls have been increased for medical devices. The ANSM can launch unannounced inspections to detect deviations from applicable technical standards, and impose fines or suspend the marketing of non-compliant products.

In the same way, post-approval controls over pharmaceutical products have improved quite significantly with the right of the ANSM to deliver marketing authorisations on a conditional basis, provided that the holder carries out safety or efficacy studies in real treatment conditions and in comparison with existing therapies within a given time frame. However, this route is very rarely used.

The inspection means should be optimised thanks to the agreement on mutual recognition on good manufacturing practice inspections entered into between the European Union and the United States; this agreement has become effective following the 1 March 2017 decision14 but remains in the transition phase until July 2019. EU Member States will now be able to use data from inspections carried out by the US Food and Drug Administration (FDA) and vice versa (France is one of the first of 20 EU Member States whose inspection methodology has been recognised as acceptable by the FDA).

Pharmacovigilance reporting obligations have also been broadened. For example, pharmaceutical companies must report to the European database EudraVigilance all suspected adverse effects within 15 days of obtaining knowledge any serious side effects and within 90 days of others. Moreover, as specified in the marketing authorisation, periodic safety update reports must be transmitted regularly to the European Medicines Agency.

viii Manufacturing controls

Recurrent issues relating to the shortage of certain medicines, including those of high therapeutic value or without therapeutic equivalent, have given rise to several changes in the regulations.

Decree No. 2016-993 of 20 July 2016 obliges companies themselves to identify medicines with high therapeutic value, for which they must elaborate detailed alternative supply plans and organise emergency call centres to dispatch products in the event of an actual shortage. Any suspected shortage must be notified to the ANSM. In addition,
pharmacists are allowed to import alternative products in the event of a shortage. Despite these measures, the ANSM registered 405 shortages in 2016. The French Senate published a report recommending implementing a new set of measures, including the creation of a national shortage management unit under the authority of the Prime Minister, or the purchase of medicine reserves for some patient populations.

ix Advertising and promotion
Following the Bertrand Law of 29 December 2011 relating to the strengthening of the safety of medicines and health products, any kind of advertising and promotion of medicines and certain medical devices now requires prior approval from the ANSM.

Advertising and promotional materials for medicines must be submitted to the ANSM following a specific timetable determined by the ANSM: quarterly for advertising to HCPs, and during one of the eight weeks stipulated by the Director General of the ANSM for 2019 for advertising to the public. In the absence of a negative answer from the ANSM two months after the expiry date of each period determined by the ANSM for the receipt of proposed advertising, the advertising is deemed approved and will be valid for two years.

The approval process is the same for advertising and promotional materials for medical devices, except that submissions are not bound by the trimestral timetable.

In addition, the distribution of samples is now restricted to new medicines or for new indications within the first two years of their launch, and only in reply to a written request placed by an HCP.

x Distributors and wholesalers
Wholesale activities have been affected by various measures aiming to address shortages of some key products. Wholesalers, who in France are entrusted with certain public service duties, must notify the ANSM of their geographical area of activity. In addition, the Public Health Code states that wholesalers must first distribute their products to meet the health needs in the notified geographical area before exporting them. As a result, pharmaceutical companies shall ensure an appropriate and continuous supply of products to any and all wholesalers, to enable them to comply with these duties.

The ANSM has audited compliance with wholesalers’ requirements and has suspended several wholesale licences of distributors whose activity had deviated from the coverage of the French territory to the export of medicines.

Distribution in pharmacies has also been significantly affected by several changes, as outlined below.

First, medicines and medical devices fall within the pharmaceutical monopoly, namely only a pharmacy that has been granted an authorisation from a regional health agency (ARS), based on the number of residents within its market area, can sell those products to the public. Law No. 2014-344 of 17 March 2014 has removed contact lens solutions, pregnancy tests and ovulation predictors from the monopoly, allowing their distribution in grocery stores.

xi Online sales
The transposition into French law of Directive No. 2011/62/EU on the sale of falsified medicines was rendered difficult by the classification of pharmaceutical products. Indeed, France first restricted online sales to a subcategory of non-prescription drugs, registered on
the list of products available by direct access to the public.\textsuperscript{15} The Administrative Supreme Court annulled this provision on the grounds of non-compliance with the EU directive that envisaged online sales of any and all over-the-counter products.\textsuperscript{16} Consequently, all over-the-counter products are now available online.\textsuperscript{17}

More specifically, online sales of medicines are regulated by ordinance No. 2012-1427 of 19 December 2012. The obligations imposed on the functioning of online pharmacies are quite similar to those for brick-and-mortar pharmacies. An authorisation from the ARS is required. Pure players are not allowed as online pharmacies must rely on traditional brick-and-mortar ones.\textsuperscript{18} Two ministerial orders of 28 November 2016 set out good distribution practices for pharmacists, covering all types of situations, including online distribution, as well as the technical requirements for websites, aiming at ensuring the same level of confidentiality and safety as with physical distribution. The Administrative Supreme Court recently overruled some provisions of these two ministerial orders that were deemed a restriction on online pharmacies, in breach of EU law.\textsuperscript{19} For instance, the Court considered it not possible to ban any kind of promotion by online pharmacies, whereas this is not the case for bricks-and-mortar pharmacies.

\textbf{xii Imports and exports}

Adopted on 26 January 2016 with a view to modernising the French health system, the Health Bill has introduced a prohibition on wholesalers exporting any medicine of high therapeutic value or without therapeutic equivalent. In addition, the Public Health Code states that other medicines may only be subject to export once national needs are covered; furthermore, it states that a trial or pilot scheme should be carried out whereby wholesalers would notify an independent third party of the volumes not distributed on the French territory. However, an order setting out the conditions for undertaking such a trial has never been published.

\textbf{xiii Controlled substances}

Controlled substances are classified into three categories (narcotics, psychotropics, and drugs on controlled substance Lists I or II), depending on their level of danger. Registration is made by a ministerial decree, following the opinion of the ANSM when the substances are medicines. Drugs can receive a categorisation different from that of one of their compounds and, in the event of doubt or multiple categorisations, the stricter category will prevail.

Controlled substances in the form of active ingredients are subject to administrative requirements of traceability to track the precise volume used.

Drugs included on Lists I or II will be subject to specific requirements in terms of storage in separate and secured premises, labelling with a symbol for death, limited volume of product delivered and, concerning narcotics, use of secured prescriptions.

\textsuperscript{16} Administrative Supreme Court, 17 July 2013, No. 365317.
\textsuperscript{17} Ordinance No. 2016-966 of 15 July 2016.
\textsuperscript{18} Article L. 5125-36 of the French Public Health Code.
\textsuperscript{19} Administrative Supreme Court, 26 March 2018, No. 407289 and 4 April 2018, No. 407292.
xiv Enforcement

The enforcement of regulations relating to health products is the responsibility of several authorities. For instance, the ANSM is the main sanctioning authority with regard to health products. The ANSM’s powers and sanctions have been strengthened by Ordinance No. 2016-966 of 15 July 2016 through a simplification of the scope of its activity. The Directorate General for Competition Policy, Consumer Affairs and Fraud Control is also entitled to sanction certain behaviours, such as infringements of the anti-kickback law.

III PRICING AND REIMBURSEMENT

Pricing and reimbursement activities are governed by framework agreements entered into between the CEPS and the professional organisations representing the medical devices industry on the one hand, and medicines and drug industry on the other.20

The framework agreement concerning medical devices was signed for the first time on 16 December 2011. Its main aim is to define a template for each agreement on the pricing of medical devices, applicable procedure and time limits. Its duration was initially envisaged to be three years but it has not been amended since then.

The framework agreement concerning medicines (which entered into force on 31 December 2015 for the period 2016–2018 and has been amended to apply until the end of 2019) provides a comprehensive framework for the determination and evolution of prices. In particular, it allows for an acceleration of the procedure applicable to determine the price of innovative products, by accepting a mechanism whereby the company declares its selling price and the CEPS accepts it within two to three weeks, as long as it is consistent with prices in Germany, Italy, Spain and the United Kingdom, and provided that the company commits to compensating sales above its forecasts for four years. As a result of Brexit, the United Kingdom will be excluded from this list and replaced by another EU reference Member State. This matter will probably be subject to negotiations between the CEPS and the French Pharmaceutical Companies Association when entering into the new framework agreement.

Outside this specific scheme, the CEPS undertakes that products recognised as having an important therapeutic benefit (with an ‘added clinical value’ (ASMR) rating of I, II or III) will not be priced below the lowest of the prices in the aforementioned countries for a five-year period, extended by one additional year for paediatric indications. Other provisions concern paediatric and orphan drugs, including the possibility of agreeing on a provisional price, pending its confirmation following agreed studies. However, the parties did not manage to agree on rules to apply to biosimilars and their originator products; this will be one of the most important points in the new framework agreement to be negotiated during 2019 and is probably the reason why the agreement has been renewed for one more year.

Health technology assessment (HTA) procedures were implemented in France by a decree of 2 October 2012.21 They concern the pricing and reimbursement of products (medical devices and medicines) that claim an important medical benefit (with an ASMR and ‘added service value’ rating of I, II or III) and that may have a significant impact on the social security budget. The latter criterion is deemed to be fulfilled if the turnover is above

20 See footnote 12.

21 Ministerial Decree No. 2012-1116 of 2 October 2012 relating to the Medico-economic Functions of the Health Authority.
€20 million as from the second full marketing year. However, the HAS may also produce a medico-economic opinion on other products it deems to have a significant impact on the organisation of the healthcare system, according to the claims for the product.

The procedure is similar to the procedure relating to opinions issued by the transparency committee for the eligibility for reimbursement by social security: the HAS first issues a draft opinion and then companies can request a hearing within eight days. In guidelines issued in November 2016, the HAS clarified the methodology of HTA studies, notably the fact that the financial expectations should cover a three- to five-year term.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The Administrative Supreme Court reviews the legality of health authority decisions that have a mandatory effect.

Recent case law has significantly increased the monitoring of the CEPS’s room for manoeuvre in setting prices. The Administrative Supreme Court does not hesitate, even in summary proceedings, to request from the CEPS detailed economic justifications explaining the level of price decrease imposed. The CEPS cannot impose a price decrease simply to maintain the global increase in spending authorised by parliament; objective and transparent criteria must be met. In the same way, the Administrative Supreme Court verifies the legality of the criteria used by the CEPS and does not hesitate to overrule any decision based on criteria that cannot be the sole legal ground for price decrease decisions. In addition, on the basis of the Transparency Directive dated 21 December 1988, the CEPS has been sanctioned for not having published the criteria followed for the refusal to reimburse a product. As a consequence of this judgment, the Social Security Finance Bill for 2017 significantly amended the circumstances in which price decreases can be imposed. But this was not sufficient to retroactively validate decisions refusing the reimbursement of a product adopted before that publication. The Court also stressed that the CEPS should adhere to the set criteria for the determination of the price. For instance, the Court criticised the fact that it took into account only 50 per cent of the value of trademark rights, whereas its assessment was based on the total cost of the goods. On the basis of the same Transparency Directive, the Court also cancelled an implicit refusal opposed by the Ministry for not having provided the reasoning behind the refusal. It is interesting to note that one of the arguments is based on confirmation that the opinions of the Transparency Commission are not binding on the Ministry. As such, they cannot be directly challenged before the Court. On the other

22 Letter from HAS and CEPS of 24 September 2013, DEMESP/SEESP/CRP/IBD/AT DIR 2013_45.
23 Administrative Supreme Court, 18 April 2016, No. 397909, Advanced Technical Fabrication.
26 Administrative Supreme Court, 27 June 2016, No. 386332, GSK.
28 Administrative Supreme Court, 14 June 2017, No. 400608, Roche.
29 Administrative Supreme Court, 13 May 2016, No. 381148, Teofarma.
30 Administrative Supreme Court, 17 November 2017, No. 398573, Abbvie.
hand, the opinion is not deemed to provide sufficient grounds for an implicit refusal, in the sense of the Transparency Directive. This ruling should significantly reduce the number of implicit refusals, which, by their nature, do not detail their reasoning.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The French transparency regime was established by the Bertrand Law, and amended by a decree and a governmental circular published on 21 and 29 May 2013 respectively.31 The reforms became effective on 1 June 2013, and have been applicable to the relationships between HCPs and the health industry since 1 June 2012.

That transparency legislation aims to make public any kind of advantages, whether in cash or in kind, amounting to €10 or more for each advantage granted by any company that manufactures or markets pharmaceutical products or medical devices (regardless of their status in relation to reimbursement by social security), and any company delivering services in connection with such products, including marketing, public relations and events agencies, directly or indirectly to HCPs registered in France and their professional associations, as well as students, patient associations, foundations, healthcare centres, prescription software editors, the media and professional training institutions. In addition, pharmaceutical and medical device companies (as defined below) must also disclose the existence of any agreement entered into with HCPs. The Health Bill, as amended by Ordinance No. 2017-49 of 19 January 2017, broadened the disclosure obligations to the detailed object of the agreement, its date, the identification of the direct and final beneficiaries and the remuneration paid to HCPs above a threshold of €10.

Publication occurs biannually: on 1 October for the first half of the year, and on 1 April of the following year for the second half of the year. All data will remain available for five years, or longer if an agreement is entered into for more than five years.

The Ordinance of 19 January 2017, which entered into force on 1 July 2018, has also significantly reshaped the French anti-kickback rules. The scope is broadened regardless of the status of the products with regard to reimbursement. Any type of advantage proposed or procured is prohibited. However, it is now specified that royalties paid in connection to IP rights are not deemed an advantage. Fees paid for research or consultancy, grants, professional training and hospitality are subject to a written agreement and prior authorisation from the physicians’ professional board. The maximum criminal fines have been increased to up to €150,000 for natural persons and €750,000 for legal persons. Although the implementing decree of the Ordinance is still subject to discussions, the draft decree provides that the amount beyond which agreements shall be authorised depends on the kind of benefit granted (e.g., compensation, donation).

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The Health Bill introduced into French law, for the first time, a class action for compensation for physical damage caused by health products. The action will be opened retroactively as well.

for damage caused by products that are no longer on the market. Actions may be brought by associations of healthcare system users and will be initiated by a single judgment on liability. Expert evidence may, however, be necessary at this early stage to establish the defect and causality in relation to damage caused and corporate responsibility. The judgment will list the damage eligible for indemnification, as well as publicity measures. Victims will have between six months and five years to opt into the action. The judgment may also, with the agreement of the parties, appoint a mediator for the determination of the indemnification level.

Importantly, the first phase of the class action procedure will suspend the time limit for individual actions.

The class action regime has been effective since the publication of Order No. 2016-1249 of 26 September 2016, but, contrary to the practice in the United States, it has not been widely used in France.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

EU and French competition laws prohibit anticompetitive agreements and abuse of a dominant position. In this respect, at the national level, agreements between companies that have as their object or effect the prevention, restriction or distortion of competition within the French market are forbidden by French competition rules.32 In the pharmaceutical sector, this may apply to price fixing, co-marketing or co-promotion agreements, which may also give rise to illegal exchanges of sensitive information insofar as they lead to a restriction of competition among the concerned companies. In addition, unilateral conduct by a dominant undertaking that acts in an abusive manner is also prohibited.33 When there is a suspicion of such conduct – which may be brought through a claim by the victim of the conduct – the French Competition Authority (FCA) is empowered to conduct an investigation at the undertaking’s premises (in practice, extensive investigative powers apply) or to send a request for information. Fines for this kind of anticompetitive behaviour can reach 10 per cent of the group’s worldwide turnover.34 The FCA may order interim measures in urgent and extreme cases.

In this context, the FCA issued two decisions in 2013, fining Sanofi and Merck (€40 million and €16 million respectively) for having abused their dominant position in relation to generics. On 18 October 2016, the Supreme Court validated the fine imposed on Sanofi in the Plavix case. More recently, the FCA fined Janssen Cilag up to €25 million on 20 December 2017 for having abused its dominant position on fentanyl transdermal patches by disparaging generics, discouraging HCPs from switching, and influencing health agencies in charge of granting generics marketing authorisations by ‘illegally’ or ‘illegitimately’ using regulatory paths.

The FCA made a specific case with respect to these pharmaceutical companies, because of the context in which they operated. Moreover, it considered that a communication about a pharmaceutical product that faces a competing generic product may constitute a quasi-automatic abuse to the extent that the communication is capable of having a negative impact on the generic product. This could happen, for example, if the originator did not

34 Article L. 464-2 of the French Commercial Code.
limit itself to pointing out the objective qualities of its own product and did not refrain from emphasising the differences between the originator product and the generic drug. Such communication is analysed both in detail and within the general context. As such, isolated elements, while in themselves not illegal, may be punished by the FCA as a global, coherent and structured communication strategy, the goal of which is considered to be preventing or limiting the entry of the generic medication onto the market.

Moreover, in a decision dated 20 November 2017, the FCA announced the opening of a wide investigation covering the pharmaceutical sector, with a focus on the pharmaceutical distribution chain and the medicines price-setting process.

This new inquiry, which follows the investigation conducted in 2013, focuses on conditions of over-the-counter medicine sales to pharmacies, but also the interplay between competition and pricing discussions with the CEPS (particularly regarding the contractual rebate mechanism), and competition in calls for tenders organised by healthcare institutions.

While the FCA was expected to issue its first recommendations regarding medicine distribution schemes and the field of medical biology in 2018, after analysis of the responses, supporting documents and interviews with various stakeholders, it recently launched a public consultation with relevant professionals (physicians, pharmacists, wholesalers, etc.) to complement its initial findings. These findings have highlighted the need to amend the current inadequate French regime in this area, and at the time of writing, the FCA’s final recommendations were expected to be adopted at the beginning of 2019. The findings from the analysis of the price-setting process should be issued in summer 2019.

ii Transactional issues

Given the size of the potential combined turnover in question, mergers in the health area often give rise to an analysis from a competition law standpoint. A key element in this respect is the determination of the relevant market in respect of which the potential effects of the contemplated merger will be assessed. The case law is not fully settled in this field. Indeed, although the competition authorities consider the ATC/DDD classification, at Level 3, as a starting point, the FCA may then combine various classes in light of the products’ therapeutic indications or galenic form. In addition, the analysis may narrow to Level 4 or even Level 5, at the molecular level. Indeed, this was the approach taken by the FCA in a recent case, where it cleared a concentration by analysing the market shares of two companies from ATC/DDD Levels 3 to 5.36

VIII CURRENT DEVELOPMENTS

As an extension of the policy implemented in recent years by the French government to limit pharmaceutical companies’ bargaining power regarding pricing, the Social Security Finance Bill for 2019 contains various provisions aimed at reducing Social Security expenses. For example, the price of health products used in combination may be set unilaterally by the CEPS, which will be able to impose rebates if an agreement between the manufacturers and the CEPS cannot be reached.

35 The World Health Organization’s Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD).
36 Decision No. 13-DCC-106 of 6 August 2013 related to acquisition of sole control of Warner Chilcott Company by Actavis Inc.
Moreover, to promote the use of generics and biosimilars, which are cheaper than their originator products, this Bill regulates the use of ‘non-substitutables’ by physicians. A ministerial order is expected to be adopted to strictly define medical cases for which healthcare professionals are allowed to prescribe an originator product instead of a generic or a biosimilar.
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...
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.

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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

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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 innovator’s 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. 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

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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.
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.

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.

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

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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

i Regulatory framework
The regulatory framework for medicinal products in Ireland is based on Directive 2001/83/EC on the Community code relating to medicinal products for human use (as amended) (the Community Code). This was implemented in Ireland by the Irish Medicines Board Act 1995 (as amended) (the IMB Act) and domestic regulations, most notably the Medicinal Products (Control of Placing on the Market) Regulations 2007² (as amended) (the Marketing Regulations).

The regulatory framework for medical devices in Ireland is based on the following directives that have been transposed into Irish law: Directive 93/42/EEC concerning medical devices, Directive 90/385/EEC on active implantable medical devices (as amended) and Directive 98/79/EC on in vitro diagnostic medical devices (the IVD Directive) (as amended). National legislation transposing those Directives (as amended) include the European Communities (Medical Devices) Regulations 1994³ (as amended in 2001, 2002 and 2009), the European Communities (Active Implantable Medical Devices) Regulations 1994⁴ (as amended in 2009), the European Communities (In Vitro Diagnostic Medical Devices) Regulations 2001⁵ (as amended in 2012), the European Communities (Medical Devices) (Reclassification of Breast Implants) Regulations 2003⁶, the European Communities (Medical Devices) (Tissues of Animal Origin) Regulations 2003⁷ and the European Communities (Medical Devices) (Reclassification of Hip, Knee and Shoulder Joint Replacements) (Amendment) Regulations 2007⁸ (collectively, the Medical Devices Legislation). The existing Medical Devices Legislation is due to be overhauled when the new EU Regulation 2017/745 on medical devices and Regulation 2017/746 on in vitro diagnostic medical devices (which formally entered into force at the end of May 2017) come into effect – 2020 for medical devices and 2022 for in vitro diagnostic medical devices. These two Regulations represent

¹ Colin Kavanagh is a partner and Ciara Farrell and Bridget McGrath are associates at Arthur Cox.
a significant development and updating of the existing regulatory system for medical devices in Europe and will replace the original EU Directives, which have been in place for over 25 years.

ii Regulatory authorities

The Health Products Regulatory Authority (HPRA; formerly the IMB)\(^9\) is the competent authority responsible for regulating medicinal products, medical devices, cosmetics and other health products in Ireland. The National Standards Authority of Ireland (NSAI) is the notified body in Ireland designated by the HPRA to carry out conformity assessment procedures to ensure compliance with the Medical Devices Legislation. The HPRA’s main areas of responsibility are:

- ensuring the quality, safety and efficacy of medicinal products (including veterinary medicinal products) available in Ireland, participating in systems designed to do so throughout the European Union, and monitoring the quality of medicinal products and their manufacturing and distribution processes;
- acting as the competent authority for the implementation of EU and national legislation relating to blood, blood components, tissues, cells and medical clinical research, and cosmetics;
- regulating medical devices on the Irish market;
- regulating the protection of animals used for scientific purposes; and
- regulatory functions in respect of organs intended for transplantation.

II THE REGULATORY REGIME

i Classification

The decision as to whether a product will be deemed a medicinal product, a medical device or other regulated product will largely depend on the particular intended use of the product, as assigned by the manufacturer, and on the demonstrated mode of action. In arriving at any decision with regard to classification, the applicant must provide the HPRA with sufficient information about the product and its intended usage, including all promotional material. This includes not only labels, leaflets and all advertising materials but also any websites linked to that literature. In the event that the HPRA determines that the product could potentially be a medicinal or other product, the product may be referred to the HPRA Classification Committee, which meets once a month and is responsible for assessing products for which classification is not obvious, including those that are borderline medical devices or medicinal products. Alternatively, classification requests for borderline products may be sent directly to the Classification Committee as opposed to being referred by the HPRA.

Decisions made by the Classification Committee can be appealed to the HPRA Management Committee, which may request the advice of the Advisory Committee on Human Medicines (ACHM) set up under the IMB Act. The decision of the Management Committee is final.

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9 See www.hpra.ie.
II Non-clinical studies

Non-clinical studies (e.g., non-interventional studies) are not regulated by the applicable laws and guidance for clinical trials in Ireland. They do not require the positive opinion of an ethics committee. There is, however, general legislation that applies, such as data protection legislation, the common law on consent for medical treatment and research, animal welfare protection laws and good laboratory practice.

Directive 2010/63/EU was transposed into Irish law in December 2012 by the European Union (Protection of Animals used for Scientific Purposes) Regulations 2012\(^{10}\) (as amended). This legislation aims to improve the welfare of animals used for scientific purposes and to promote the principles of the three Rs – replacement, reduction and refinement:

- **Replacement** refers to the use of alternative methods that substitute the use of animals for scientific purposes. Where replacement is not possible, animal use must only be permitted where justified and where the expected benefits outweigh the potential adverse effects.
- **Reduction** measures must be applied so as to minimise the number of animals used in each research project.
- **Refinement** measures must also be applied to enable procedures to be carried out in the most humane manner possible and to minimise pain, suffering, distress and lasting harm.

The European Communities (Good Laboratory Practice) Regulations 1991\(^{11}\) (as amended) give effect to Commission Directive 2004/10/EC, which requires certain testing on chemicals to be carried out in accordance with the principles of Good Laboratory Practice. The Irish National Accreditation Board has statutory responsibility for enforcement of these regulations.

III Clinical trials

**Medicinal products**

Clinical trials in Ireland are regulated by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 to 2009 (the Clinical Trial Regulations), which implement Directive 2001/20/EC on the conduct of clinical trials (the Clinical Trials Directive) and Directive 2005/28/EC on good clinical practice for medicinal products for human use (the GCP Directive).

The Clinical Trial Regulations apply to clinical trials conducted with human subjects and involving investigational medicinal products (IMP). On 16 April 2014, the new Clinical Trials Regulation\(^{12}\) was adopted. It will repeal the Clinical Trials Directive and its aim is to simplify and harmonise the authorisation of clinical trials across the European Union. The new Regulation is expected to enter into force six months after a new EU database and single online EU portal created under the new Regulation become fully functional. Clinical trials will, however, continue to be conducted in accordance with the Clinical Trials Directive until the new Regulation becomes applicable.

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10 SI543/2012.
12 Regulation No. 536/2014.
Authorisations

A clinical trial authorisation (CTA), issued by the HPRA, must be obtained by a sponsor or person authorised to act on his or her behalf prior to commencing a clinical trial. An investigational medicinal product dossier should be submitted to the HPRA providing clinical and non-clinical supporting data for the investigational medicinal product, with evidence of the favourable ethics committee opinion and the sponsor’s EudraCT\(^\text{13}\) number (see ‘Trial preconditions’, below).

Informed consent

The sponsor must obtain each trial subject’s informed consent and inform each trial subject of the trial procedure and his or her right to withdraw at any time. Other conditions apply with respect to the requirements of the applicable data protection legislation and the Clinical Trials Regulations. Documentation relating to these matters must be submitted to the ethics committee for opinion before the application for a CTA is made to the HPRA (see below).

Trial preconditions

The following items must be satisfied before a clinical trial can commence:

\(a\) the sponsor, or the person authorised to act on his or her behalf in relation to the trial, is established in the European Union;

\(b\) the sponsor has registered with the European Economic Area (EEA) system for monitoring drug safety, EudraVigilance;

\(c\) a favourable ethics committee opinion in relation to the trial protocol has been obtained;

\(d\) the HPRA has granted a CTA; and

\(e\) insurance and indemnity cover for the conduct of the trial has been obtained.

To facilitate the effective initiation of clinical trials and the removal of administrative barriers, a single HSE clinical trial indemnity form (CTIF) has been agreed between the State Claims Agency and the Irish Pharmaceutical Healthcare Association (IPHA) for the conduct of industry-led clinical trials in Ireland. The CTIF is applicable to the conduct of any industry-sponsored clinical trial in any state hospital in Ireland. Use of the HSE CTIF, which refers to the IPHA clinical trial compensation guidelines, provides the assurance that the company sponsoring a clinical trial will, without legal commitment, adhere to certain guidelines in the event of injury caused to a patient that is attributable to participation in the trial in question.

Medical devices

Devices carrying the CE mark may be freely marketed anywhere in the European Union.\(^\text{14}\) Clinical assessments are usually required before non-CE marked medical devices may enter the Irish market. For any clinical investigation to commence in Ireland, approval from the HPRA is required, with a positive opinion of an ethics committee. Certain clinical investigations, such as those using CE-marked devices within their intended purpose, may not require a review by the HPRA. This must be assessed on a case-by-case basis.

\(13\) European Clinical Trials Database.

\(14\) Where the medical device is to be exported outside the European Economic Area, it will be necessary to apply to the HPRA for a Certificate of Free Sale.
Typically, applications are submitted by a commercial sponsor, such as a medical device manufacturer. By this application, the manufacturer is proposing to conduct an investigation to gather the necessary clinical data to demonstrate the basic safety and performance of their device. The requirements governing the conduct of clinical investigations are laid down in Directive 93/42/EEC and in the IVD Directive, as well as various Commission guidance documents (MEDDEVs) and international standards. The HPRA reviews the regulatory, technical and clinical aspects of the application. The HPRA reviews applications to conduct clinical investigations in Ireland in parallel with the appropriate ethics committee review. An initial decision will be issued within 30 days of the application being made, and the final decision will be provided by the HPRA within 60 days of the application.

iv  Named-patient and compassionate-use procedures

Medicinal products

Named-patient programmes

Regulation 2 of Schedule 1 of the Marketing Regulations regulates named-patient programmes in Ireland. Under the Marketing Regulations, a named-patient programme permits the sale or supply of an unauthorised product in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of a practitioner for use by his or her individual patients on his or her direct personal responsibility, to fulfil the special needs of those patients.

To make use of the programme, the following conditions must be satisfied:

a  receipt of an unsolicited order from a registered healthcare professional (HCP);

b  the product must be supplied to the order or prescription of the requesting HCP;

c  the product is only provided to the HCP’s individual patient; and

d  the provision of the product is supervised under the direct personal responsibility of the HCP.

There is no formal authorisation for establishing a named-patient programme in Ireland. However, wholesalers and manufacturers that receive or import exempt medicinal products intended for distribution in Ireland under a named-patient programme must notify the HPRA of this fact within two working days of receipt of the consignment. There are a number of exceptions to this notification requirement, all of which depend on the specific supply chain in question. Packaging and labelling requirements will apply, as well as fees and record-keeping obligations in terms of pharmacovigilance and quality defects.

Compassionate use

Medicinal products for use in an authorised clinical trial are exempt from the requirement to be subject to a marketing authorisation (MA). The HPRA does recognise the option of an Expanded Access Programme (EAP) for patients who have been treated with a medicinal product during a clinical trial and wish to continue treatment after the trial is completed. If, however, the EAP fulfils the definition of a clinical trial, it is required to be authorised as such under the applicable Irish legislation. In the event that it does not fulfil the definition of a clinical trial, the medicinal product can only be supplied via a named-patient programme. This essentially means that EAPs for groups of patients at a time are only recognised in Ireland if they are authorised as clinical trials and meet all applicable legislation governing clinical trials.
Medical devices
The CE marking does not have to be present on medical devices intended for clinical investigations, custom-made devices and in vitro diagnostic medical devices for performance evaluation. The CE marking does not have to be present on medical devices intended for exhibitions, demonstrations, trade fairs, etc. However, these devices must bear a visible marking indicating that they are not intended to be marketed or put into use.

v Pre-market clearance
Medicinal products
The placing of medicinal products on the market in Ireland is regulated by the Marketing Regulations. Subject to certain exceptions, a medicinal product cannot be placed on the market in Ireland unless an MA has been granted for that product by the HPRA or the European Commission. An MA can be obtained through the following procedures:

a National procedure: an application is submitted to the HPRA and, if granted, the MA entitles the marketing authorisation holder (MAH) to place the medicinal product on the Irish market.

b Mutual recognition procedure: if the medicinal product has received an MA in another EEA Member State (the Reference Member State), the MAH can apply to one or more other Member States (the Concerned Member States) to recognise that authorisation. If a product has received an MA in another Member State, the MAH can apply to the HPRA to mutually recognise that authorisation in Ireland.

c Decentralised procedure: this can be used if the product has not yet received an MA in a Member State and the applicant wishes to apply for simultaneous authorisation in two or more Member States. The applicant nominates one of the states as the Reference Member State, whose competent authority examines the application in full and prepares a report for the competent authorities of the Concerned Member States. The HPRA is the competent authority in Ireland for these applications.

d Centralised procedure: a Community MA, which is valid throughout the EEA, can be obtained by applying to the European Medicines Agency (EMA), through the centralised procedure governed by Regulation (EC) No. 726/2004, as amended, on the authorisation and supervision of medicinal products, and establishing a European Medicines Agency (as amended) (the EMA Regulation). Following a positive assessment by the EMA, an MA is granted by the European Commission. The centralised procedure is compulsory for certain medicinal products.

Medical devices
The conformity assessment and CE marking procedures for medical devices discussed in the European Union chapter also apply in Ireland. Apart from the registration requirement below, there is little additional regulatory pre-market review and approval by the HPRA.

The Medical Device Regulations require that certain persons placing devices on the market must register their contact details and details of their devices with the HPRA. This requirement applies if that person has a registered place of business in Ireland and if that person:

a manufactures Class I or custom-made medical devices and places them on the market under his or her own name or trading name;
manufactures custom-made, active, implantable medical devices and places them on
the market under his or her own name or trading name;

c manufactures in vitro diagnostic medical devices and places them on the market under
his or her own name or trading name;

d fully refurbishes Class I devices or labels one or more ready-made devices, with a view
to placing these on the market under his or her own name;

e places medical devices bearing the CE marking on the market, in a system or
a procedure pack;

f sterilises, for the purpose of placing on the market, systems or procedure packs or
other CE-marked medical devices designed by the manufacturers to be sterilised before
use; or

g is the designated European authorised representative for a manufacturer that does not
have a registered place of business in the European community, and that places on the
market devices within the above-listed categories.

vi Regulatory incentives

Medicinal products
An application for authorisation of a generic of a medicinal product or similar biological
product can be made to the HPRA eight years after authorisation of the reference product
(i.e., the original product) when the period of data exclusivity for the reference product
expires. If the application for the reference product was made before 30 October 2005 and
the application was not in respect of a Community MA, the period is reduced to six years.

Once authorised, a generic or similar biological product cannot be placed on the
market for 10 years (depending on the exclusivity period available for the reference medicinal
product) following authorisation of the reference product. This is extended to 11 years if,
during the first eight years after the initial MA for the reference product is granted, the holder
of that MA is granted an authorisation for a new therapeutic indication of significant clinical
benefit in comparison to existing therapies.

Medical devices
There is no specific regulatory exclusivity for medical devices in Ireland. Medical devices
may be protected by a patent granted by the Irish Patents Office under the Patents Act 1992
(as amended) (the Patents Act). Patents granted under the Patents Act can be for 20 years
(full-term patent) or 10 years (short-term patent).

vii Post-approval controls

Medicinal products
The Irish requirements concerning post-approval controls reflect those discussed in the
European Union chapter.

Additional information to the HPRA
In addition to the requirements for MAHs discussed in the European Union chapter, MAHs
are required by the Marketing Regulations to provide the HPRA with certain information,
including the date that the medicinal product is placed on or removed from the market,
and any new information that may influence the evaluation of the benefits and risks of the
medicinal product.
Transfer of marketing authorisations

An MA may be transferred from the existing authorisation or licence holder to another holder using a transfer procedure. A transfer may occur before a product is authorised or after authorisation, to a company related to the existing holder or to an unrelated company. An MA can be transferred within six weeks of receipt of a valid application by the HPRA. Products can be transferred either before authorisation or once authorised. Transfer applications are subject to the national procedure, even if the product has been authorised via the mutual recognition procedure.

Medical devices

The Irish requirements concerning post-approval controls reflect those discussed in the European Union chapter.

viii Manufacturing controls

Medicinal products

Manufacturing is regulated by the Medicinal Products (Control of Manufacture) Regulations 2007\(^\text{15}\) (as amended).

The manufacture and importation of medicinal products is subject to the holding of an authorisation. This is known as a manufacturing import authorisation (MIA). To obtain an MIA, an application is made to the HPRA. The manufacturer is required to provide certain documentation as part of the application that will be verified for accuracy by the HPRA, which may include an inspection of the site where the activities take place. There is no restriction on foreign applicants applying for an MIA. However, the HPRA only issues manufacturing authorisations for Irish manufacturing or importation sites. Applications must be granted or refused by the HPRA within 90 days.

The requirements governing the information to be submitted as part of the application and those required to ensure the validity of the authorisation (e.g., a qualified person and the principles of good manufacturing practice (GMP)) are discussed in the European Union chapter.

The HPRA is responsible for monitoring compliance with MAs and GMP requirements. To this end, the HPRA can:

- enter and inspect sites;
- inspect and copy records;
- conduct tests or examinations at the site; and
- take samples for testing.

The HPRA can investigate whether a manufacturer or importer has obtained an authorisation and is complying with it, and has, at his or her disposal, a qualified person who meets the requirements and is fulfilling his or her obligations.

Medical devices

Apart from the registration requirement discussed in Section II.v, the Irish requirements concerning the manufacture of medical devices are similar to those discussed in the European Union chapter.

\(^{15}\) SI539/2007.
Advertising and promotion

**Medicinal products**

The advertising of medicinal products is regulated by the Medicinal Products (Control of Advertising) Regulations16 (the Advertising Regulations). The Advertising Regulations are enforced by the HPRA. Non-compliant advertisements can be required to be withdrawn and the person responsible for the advertisement may be required to publish a corrective statement. Breach of the Advertising Regulations is a criminal offence under the IMB Act. The Consumer Protection Act 2007 and the European Communities (Misleading and Comparative Marketing Communications) Regulations 2007 also apply to general advertising and commercial practices.

Self-regulation plays an important role and members of the IPHA must comply with the Code of Practice for the Pharmaceutical Industry17 (the IPHA Code) for prescription and non-prescription medicinal products, and the Code of Standards of Advertising Practice for the Consumer Healthcare Industry18 (the IPHA Consumer Code) for non-prescription medicinal products.

The IPHA Code fully reflects the standards of the European Federation of Pharmaceutical Industries and Associations Code on the Promotion of Prescription-only Medicines to, and Interactions with, Healthcare Professionals. The IPHA Code and the IPHA Consumer Code apply only to those pharmaceutical companies that have voluntarily agreed to be members of the IPHA. The Irish Generic Medicines Association (IGMA), the industry body representing manufacturers of generic medicinal products, has published the Code of Practice on Advertising of Medicinal Products, a similar code based on the Regulations and the Directive.

The Advertising Standards Authority for Ireland (ASAI) has published a Manual of Advertising Self-Regulation with the Code of Standards for Advertising, Promotional and Direct Marketing in Ireland (the ASAI Code). The ASAI Code applies to the advertising of medicinal products, with the exception of specialised marketing communications addressed to the medical, veterinary and allied professions. The Broadcasting Authority of Ireland has produced a General Commercial Communications Code, which applies to advertising broadcasts on radio or television channels licensed in Ireland.

**Medical devices**

The Medical Devices Legislation does not specifically regulate the advertising of medical devices.

The Irish Medtech Association Code of Ethical Business Practice (the Medtech Code) is a self-regulatory code and is binding on all members of the Irish Medtech Association (formerly IMDA). This Code is not underpinned by legislation.

The Medtech Code has been developed by the Irish Medtech Association and is largely based on that of MedTech Europe (formerly Eucomed and the European Diagnostic Manufacturers Association), the European medical technology industry association. A new common Code of Ethical Business Practice was adopted by MedTech Europe, in a move to put forward clearer and more stringent self-regulation. The new Code replaces the current

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17  Version 8.4; 2019.
18  Version 5.2; 2017.
codes of business practice and is known as the MedTech Europe Code of Business Practice, which became binding for Irish Medtech Association members on 1 January 2018. It sets the minimum standard by which industry members operate across Europe.

**x  Distributors and wholesalers**

**Medicinal products**

**Wholesaler’s distribution licence**

The wholesale or distribution of medicinal products is subject to the possession of a wholesale distribution licence (WDL), as outlined in the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 to 2013. The relevant competent authority in Ireland is the HPRA. The activities that require a WDL are as follows:

- ‘procuring’ is understood as obtaining, acquiring, purchasing or buying medicinal products from manufacturers, importers or other wholesale distributors;
- ‘holding’ is understood as storing medicinal products; and
- ‘supplying’ is understood as all activities of providing, selling, donating medicinal products to wholesalers, pharmacists, or persons authorised or entitled to supply medicinal products to the public.

**Medical devices**

There is no specific authorisation for the wholesale or distribution of medical devices in Ireland.

**xi  Classification of products**

**Medicinal products**

Prescription-only medicinal products can only be dispensed by a person lawfully conducting a retail pharmacy business, and must be dispensed by or under the personal supervision of a registered pharmacist according to a prescription issued by a registered medical practitioner, a registered dentist or, in certain circumstances, a registered nurse.

Certain non-prescription drugs (as set out in the Medicinal Products (Prescription and Control of Supply) Regulations 2003, as amended) can be sold only from a pharmacy under the supervision of a registered pharmacist. General sale products can be placed on general sale, which means that they can be sold in a pharmacy and in any other outlet that is not a pharmacy, for example a supermarket.

The supply of prescription-only medicinal products in Ireland by mail order is prohibited. Supply by mail order is defined as both:

- any supply made, after solicitation of custom by the supplier, or by another person in the supply chain inside or outside Ireland; and
- without the supplier and the customer being simultaneously present and using a means of communication at a distance, whether written or electronic, to convey the custom solicitation and the order for supply.

**Medical devices**

There are no such similar restrictions on medical devices in Ireland.

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19 S1540/2003.
Imports and exports
The Irish rules governing the import and export of medicinal products and medical devices generally reflect those at EU level.

An MIA is required for the importation of medicinal products from outside the EEA into Ireland. Applications are made to the HPRA, and must include details of the:

- applicant;
- relevant medicinal products and pharmaceutical forms;
- proposed operations;
- premises, equipment and facilities; and
- site master file.

There must be a ‘qualified person’ for batch release, who ensures that each batch complies with the law, the GMP, the manufacturer’s authorisation and the MA or equivalent. The qualified person must be nominated by the applicant. Each applicant must give a written undertaking to comply with the conditions of the authorisation, if granted.

Medicinal products may only be exported by authorised manufacturers or distributors who have obtained an MIA for these export activities.

Controlled substances
Medicinal products that contain controlled substances as set out in Misuse of Drugs Acts 1977 to 2016 and the Misuse of Drugs Regulations 1988 (as amended) require a controlled drug licence. In Ireland, controlled substances are listed in the Acts and the Regulations. Depending upon which Schedule of the regulations the controlled substance is listed in, a manufacturer may be required to obtain a controlled drug licence from the HPRA before the company can legally sell the products to third parties in Ireland. It can take between two and eight weeks to obtain a controlled drug licence.

Enforcement
Medicinal products
In most cases, a breach of the applicable medicinal product regulations constitutes a breach of Section 32 of the IMB Act, which means that the offending entity shall be guilty of an offence and liable to a fine or imprisonment, or both.

For a summary conviction, a fine not exceeding €2,500 or a term of imprisonment of one year, or both, may be imposed. In addition, on summary conviction, the district court has discretion to award costs to the HPRA. On indictment, for a first offence, a person shall be liable to a fine not exceeding €120,000 or a term of imprisonment not exceeding 10 years, or both. For a second or subsequent offence, a fine not exceeding €300,000 or a term of imprisonment not exceeding 10 years, or both, may be imposed. A Section 32 offence can be prosecuted by the Minister for Health, the HPRA, the Pharmaceutical Society of Ireland or the health board in whose functional area the offence was committed. If an offence is committed by a corporate body and is proven to have been committed with the consent or connivance, or is attributable to the neglect, of any person who is an officer or shareholder (if the shareholder manages the corporate body), this person may be personally liable for the offence.

If there is a breach of the self-regulatory IPHA Code, the IPHA Code Council, which is responsible for overseeing breaches, may decide to:
a. ask the company concerned to cease the practice found to be in breach of the IPHA Code and take all necessary steps to avoid a similar breach in the future;
b. reprimand the company for the breach of the IPHA Code;
c. order the recovery of material found to have been in breach of the IPHA Code;
d. order the correction of inaccurate information by way of direct contact with the relevant HCPs or by publication, in the medical or pharmaceutical press, of a corrective notice in terms approved by the IPHA Code Council and Appeals Board;
e. order the immediate publication of the decision in whole or in part and specify how and to whom the decision is to be sent. This is in addition to the inclusion of details of the decision in the annual Code of Practice Publication of Findings Report;
f. refer the matter to the Minister for Health, in the case of difficult or persistent breaches of the IPHA Code; or
g. recommend to the IPHA Board of Directors that the offending party be suspended or expelled from the IPHA.

Administrative fees may also be charged. All findings are published at least once a year and are made available to:
a. all members of the IPHA;
b. all non-IPHA member Code signatories;
c. the Minister for Health or Department of Health; and
d. the HPRA.

**Medical devices**

If an authorised officer appointed by the HPRA has reasonable grounds for suspecting that an offence under the Medical Device Regulations has been committed on any premises, he or she may seek a search warrant from the district court to search those premises. Any person or body corporate found guilty of an offence under these Regulations shall be liable on summary conviction to imprisonment for up to six months or a fine, or both. When an offence is committed by a body corporate with the consent, connivance or by the negligence of any person who is a director, manager, secretary or other officer of that body corporate, that person may also be personally liable.

If there is a breach of the self-regulatory Irish Medtech Code, the Board of the Irish Medtech Association responsible for overseeing breaches may decide to:
a. issue a formal letter of reprimand to the member company;
b. issue a formal letter of reprimand to the member company and also recommend to suspend that member company from membership of the Irish Medtech Association for a specified period or to impose conditions for readmission; or
c. recommend to expel the offender from the Irish Medtech Association.

Administrative fees may also be charged.

### III PRICING AND REIMBURSEMENT

The Health (Pricing and Supply of Medical Goods) Act 2013 (as amended) (the Health Act) and the newly agreed 2016 IPHA Framework Agreement (discussed below) are the key documents regulating the prices of medicinal products in Ireland.
Medicinal products dispensed in the community are funded by the state, through reimbursement of the pharmacist, where the patient in question is eligible under one of the reimbursement schemes, and where the medicinal product being dispensed is eligible for reimbursement.

i  Reimbursement schemes

The HSE Primary Care Reimbursement Service (PCRS) operates a General Medical Services (GMS) Scheme in addition to a number of other community reimbursement schemes (Community Drug Schemes) under which it reimburses primary care contractors, including pharmacists, for the cost of providing health services and medicinal products to the public.

The GMS Scheme provides free general medical services, including access to doctors, surgeons, dentists and medicinal products, to those who cannot afford such services. The Community Drug Schemes include the Drugs Payment Scheme, the Long-Term Illness Scheme, the High-Tech Drugs Scheme and the EEA Scheme, among others.

ii  Pricing

In setting the price for a listed medicinal product, the HSE is required to take into account:

a  the ability of suppliers of the relevant items to meet patient demand;

b  the value for money provided by the relevant items;

c  the equivalent relevant prices (if practicably available) of the relevant items in all other Member States where one or more than one of the relevant items is marketed;

d  the relevant prices of therapeutically similar items;

e  the resources available to the HSE; and

f  the terms of any agreement in place (whether entered into before, on or after the commencement of the Health Act) between the HSE and any representative body of the suppliers of drugs, medicinal products, or medical or surgical appliances, where the agreement relates, whether directly or indirectly, to the price of one or more of those items. This final point requires the HSE to take into account the terms of the agreements entered into by the HSE with the IPHA and with the IGMA (formerly the Association of Pharmaceutical Manufacturers in Ireland), the industry body representing manufacturers of generic medicinal products (see Section III.iii).

iii  IPHA Framework Agreement

The IPHA Framework Agreement, which came into effect on 1 August 2016 and will operate for four years, only applies to IPHA member companies that are listed in Schedule 2 of the agreement. It governs the pricing and supply of medicinal products that are included on the HSE Reimbursement List, supplied to, or reimbursed by, the HSE, state-funded hospitals or any other publicly funded entities and state agencies providing similar services (hospital medicinal products) or subject to an application for inclusion on the Reimbursement List, or for supply or reimbursement as a hospital medicinal product.

The new agreement introduces five additional EU Member States bringing the proposed price of a product in line with the average ex-factory price in 14 Member States. The IPHA Agreement includes an annual downward-only price realignment, which commenced on 1 August 2016 and on 1 July for each subsequent year. The price realignment will be set as the average ex-factory price of the 14 Member States for patented medicinal products, and for off-patent medicinal products for which there is no identical pharmaceutical form available for prescription within the reimbursement schemes, to the currency-adjusted average price
to the wholesaler in the nominated EU Member States in which the medicinal product is available. The price of a medicinal product that has lost patent protection, and for which a generic product has become available, will fall by 50 per cent from the original ex-factory price. Patent-expired biological products are subject to a 20 per cent reduction in price once a biosimilar enters the market.

Significantly, the Agreement has introduced the involvement of the Department of Health in the decision-making process when reviewing products that cannot be funded from within existing HSE resources, such as products that exceed the budget impact or a certain cost-effectiveness threshold. The HSE leadership assesses a product at first instance and, if the HSE cannot reimburse the product, the HSE can inform the Department of Health, which may apply to the government to request consideration of funding for the product.

iv  Reimbursement procedure

A medicinal product is eligible for reimbursement if it:

a  has a current MA;

b  is approved for reimbursement by the HSE;

c  is prescribed by a doctor; or

d  is dispensed by a doctor or pharmacist.

New medicinal products for which an MA has been granted may become reimbursable within 75 days of application to the HSE for reimbursement approval, subject to certain exceptions. New and existing technologies that are of high cost or that may have a significant impact on the Irish healthcare budget may be referred by the HSE for pharmacoeconomic assessment.

Payments to pharmacists are regulated by HSE Community Pharmacy Contractor Agreements and the Health Professionals (Reduction of Payments to Community Pharmacy Contractors) Regulations 2013, as amended.20

v  Medical devices

Reimbursement of medical devices is conducted through the Aids and Appliances Scheme operated by the Health Services Executive. Increasingly health technology assessments (HTAs) are playing a role, with the Health Information Quality Authority (the body with responsibility for conducting HTAs in Ireland) producing various sets of guidelines governing these evaluations (e.g., the Guidelines for Budget Impact Analysis of Health Technologies in Ireland and the Guidelines for the Economic Evaluation of Health Technology in Ireland).

IV  ADMINISTRATIVE AND JUDICIAL REMEDIES

Public decisions made by administrative bodies such as the HPRA, NSAI and the HSE may be judicially reviewed by the High Court. In a judicial review, generally the Court is not concerned with the merits of the decision but rather with the lawfulness of the decision-making process (i.e., how the decision was made and the fairness of it). Applicants must demonstrate ‘sufficient interest’ in the proceedings and that they have an arguable case (i.e., the case has grounds).

20  SI279/2013.
There are a number of various grounds upon which an application for judicial review in this jurisdiction may be based. Where it is satisfied that there are grounds for quashing a decision to which the application relates, the Court may, in addition to quashing it, remit the matter to the authority concerned with a direction to reconsider it and reach a decision in accordance with the findings of the Court.

The High Court may also quash or cancel the decision by issuing an order known as certiorari. The High Court can also order a decision-maker, who is obliged to make a decision but has failed or refused to do so, to actually make the decision; this is known as an order of mandamus. An order of prohibition may also be granted in appropriate circumstances (i.e., an order prohibiting a decision-maker from making a decision). Other orders that are available include declarations, injunctions of an interim, interlocutory or permanent nature, or an award of damages. There are certain time frames for submitting an application for leave to apply for a judicial review.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

i Medicinal products

The promotion of medicinal products to healthcare establishments and professionals is governed by the Advertising Regulations and, for IPHA members, the IPHA Code.

The rules reflect those of the European Union, with the broad prohibition on gifts (including promotional aids), pecuniary advantages or benefits in kind supplied, offered or promised to persons qualified to prescribe or supply by a pharmaceutical company, subject to any regulations for the time being in force relating to prices, margins and discounts.

The IPHA Code also provides specific detailed guidance on interactions with HCPs in Ireland. For instance, items of medical utility aimed directly at the education of HCPs and patient care are not considered gifts and can therefore be supplied, provided they are inexpensive and do not offset the cost of routine business practice of the recipient.

A further update to the IPHA Code, which took effect from 1 January 2015, requires that direct and indirect transfers of value (subject to limited exceptions) from pharmaceutical companies to HCPs and healthcare organisations are documented and publicly disclosed on an annual basis by pharmaceutical companies. Public disclosures commenced in 2016 in respect of transfers of value occurring in 2015.

The Criminal Justice (Corruption Offences) Act 2018 and the Ethics in Public Office Acts 1995 (as amended) and the Civil Service Code of Standards and Behaviour are also relevant. Holders of certain public positions (including senior personnel within the HSE, HPRA, the Department of Health and in voluntary hospitals) must disclose certain interests to the Standards in Public Office Commission. These include gifts or the provision of travel facilities, living accommodation, meals or entertainment above a certain threshold in any given year, or both. While responsibility for compliance rests with the recipient of the gift, the provider of the gift can be requested to assist the Standards in Public Office Commission in its investigations, and failure to do so can be a criminal offence.

ii Medical devices

There are no Irish laws or regulations governing interactions between prescribers and payers.
However, the Irish Medtech Code governs interactions between medical technology companies who are members of the Irish Medtech Association and HCPs, including payers, and it is supplemented by detailed guidelines that clarify and distinguish between appropriate and inappropriate activity in areas such as:

- appropriate support of scientific and educational conferences;
- legitimate consulting agreements with HCPs;
- provision of educational grants and charitable donations; and
- provision of modest hospitality and gifts.

The Code aims to ensure that interactions between industry and healthcare professionals cannot be misused to influence, through undue or improper advantages, purchasing decisions, nor should such interactions be contingent upon sale transactions or use or recommendation of products.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The purchaser or a user of medicinal products or medical devices can seek recourse for regulatory and legal infringements through the Irish courts (i.e., using product liability rules). In Ireland, liability for defective products falls under four main categories: statute, tort, contract and criminal. The principal product liability statute in Ireland is the Liability for Defective Products Act 1991. This Act provides for a strict liability regime, making a producer of the defective product liable in damages in tort for damage caused wholly or partly by a defect in the product. A purchaser or user may also sue in tort for any reasonably foreseeable damage caused to them, or in contract where the pharmaceutical or device was not of merchantable quality.

Compensation schemes have been set up from time to time, usually in circumstances where an organ of the state may have liability. Such schemes have been established on both a statutory and non-statutory basis. An example of a statutory compensation scheme is the Hepatitis C Compensation Tribunal. An example of a non-statutory scheme is the symphysiotomy ex gratia payment scheme.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Irish competition law is based on equivalent EU competition law and is interpreted and applied by analogy. There is no equivalent under Irish competition law to the EU Technology Transfer Block Exemption Regulation,21 but Irish competition law would be interpreted in a manner consistent with it. Specific issues have not arisen in any reported Irish competition law cases involving technology transfer licensing agreements or patent licensing.

Arrangements that prevent, restrict or distort competition in trade in any goods or services in Ireland are prohibited and are rendered void (Section 4(1), Competition Act

Horizontal agreements between competitors involving price-fixing, market sharing or output limitation would constitute a serious cartel offence in breach of Section 4(1), which would be investigated and prosecuted on a criminal standard.

Vertical agreements between pharmaceutical suppliers and independent wholesalers and agreements between wholesalers and retailers can also fall under Section 4(1), particularly where there is resale price maintenance, and are likely to be investigated and enforced on a civil standard. Apart from public enforcement, parties who claim to be aggrieved by a competition law infringement can take proceedings in the Irish courts and claim damages. There are no reported private competition law actions in the pharmaceutical sector to date.

ii **Abuse of a dominant position**

Abuse by one or more undertakings of a dominant position in trade for any goods or services in Ireland or any part of Ireland is prohibited (Section 5(1), Competition Act 2002 (as amended)). Therefore, dominant undertakings should exercise caution when engaging in certain practices. For example, a refusal to supply pharmaceutical products could be deemed to be an abuse of a dominant position unless there is an objective justification.

iii **Transactional issues**

The considerations and issues outlined in the European Union chapter apply equally in Ireland.

**VIII CURRENT DEVELOPMENTS**

The Irish and EU regulatory environment in the life sciences sector is constantly in flux, but recent regulatory changes at EU level are arguably among the most significant yet. New legislation coming into force (the Clinical Trials Regulation, the Medical Devices Regulations and ISO 13485) will affect current organisational structures, governance, processes and technology. We see regulators expanding their efforts in this sector. For instance, the HPRA is expanding its team and capabilities with a view to playing a greater role as a leading regulator in the European Union, particularly as the UK equivalent (the MHRA) potentially bows out.

There are signs of increased levels of criticism in recent years in terms of pricing of medicinal products and the resulting costs to the state, which culminated in delays in pricing and reimbursement approvals and protracted negotiations on the new IPHA Framework Agreement. In light of the changes in the new Framework Agreement and a changing political landscape, there will be a greater onus on companies to be more prepared and informed when navigating the reimbursement process in Ireland.
I INTRODUCTION

i Competent authorities
The Italian life sciences sector is governed by two main regulatory authorities: the Ministry of Health (Ministry), which is responsible for the governance of the Italian health system and has specific competencies in relation to medical devices, and the Italian Agency of Medicines (AIFA), which is in charge of regulations, oversight and enforcement concerning the manufacture and distribution of medicines.

ii Legislative framework
The legislative framework applicable to the marketing of medicines and medical devices in Italy mainly consists of:

a Legislative Decree No. 219/2006 (Code of Medicines), which implemented Directive 2001/83/EC;
b Legislative Decree No. 46/1997, implementing Directive 93/42/CEE; and

National legislation on medical devices will be replaced by Regulation (EU) 2017/745 on medical devices and Regulation 2017/746 on in vitro diagnostic medical devices, when they become fully applicable.

II THE REGULATORY REGIME

i Classification
Italian legislation does not address the issue of the distinction between medicines, medical devices and other regulated products (e.g., foods, cosmetics, chemicals and general consumer products). However, Italy applies the guideline documents issued by the European Commission to support manufacturers of medical devices in the classification of products, such as, for instance, the Manual on Borderline Classification of Medical Devices, Version 1.18 (12-2017) and the MEDDEV documents. In addition, the Ministry occasionally issues guidelines to address specific products and clarify their classification criteria (e.g., surgical gloves).

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1 Marco Blei is a counsel, Luca Gambini is a partner, Enzo Marasà is a counsel and Elisa Stefanini is a counsel at Portolano Cavallo.
Pursuant to the Code of Medicines, if there is any doubt about the classification of a product as a medicine, the Code of Medicines itself shall apply.

ii Non-clinical studies

Annex 1 of the Code of Medicines states that non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the good laboratory practice (GLP) laid down in Directive 87/18/EEC (now replaced by Directive 2004/10). Directive 2004/10 was implemented by Legislative Decree No. 50/2007, which regulates the application of GLP to non-clinical tests aimed at assessing the effects on human beings, animals and environment of all chemical products, including cosmetics and medicinal products. Pursuant to this decree, the Ministry, following inspection, issues the GLP certification to the relevant laboratory and includes it in a public list of the GLP-compliant centres.\(^2\) ICH\(^3\) rules are also applied in Italy.

No specific legislation governs non-clinical studies concerning medical devices. This matter is regulated by the vertical rules ISO, CEN and UNI (at national level), which specify, for each category of devices, the modalities to conduct such studies, analyse the results and draft the relevant reports to be attached to the technical file and included in the investigator's dossier.

In addition, any non-clinical research that involves human samples (and related personal data) that can be referred to identified persons shall be approved by the competent ethics committee and be subject to data protection legislation.

Trials on animals are subject to the Ministry's authorisation, to be filed by the committee responsible for the animal welfare, established at the scientific entity where the research is carried out, pursuant to Legislative Decree No. 26/2014.

iii Clinical trials

Medicines

Legislative framework


The new Law No. 3 of 11 January 2018 (the Delegation Law) gives the government the power to issue, within the next 12 months, legislative decrees to prepare the application in Italy of the Clinical Trials Regulation (EU) No. 536/2014 (CTR). This law provides for, among other things:

a a reduction in the current number of ethics committees and a reorganisation of their functioning with particular regard to their involvement in the clinical trials authorisation procedure, to ensure alignment with the AIFA's assessment and compliance with the

\(^2\) This procedure was updated by Ministerial Decree of 13 January 2016.

\(^3\) The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
timing required by the CTR; to that end, a central committee for the coordination of local ethics committees is provided for in Article 2. This provision was implemented by the Ministerial Decree of 19 April 2018 setting up such coordination committee;

b  the identification of the centres authorised to conduct clinical trials from Phase I to Phase IV, including the setting of the minimum requirements for centres dedicated to Phase I trials; and

c  the identification of minimum common contents of clinical trial agreements on a national basis.

**Application and authorisation**

Any clinical trial shall be authorised by the AIFA and receive approval by the competent ethics committee. Until the application of the CTR, the authorisation procedure is established by Legislative Decree No. 211/2003, as detailed by Ministerial Decree of 21 December 2007, which also sets out rules for communicating amendments, declaring the end of the trial, requesting opinions to the ethics committee, and so on.

The request for authorisation shall be submitted by the sponsor (which must be established in the European Union or have appointed a legal representative in the European Union) to AIFA through the national database of clinical trials. AIFA can authorise the trial within 60 days and, in the event of there being no answer within the same term, the authorisation shall be considered as granted (except for certain trials), provided that the competent ethics committee has issued an approval. The time frame is reduced to 35 days for the approval of any substantial amendment to the protocol.

**Other main requirements**

**Informed consent**

Clinical trials shall be conducted in strict compliance with the informed consent principle, which is assessed by ethics committees. In this regard, the Delegation Law provides for a simplification of the procedures to use biological materials residual from previous diagnostic or therapeutic activities for clinical research purposes, subject to the collection of patients’ informed consent.

From a data protection perspective, participants must give their informed consent to the processing of their personal data for specific research purposes. Further processing of health data (but not genetic data) without the data subjects’ consent can be authorised by the Italian Data Protection Authority for scientific and statistical purposes only if appropriate measures are taken to protect data subject’s rights and freedoms, such as the anonymisation of data (Article 110 bis of Legislative Decree No. 196/2003, as introduced by Legislative Decree No. 101/2018).

**Insurance policy**

Sponsors shall hold a specific insurance to protect participants in clinical trials, which is assessed by ethics committees. According to the Ministerial Decree 14 July 2009, the insurance policy should include specific cover for reimbursement of any damages caused

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4 Osservatorio Nazionale della Sperimentazione Clinica.
to the participants, any civil liability of the investigator and sponsor, without excluding any damage that may be unintentionally caused by accident or be attributed to negligence, imprudence or inexperience (provided that certain time limits to claim damages are met).

Safety reporting
Under Legislative Decree No. 211/2003, the investigator shall immediately inform the sponsor of any suspected unexpected serious adverse reactions that have either proved to be lethal or endangered the life of a patient; the sponsor shall register and notify them to the Ministry, as well as to the ethics committees concerned, as soon as possible and in any case within seven calendar days of being aware of the incident, while any additional information shall be notified within the following eight days. All other suspected unexpected serious adverse reactions are reported to the Ministry and the ethics committees concerned as soon as possible within 15 days.

Investigator-initiated studies
Investigator-initiated studies (i.e., not-for-profit studies) are governed under the Ministerial Decree of 17 December 2004, which set outs the following main conditions, to be assessed by the competent ethics committees, for a study being considered ‘not for profit’ and enjoy the related benefits:

_\(a\) the sponsor is a public entity or scientific association or non-profit research organisation;_
_\(b\) the sponsor does not own the medicine patent or the marketing authorisation;_
_\(c\) the collected data, including trial results, is owned by the sponsor;_
_\(d\) the trial is neither finalised nor used for industrial development of the medicine; and_
_\(e\) the trial is aimed at improving clinical practice (an exception to this requirement applies to those studies that are not suitable to have an immediate impact on the improvement of clinical practice, for instance because they are still in Phase I)._

The Delegation Law provides that the requirement under point (d) above shall be amended by future decrees to allow the transfer of the clinical trial data to pharmaceutical companies and its use for the industrial development of medicines, under the condition that the companies concerned reimburse all direct and indirect costs of the trial, as well as all the missed outcomes deriving from the classification of the trial as ‘not for profit’.

Medical devices
Pre-market studies shall be notified to the Ministry, with all relevant documentation, and, if the studies concern Class III or Ila or Iib invasive devices, they cannot start before the Ministry gives its clearance or before the 60-day term of the notification has expired. Conversely, post-market studies only need to be communicated to the Ministry. In any case, both pre- and post-market clinical trials concerning any class of device require the approval of the competent ethics committee. Clinical studies concerning medical devices are also subject to the GCP principles set out by UNI EN ISO 14155 of January 2012 and to the MEDDEV documents.
iv Named-patient and compassionate use procedures

Medicines

The supply of non-authorised medicines can occur under one of the following methods:

- through a compassionate use (CU), that allows the free supply by companies of medicines not yet available on the market;
- on a named-patient basis; or
- through the application of Law No. 648/1996.

Compassionate use

On 7 September 2017, the Ministry issued a new decree on CU of medicines that replaced the Ministerial Decree of 8 May 2003. Under this decree, CU can apply with regard to:

- non-authorised medicines, under clinical trials at Phase III or, in exceptional cases, Phase II (in the case of rare diseases or cancers, results of completed Phase I trials are also accepted, and this is one of the key new aspects of this decree);
- authorised medicines to be used ‘off-label’; and
- authorised medicines not yet available in Italy.5

Patients who can benefit from CU are those:

- suffering from very serious diseases who have no valid therapeutic alternatives;
- already being treated with clinical benefit in a closed clinical trial to assure therapeutic continuity;
- who cannot be included in a clinical trial.

Named-patient basis

Another option for the supply of non-authorised medicines is the named-patient basis, that is, in response to a physician’s written unsolicited request for the supply of the unauthorised medicine to a patient under the personal responsibility of the physician.

Law No. 648/1996

Finally, pursuant to Law No. 648/1996, a medicine that is not authorised in Italy may be provided to patients and fully reimbursed by the National Health System (NHS) if:

- there is no valid authorised therapeutic alternative; or
- a valid authorised therapeutic alternative does exist but the medicine is intended to be used ‘off-label’ (i.e., for a therapeutic indication different from the authorised one), on

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5 This provision is to be read in connection with the procedure introduced by Law No. 189/2012 to allow the placing on the market of medicines, as soon as they get the marketing authorisation and while the price and reimbursement negotiations are still ongoing, under a ‘not negotiated class’ (C-nn). Under the Ministerial Decree of 8 May 2003, after the inclusion of a medicine in Class C-nn, new patients could no longer benefit from CU, even if the medicine was not yet available on the Italian market. AIFA established a system to avoid this consequence, which was endorsed by the Supreme Administrative Court (Consiglio di Stato’s Opinion No. 2356 of 14 November 2016). This issue was finally clarified by the new Ministerial Decree.
the condition that the off-label indication is consistent with national and international medical research, and that the off-label marketing is ‘appropriate’ and economically viable.\(^6\)

If the AIFA assesses that these conditions are satisfied, the medicine is included in a specific list and can thereafter be supplied to patients at the NHS’s expense.

**Medical devices**

The Ministry may authorise CU of medical devices for which conformity assessment procedures have not been completed, for the treatment of individual patients, in exceptional cases of need and urgency. The relevant request may be submitted by public or private healthcare facilities, by providing a report from the doctor, justifying the request for a specific patient, and the approval of the competent ethics committee (or, in the case of urgency, evidence of the filing of the request).

\[\text{Pre-market clearance}\]

**Medicines**

**Ordinary procedure**

No medicines may be placed on the Italian market without having obtained a marketing authorisation (MA) from the AIFA or the EMA, according to the centralised procedure provided for by Regulation (EC) No. 726/2004. To get an MA in Italy, the applicant shall be established in the European Union and have appointed a representative in Italy.

In the case of national procedure, the AIFA shall issue its decision on the authorisation within 210 days of the application being filed (but this term is suspended if additional documents are required).

In exceptional circumstances, the authorisation may be granted on condition that the applicant fulfils certain obligations, in particular related to the safety of the medicine, which are assessed annually.

**Procedures for special category of products and follow-on products**

For certain categories of products, such as homeopathic medicines, herbal medicines and follow-on products (generic and biosimilar medicinal products), the authorisation procedure is simplified.

In particular, if the request for MA concerns a generic medicine of a reference medicine which has been authorised for at least eight years in Italy or in the European Union, the applicant is not required to provide the results of the preclinical and clinical trials. In the case of biosimilar medicines, the applicant is required to provide the results of preclinical or clinical trials related to those aspects that, for the peculiar characteristics of these products, vary compared to the reference medicine (e.g., raw materials or production processes). The results of other tests contained in the reference medicine’s dossier are not required.

\(^6\) This hypothesis was added by Law No. 79/2014, following the famous *Roche-Novartis/Farmaci Avastin and Lucentis* case (see Section VII.i).
Validity
The MA is valid for five years from its publication in the Official Gazette and can be renewed following a re-evaluation of the risk-benefit balance. After the first renewal, the MA is valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. The MA can lose its efficacy when the medicine is not placed on the market within three years as of the issuance of the MA, and in any event when it is no longer marketed for three consecutive years (sunset clause).

Medical devices
The placing on the market of medical devices in Italy is permitted only for devices bearing the CE mark (except for custom-made devices). The procedure and the requirements for obtaining the CE mark vary depending on the class of the device, in compliance with EU legislation.

In addition, all medical devices to be placed on the Italian market should be notified to the Ministry and registered in a dedicated register of medical devices, which is publicly available. Finally, to be purchased by public entities (i.e., at the NHS’s expense), medical devices should also be included in another register, governed under Ministerial Decrees 21 December 2009 and 23 December 2013 (respectively for medical devices and IVD medical devices).

vi Regulatory incentives
The Code of Medicines provides for the same regulatory incentives for originators as those set out under EU legislation, such as market and data exclusivity.

No patent linkage is specifically provided under Italian law, except for the provision of Law Decree No. 158/2012 (Article 11), according to which generic medicines cannot be included among the medicines reimbursed by the NHS before the expiry date of the patent or supplementary protection certificate of the corresponding originators’ product. The AIFA considers this provision to be applicable only to patents and supplementary protection certificates covering active ingredients, and not to second-use patents. The Regional Administrative Court of the Lazio Region (Decision No. 6739, dated 26 June 2014) held this provision not to be applicable in relation to process patents. The Administrative Supreme Court (Decision No. 4394, dated 27 August 2014) stated that Article 11 is applicable only if the active ingredient claimed by the patent of the originator has a different and additional therapeutic effect to those of the medicines already on the market.

Incentives for innovative medicines
To encourage development of products for rare diseases and innovative medicines, Italian law provides for certain advantages, especially relating to the establishment of a fund to finance the expenses incurred by the NHS in purchasing innovative medicines (new criteria for the classification of a medicine as innovative was established by the AIFA’s resolution of 31 March 2017).

7 Banca dati dei dispositivi medici.
8 Repertorio generale dei dispositivi medici.
9 Converted into Law No. 189/2012.
Moreover, Italy was one of the first European countries to put in place managed entry agreements and conditional reimbursement agreements to support the marketing of innovative medicines that meet a therapeutic need, although their benefit is not yet entirely proven.

vii Post-approval controls

Medicines

Infrastructure and staffing requirements for MA holders

Any MA holder in Italy shall:

a. appoint a qualified person, responsible for pharmacovigilance activities, and notify his or her name to the AIFA; and

b. set up a scientific service that shall be independent from the marketing department and managed by a person with specific qualifications: if the actual commercialisation of the medicine in Italy is carried out by a distributor, this requirement shall be met by both the MA holder and the distributor.

Pharmacovigilance and safety reporting

Pharmacovigilance duties are set out by the Ministerial Decree of 30 April 2015, according to which the MA holder, in addition to the appointment of a person responsible for pharmacovigilance, must, *inter alia*:

a. maintain detailed records of suspected adverse events;

b. submit periodic reports on product safety to the AIFA; and

c. adopt a risk management system for each medicine.

No significant country-specific obligations are provided for by Italian law.

Suspension or revocation of product approvals

Any MA can be both suspended and revoked by the AIFA, if the Agency assesses that the requirements on the basis of which the authorisation was granted are no longer met.

In particular, revocation, which triggers the definitive withdrawal of the medicine from the market, is ordered by AIFA when:

a. the medicine is harmful under normal conditions of use;

b. the medicine does not enable the user to obtain the required therapeutic effect;

c. the risk-benefit ratio is not favourable; and

d. the medicine does not have the same qualitative and quantitative composition as declared.

If, in the same cases listed above, it is advisable to request further information (or in the case of slight irregularities, which can be remedied within a reasonable period of time), the AIFA suspends the MA, which entails a temporary prohibition to sell the medicine. In place of revocation or suspension, the AIFA may amend an MA, specifying the period within which the unmodified packaging must be removed from the market.

Variations and transfer of ownership of product approvals

Variations of MAs issued by the AIFA are also subject to Regulation (EU) No. 1234/2008, which classifies variations on the basis of their impact on the safety and efficacy of the medicine.
The process for transferring an MA starts with filing the relevant request and the transfer agreement with the AIFA, and is completed with publication of the AIFA’s decision in the Official Gazette. The transferee must include in its application a declaration of the qualified person at the manufacturing site for the medicines concerned to continue manufacturing after the MA transfer. According to the AIFA internal regulations, this process takes 90 days but it can be longer and it is advisable that the parties regulate their relationships during this period, especially in the context of asset deals.

**Medical devices**

Manufacturers of medical devices must report to the Ministry any ‘incident’, defined as any malfunction, failure or deterioration in the characteristics of a device that could lead to the serious deterioration of a patient’s state of health or to his or her death, as well as technical or health reasons that are grounds for any decision to recall a certain category of products from the market.

**viii Manufacturing controls**

The manufacture of medicines requires an authorisation to be issued by the AIFA after verification that the applicant hires qualified staff, including the qualified person responsible for manufacturing, and possesses the appropriate technical facilities and equipment. Authorisation is also required for the execution of specific operations only, such as packaging, quality control and batches release, and shall specify the medicines and the pharmaceutical forms that are intended to be manufactured.

The authorisation should be granted within 90 days of receipt of the application, but this term is suspended if the AIFA requires supplementary information. Amendments to the authorisation shall also be approved by the AIFA within 30 days of the application being made, except if they are classified as not essential under the AIFA’s guidelines: in this case, they only need to be notified. Administrative amendments to the authorisation are generally classified as non-essential and, thus, they do not require a specific approval.

To obtain and maintain the authorisation, the manufacturing site must also hold the GMP certification, which is issued by the AIFA following inspection. The list of authorised manufacturing plants is published on the AIFA website.

No specific authorisation is required by the law to manufacture medical devices.

**ix Advertising and promotion**

**Borders between information and advertising**

The definition of advertising in the Code of Medicines is very broad and focuses on the purpose of the information, namely the promotion of the product.

A recent ruling of the Civil Court of Milan (No. 8240 of 24 July 2017) addressed the issue of the border between information and advertising of medicines, stating that the publication of certain information (on the internet and in printed journals) is to be intended as advertising, although it does not include any promotional message, if the information published has been (1) selected and (even minimally) manipulated (e.g., by indicating the excipients) compared to the scientific information available on the AIFA website, and (2) disseminated with techniques that do not require any active research by the users.
Conditions and requirements for advertising medicines and medical devices to the public

Advertising to the public of both medicines and medical devices that can be purchased only with a prescription from a healthcare provider (HCP) or can be used only with the assistance of an HCP, as well as of medicines to be (even partially) reimbursed by the NHS is forbidden. Advertising to the public of other medicines and medical devices is allowed subject to prior authorisation from the Ministry. This authorisation is considered to be granted if the Ministry does not raise any objection within 45 days of the request being filed.

More detailed instructions on advertising of medicines and medical devices through different communication channels, with particular regard to the internet, SMS/MMS and, more recently, social networks, are set out under guidelines issued by the Ministry, such as those issued on 6 February 2017 and 25 July 2017 for over-the-counter (OTC) medicines and on 20 December 2017 for medical devices; the most recent were issued on 25 July 2018 for advertising of OTC medicines on Facebook, and 7 May 2018 with regard to advertising of medicines without prescription other than OTCs (see Section II.xi).

Conditions and requirements for advertising medicines and medical devices to HCPs

Advertising of medicines to HCPs is regulated under the Code of Medicines, with particular regard to the role and the qualification of medical sales representatives, the requirements of the advertising materials to be provided to HCPs, etc. Certain general principles set out under the Code of Medicines are also applied to the medical devices sector.

Advertising addressed to HCPs is also governed under guidelines of the Ministry that clarify that it does not need to be previously authorised, on the condition that the message is strictly addressed only to HCPs (e.g., with regard to advertising on the internet, advertising to HCPs shall be separated from the remaining content of the website and protected with a password, in the case of medicines, or a disclaimer, in the case of medical devices).

The advertising of both medicines and medical devices to HCPs is also regulated by codes of conduct, especially the Farmindustria Code, applied by the companies who are members of the Farmindustria association, and the Assobiomedica Code, issued by the Italian association of medical devices companies. The advertising of medicines to HCPs is also subject to the guidelines issued by the committee of the representatives of the government and the Italian regions on 20 April 2006, and guidelines issued by single Italian regions, some of which are also applicable to medical devices.

A draft guideline on the advertising of medicinal products to HCPs was issued by AIFA on 16 March 2018 and is currently undergoing consultations by stakeholders. This is an important document, which had been anticipated for a long time, that will provide for the first time a complete framework on the modalities of advertising medicines to HCPs.

Financial duties connected with advertising activity

Companies are required by law to pay an annual contribution equal to 5.5 per cent of the costs for the promotion of medical devices and 5 per cent of the costs for the promotion of medicines borne in the previous year, as declared to the Ministry and the AIFA, respectively.

x Distributors and wholesalers

Italian legislation does not provide for any specific regulation applicable to the distribution of medical devices. Therefore, the sections below refer only to the distribution chain of medicines.
Distributors

The MA holder (MAH) can appoint a sales agent\(^\text{10}\) for the exclusive distribution of its medicines within the Italian territory. These distributors are generally entitled to carry out promotional activities addressed to both the general public and HCPs, according to an agreement executed with the MAH. Conversely, pharmacovigilance obligations remain with the MAHs. The appointment of a sales agent must be notified to the AIFA by the relevant MAH. The name and the address of the sales agent may appear on the outer packaging of medicines and on the package leaflet.

Wholesalers and depositaries

The distribution chain of medicines sold to patients includes wholesalers, depositaries and pharmacies. Wholesalers and depositaries must be authorised by the competent regional government, after an inspection of the relevant facilities.

Wholesalers purchase medicines direct from MAHs with the purpose of selling them to pharmacies, while depositaries merely store medicines, pursuant to deposit agreements with the MAH, which remains their owner. Consequently, only wholesalers are responsible for complying with the public service obligation under the Code of Medicines that consists of a duty to ensure availability of a wide range of medicines to promptly supply pharmacies located in a given area.

Classification of products

Medicines

*Classes of medicines for the purpose of their reimbursement*

For the purpose of their reimbursement by the NHS, medicines are classified as follows:

- **Class A**, which includes medicines for essential and chronic diseases that are entirely reimbursed by the NHS;
- **Class H**, which includes medicines provided in hospitals, fully reimbursed by the NHS; and
- **Class C**, which includes all other medicinal products that are not reimbursed by the NHS.

The price of reimbursed medicines is set through mandatory negotiations between the MAH and the AIFA, as provided for by Law No. 326/2003 and according to the economic criteria set out in the CIPE\(^\text{11}\) Resolution of 1 February 2001 (CIPE Resolution). Conversely, for Class C medicines, the MAH is free to set the price at its own discretion (though certain statutory limitations on price increases still apply).

According to Law No. 189/2012, medicines that have been granted an MA are automatically classified under Class C-nn (i.e., Class C not-negotiated), which includes all medicines not yet assessed for reimbursement purposes. This provisional classification allows medicines to be placed on the Italian market as soon as they have been granted an MA, even if price negotiations are continuing.

\(^{10}\) *Concessionari di vendita*.

\(^{11}\) The Interministerial Committee on Economic Planning.
**Classes of medicines from a supply regime perspective**

Medicines are also classified on the basis of their supply regime, depending on whether they can or cannot be sold to patients without medical prescription. The latter category of medicines (called SOPs) includes over-the-counter medicines (OTCs).

This classification is particularly relevant for its impact on distribution and advertising. In fact, prescription medicines can be purchased only in authorised pharmacies, while non-prescription medicines can also be purchased in para-pharmacies and online, from authorised websites, owned by pharmacies or para-pharmacies. As regards the advertising regime, until very recently, only OTCs could be advertised to the general public (see Section II.ix). However, the Italian Supreme Administrative Court clarified that advertising to the public is allowed for all SOPs (Ruling No. 2217 of 12 May 2017).

**Medical devices**

Medical devices are classified on the basis of their risk in four classes, in compliance with the European criteria. In addition, from a supply regime perspective, some devices can be sold only on medical prescription or used only with the assistance of an HCP; this classification has an important effect on the advertising regime (see Section II.ix).

**xii Imports and exports**

**Medicines**

Import from countries outside the European Union of medicines to be placed on the Italian market (i.e., registered in Italy) requires a manufacturing authorisation from the AIFA that shall include, at least, the batches release activity.

Moreover, imports of medicines not registered in Italy from countries where they are legitimately marketed for the purpose of being supplied to Italian patients is governed by a Ministerial Decree of 11 February 1997. This decree provides for the following main conditions: (1) its use is for the same therapeutic indication as authorised in the country of origin; (2) there is no possibility of using any other medicines available in Italy; and (3) there is a maximum quantity of purchase (90 days of therapy).

According to this decree, only purchases made by hospitals can be borne by the NHS.

**Medical devices**

The import of medical devices is subject to a health clearance by the border authorities of the Ministry, to be issued after having assessed that certain conditions are met, including, in particular, the CE mark and registration within the Ministry’s database.

Certificates of free sale for export purposes can be requested from the Ministry by Italian manufacturers.

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12 Para-pharmacies are stores that are not authorised as pharmacies, and are only allowed to sell non-prescription drugs (Law Decree No. 223/2006). They are subject to the fulfilment of the structural, organisational and technological requirements provided for by a Ministerial Decree of 8 March 2012.
xiii Controlled substances

Narcotics and psychotropic substances are governed by Presidential Decree No. 309/1990. Under this decree, the manufacture, use, trade by wholesalers and depositaries and use for scientific research and clinical trials of these substances are subject to authorisation by the Ministry.

Authorisations are subject to specific conditions, including moral requirements of the legal representatives of the companies. They are valid for two years and can be renewed but they cannot be transferred to other subjects. The Ministry also issues specific import and export permits to companies authorised to manufacture, use or trade narcotics.

xiv Enforcement

Enforcement is assured by the Ministry and the AIFA by means of (1) inspections (both planned and unexpected), aimed at checking compliance with GLP, GCP or GMP, the pharmacovigilance system, etc., or (2) other forms of documentary control.

For certain activities, the Ministry is supported by the NAS, the anti-adulteration unit of the Carabinieri Corps. For instance, the NAS is very active in the search for counterfeit medicines and illegal sales of medicines on the internet. In addition, the Maritime, Aviation and Border Health Offices can perform inspections and check goods being imported into Italy.

On 19 January 2017, the AIFA entered into a cooperation agreement with the Italian Competition Authority (ICA), setting out a protocol to exchange information on current investigations to foster each other's monitoring and enforcement activity.

Enforcement activity may lead to an order to stop illegal activities and administrative sanctions. If the illegal activities have criminal relevance, the competent authorities for criminal prosecution are also informed.

III PRICING AND REIMBURSEMENT

i Medicines

Price negotiations

As stated in Section II.xi, if a medicine is reimbursed by the NHS, its price is determined following negotiations between the MAH and the AIFA, which should be conducted having regard to the criteria set out in the CIPE Resolution, which include, *inter alia*, cost-effectiveness and the risk-benefit ratio of the new medicine compared to those already distributed for the same indication.

Pursuant to the CIPE Resolution, the price agreement is valid for 24 months and may be tacitly renewed but also renegotiated early if the conditions relating to the level of use of the medicine are different from those originally estimated.

The CIPE Resolution also stipulates that the AIFA and the MAH may agree that the price is subject to the condition that certain sale volumes are not exceeded (i.e., the brand-specific budget) and that if it happens, certain consequences occur (e.g., reimbursement by the MAH, reduction of the price, termination of the agreement, exclusion of that medicine from the reimbursement by the NHS).

According to the budget law for 2019 approved at the end of December by Law No. 145/2018 (Budget Law 2019), a ministerial decree will have to update the criteria for setting the price of medicines reimbursed by the NHS by 15 March 2019. Moreover, the Budget
Law 2019 provides that AIFA can open new negotiations on the price of medicines even before the expiration of the agreement with the MAH if market variations have occurred that may lead to an increase of the use of that medicine or a different (and less favourable) cost-benefit assessment compared to the other alternative medicines available on the market.

The price agreed between the company and the AIFA is called the ‘ex-fabrica price’ and represents 66.65 per cent of the final price to the public. For medicines distributed through the retail chain, the final price is then determined by adding margins for the distribution chain – wholesalers and pharmacies – which are fixed by law, and the VAT amount (10 per cent). When medicines are sold to local health authorities and hospitals, the final price is subject to rebates and discounts connected with the performance of tenders.

Cost containment measures

The main measures adopted as of 2006 to contain the public pharmaceutical expenditure are:

a. the discounts mechanism, which entails a mandatory 5 per cent discount on the final price of any Class A medicine, with the faculty for MAHs to request the AIFA to be exempted from applying this price reduction by undertaking to pay the corresponding amount directly to the regions (an additional amount of 1.83 per cent of the final price of medicines supplied by the NHS is also required); and

b. the payback system, under which if, each year, the total pharmaceutical expenditure incurred by the NHS exceeds certain thresholds, MAHs of reimbursed medicines shall contribute to refund the NHS in proportion to their market share (which is calculated by AIFA on the basis of the company’s turnover generated by the sale of medicines to the NHS, taking into account the data of the electronic invoices issued in the reference calendar year).

ii Medical devices

There is no specific legislation on price and reimbursement of medical devices. They are paid for by the NHS when they are purchased by hospitals and other facilities belonging to the NHS by means of public tender procedures. A national programme for the health technology assessment of medical devices, managed by a dedicated committee, was launched in 2015 and, in September 2017, this committee published a document reporting a list of actions and priorities.

According to the Budget Law 2019, the payback system will operate for medical devices starting from 2019. To calculate if a public over-expenditure for the purchase of medical devices actually occurs, the Budget Law 2019 provides that the turnovers of the companies selling devices to the NHS shall be added and any over-expenditure shall be declared by the Ministry by 30 September of each year. The first calculation will be made in 2020 to assess any over-expenditure occurred in 2019. If, each year, the public expenditure incurred by the NHS exceeds certain thresholds, medical devices companies shall contribute to refund the NHS in proportion to their contribution to the over-expenditure.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

All final decisions issued by public authorities, including the Ministry and the AIFA, may be disputed in administrative courts.
In particular, decisions can be challenged, within (normally) 60 days of their notification to (or knowledge by) the interested party, on condition that the claimant is able to prove a concrete interest that is directly affected by that decision.

Administrative decisions are challenged in the first instance before the regional administrative courts (TAR) and, in the second (and last) instance, before the Supreme Administrative Court. For decisions issued by the Ministry and AIFA, the competent TAR is that of the Lazio Region, located in Rome. Litigations before the TAR and the Supreme Administrative Court are governed by the Code of Administrative Proceedings (Legislative Decree No. 104/2010).

Alternatively, an administrative decision can be challenged before the President of Italy within 120 days of the notification or knowledge of the decision.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Financial relationships between companies and HCPs are governed under both the Code of Medicines and the codes of conduct of the associations of pharmaceutical and medical devices companies (e.g., Farmindustria, Assobiomedica). These provisions mainly concern:

a. the supply of gifts to HCPs (which is allowed on the condition that they have a negligible value and are job-related);

b. the sponsorship of congresses and the rules on payments of HCPs’ travel and accommodation expenses; and

c. the options for companies to execute consultancy agreements with HCPs, which are subject to strict transparency rules.

Italian companies also apply the EFPIA Code.

Financial relationships that do not meet these requirements are subject to criminal sanctions (for corruption or comparaggio, which is a similar crime applied exclusively in the context of relationships with HCPs) and may expose the company to the risk of administrative liability for crimes committed by its employees under Legislative Decree No. 231 of 8 June 2001.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Compensation of persons injured by medicines or medical devices is subject to the general provisions of the Italian Civil Code on tort liability (i.e., Sections 2043 and 2050) and the Italian Consumer Code (i.e., Section 120 on damage caused by defective products). Special systems are established by the law only in very specific cases, such as to compensate persons injured by compulsory or recommended vaccinations, or by infected plasma transfusions (Law No. 210/1992 and Law No. 299/2005).

Furthermore, compulsory insurance is required for healthcare facilities and operators by Law No. 24 of 8 March 2017 and for sponsors of clinical trials (see Section II.iii).
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

During the past few years, the ICA has carried out several investigations and issued steep fines against pharmaceutical companies for abusive conducts and anticompetitive agreements.

A common issue underlying these investigations is whether the way pharmaceutical companies use (or allegedly ‘misuse’) the regulatory framework or patent protection regime can infringe national or EU competition law. Indeed, any misuse of regulatory provisions, as well as of regulatory gaps, by a dominant manufacturer or MAHs to artificially extend market or data exclusivity protections and resulting in the exclusion or delay of competition, or in the exploitation of market power to escalate prices without justification, may be deemed abusive by the ICA (being the result of an ‘abuse’ or ‘misuse’ of rights).

For instance, in Case 1760 of 27 February 2014 (Roche-Novartis/Farmaci Avastin and Lucentis), the ICA found that the parties infringed Article 101 TFEU by concerting activities aimed at artificially differentiating potentially competing drugs through a speculative interpretation of the regulation on the off-label use of drugs and pharmacovigilance duties, with a view to manipulating the demand and sharing monopolistic profits (this decision was confirmed by the judgment of the ECJ in Case C-179/16 of 23 January 2018. In Case A480 (price increase of Aspen’s pharmaceuticals), the ICA has maintained that the way Aspen renegotiated the price of a reimbursable, life-saving drug for a rare disease with the AIFA constituted an abuse of dominance by means of the imposition of excessive pricing conditions and ordered that the conduct be ceased. Subsequently, in March 2017, the ICA initiated proceedings for non-compliance with the decision, alleging that Aspen was not effectively and in a timely manner renegotiating the drugs’ prices with AIFA to cease the abusive conduct. To avoid a further fine, Aspen accepted reaching an interim agreement with AIFA to temporarily apply retroactive discounts pending the procedure for re-negotiation of the drug’s prices. In June 2018, Aspen and AIFA finally reached a conclusive agreement on lower prices for the drugs and the ICA closed the non-compliance proceedings without a finding of infringement.

Further, the ICA has been particularly active in pursuing anticompetitive agreements in the public sector, all the more so where they occur in the context of the supply of reimbursable drugs to the NHS or in relation to public tenders (Case I639 of 26 April 2006 – Disinfectants; Case I770 and Case I792 of 21 December 2016 – Tenders for oxygen and ventilation therapies). This is confirmed by the public cooperation agreement entered into with the AIFA on 19 January 2017 (see Section II.xiv).

In 2018, the ICA initiated two investigations for breach of competition law in the life sciences sector, one of which is pending, while the other one was closed without a finding of infringement because of lack of evidence. In February 2018, following complaints by independent medical instruments maintenance providers, the ICA opened proceedings against three manufacturers (including the Italian subsidiaries and their foreign parent companies) of diagnostic imaging devices for an alleged abuse of dominance in the after-market for the maintenance of the original equipment, on the grounds that the manufacturers hindered independent maintenance firms by providing only limited access to software and not handing out the necessary passwords, refusing to supply original spare parts and by denigrating the services offered by independent providers (pending). In January 2018, the ICA started investigations against firms collecting human-blood plasma for suspected collusion by participating in a public tender through a joint venture, but dropped the probe
in December 2018 after finding that economic evidence submitted by the firms substantiated plausible efficiencies or pro-competitive effects in participating as a joint venture rather than individually as competitors.

ii Transactional issues

In life sciences mergers and acquisitions deals, the peculiarities of the industry should be properly addressed from a contractual standpoint. These peculiarities usually affect the purchase price mechanisms (especially earn-out), representations and warranties and closing and post-closing covenants. Depending on the business of the target company and the life cycle of its products, the parties may need to add specific closing conditions (e.g., obtaining an MA, successful outcome of a certain clinical trial phase, issuance of the CE mark) and post-closing covenants (e.g., ‘commercially reasonable efforts’ standard to achieve milestones triggering the payment of earn-outs).

The parties should pay particular attention to and properly address any issues and potential liabilities connected with the payback and the company budget system as well as the transfer of MAs (in the context of an asset deal), also regulating the interim period between the closing and publication in the official gazette of the AIFA’s transfer decisions (see Section II.vii (Medicines)).

VIII CURRENT DEVELOPMENTS

The main recent changes in policy and legislation focus on:

a the clinical trials sector, for the implementation of the Delegation Law that is still largely incomplete (see Section II.iii on ‘Medicines’);

b the scientific research sector, since certain recent amendments to the Italian data protection code may have a significant impact on the use of health and genetic data for research purposes; and

c the governance of medicines and medical devices, since the Budget Law 2019 provides for several measures that will have to be implemented in the next months and will have a significant impact on the governance of the pharmaceutical and medical devices sector (see Section III).
Chapter 16

JAPAN

Takeshi S Komatani

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 market medical products, the following 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, 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.

Protection of intellectual property rights is effected 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;

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1 Takeshi S Komatani is a principal at Shusaku Yamamoto.
2 Known in Japan as Kôseirôdôshô or Kôrôshô.
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, recent law amendments have introduced some regulation and protection of valuable data including clinical trial data and real world data.

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:

- Drug or medicines;
- Quasi-drugs or quasi-medicines;
- Cosmetics;
- Medical devices; and
- 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):

- Foods in general; and
- Foods with health claims:
  - Foods for specified health uses;
  - Foods with nutrient function claims; and
  - Foods with function claims.

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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 Article 2 of the PMD Act.

6 ‘Medicines’ and ‘quasi-medicines’ are often translated as ‘drugs’ and ‘quasi-drugs’, respectively, and these have the same meaning.

7 Iyakubugaihin.

8 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).

9 Tokutei Hoken'yô Shokuhin or Tokuho.

10 Eiyô Kinô Shokuhin.

11 Kinôsei Hyôji Shokuhin.
Foods in general are regulated by the Food Sanitation Act, whereas ‘foods for specified health use’ and ‘foods with nutrient function claims’ are regulated by the Health Promotion Act under the supervision of the MHLW, and ‘foods with function claims’ are regulated by the Food Labelling Act under the supervision of the Consumer Affairs Agency.

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.12

**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 I, the 17th Edition, issued on 1 December 2017], 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 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.13

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.

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13 Defined in Article 2(9) of the PMD Act.
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.

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 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

14 See also Article 14(3) of the PMD Act.
16 See also Articles 2 and 80 bis of the PMD Act; Article 268 of the Rule for implementing the PMD Act.
17 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).
Association, also provides guidelines for GCP, etc.\textsuperscript{18} Clinical trials specifically for marketing approval are called \textit{chiken} under the Japanese practice, and are different from other types of clinical trial. Some clinical trials other than \textit{chiken}, classified as ‘specified clinical research’, are controlled under the Act on Clinical Research, which was enacted on 7 April 2017, and will come into effect within one year from that date.\textsuperscript{19}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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.

\textsuperscript{18} www.jmacct.med.or.jp/plan/guideline.html.

\textsuperscript{19} www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000163417.html.
**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.

**Special procedure for importing drugs or medical devices**

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:

a. marketing authorisation has been obtained in another country that has a marketing authorisation system equivalent to that in Japan;

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

c. the drug or medical device is specifically designated through an administrative order.

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.

**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. 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.

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.

Authorisation conditions

In reviewing an application, key consideration is given to the following: 22
a quality;
b efficacy/effectiveness;
c safety;
d the applicant’s marketing business licence; 23 and
e the proposed manufacturer’s manufacturing business licence or accreditation as a foreign manufacturer 24 in which good manufacturing practice (GMP) is also checked.

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

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23 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.
24 Article 13, 13-ter of the PMD Act.
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).25 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 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.

**Standard 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

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25 See www.pmda.go.jp/files/000214630.pdf, which has been updated as of 25 November 2014.
improvement in the quality of medical care for the subject disease. 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.

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 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 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.

Procedures for conditional and time-limited approval
Oncology drugs and orphan drugs may be subject to a conditional approval system. Additionally, with respect to regenerative medical products, a new process called the ‘conditional and time-limited approval system’ has been introduced by means of the 2014 Amendment. Under the new regime, 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.

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. 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

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26 Article 14(7) of the PMD Act.

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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.

**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. 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. 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.

**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

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28 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.


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.

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:

a conduct a drug recall campaign;
b report the discovery to the PMDA;
c issue public notices if the issue is important; and
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.

31 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 quinquies, and 79 of the PMD Act; Article 228 vicies 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.

32 Articles 74 bis and 80(2) of the PMD Act.
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.

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).

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:

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33 A manufacturer of a medical device is subject to a prior registration requirement, and is not required to obtain a manufacturing business licence.

34 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.

35 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.
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;

b 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;

c 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

d 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.

**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.

**Advertising and promotion**

**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.\(^{36}\) 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.

\(^{36}\) 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.
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).

x 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.37 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.38 As such, wholesalers and retailers of drugs, regenerative medical products or medical devices are subject to separate business licence requirements.

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.

xi 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

37 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.
38 Additionally, the leasing of strictly controlled medical devices requires a leasing business licence.
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.39 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:40

- drugs that cannot be used effectively or safely without proper selection based on a doctor’s diagnosis;
- drugs that require periodic medical checks to avoid serious adverse effects; and
- 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 (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.41

**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:

- accreditation as a foreign manufacturer by an offshore manufacturing factory for the products being imported;
- 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);
- a marketing business licence held by a marketer, for marketing the imported products;
- a marketing authorisation held by a marketer, for marketing the imported products; and
- an import report from a marketer, for customs clearance.

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39 Articles 3, 4(5), 14, 14 quater, 36 septies, 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.

40 Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 0210001, 10 February 2005.

41 Notification from the MHLW No. 24.
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 manufacturing business licence held by a domestic factory for manufacturing products for export; and
- 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:

- 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);
- 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
- when exporting products without having obtained authorisation under the PDM Act, it would be necessary to obtain a manufacturing business licence and an export report.

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. 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.

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42 Article 80 of the PDM Act, Articles 71 and 74 of the PDM Act Implementing Ordinance, and Article 265 of the PDM Act Implementing Regulation.
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 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 PRIMS or ethical *Kampo* drugs.

xv 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

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45 Notification from the director of Evaluation and Licensing Division, Department of Pharmaceuticals and Food No. 322001, 22 March 2007.

46 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.

47 Notification from the director of the Pharmaceutical Safety and Environmental Health Bureau No. 0328-1, 28 March 2017.

48 Section 13 of the PMD Act.
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
- 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.49

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.

49 Articles 13 bis (5), 13 bis-7 (6), 14-bis (6), 23 viciester (5) and 80 decies (5) of the PMD Act.
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.

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 awarded.

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 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 is, however, still in the transition period until the end of March 2019. Any trials conducted before the end of March 2019 will be processed according to the old regulation, in which no strict rules are 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.

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.

X LIMITED PROVISION DATA

The Amendment to the Unfair Competition Prevention Act was enacted and promulgated in June 2018. 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 will
provide 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.

XI EXPECTED AMENDMENT TO THE PMD ACT

In 2018, the PMD Act was scheduled for review as the Amendment, which was introduced in November 2013, stipulated that a review must be scheduled within five years. The government has published results of such an initial review of the PMD Act. The publication proposed to introduce:

a a rational market authorisation examination regime to expedite new drugs, allowing rapid access by patients in need of them;

b internationally harmonised quality control measures including GMP and good gene, cellular and tissue-based products manufacturing practice (GCTP);

c review of the quality management system adaptation;

d modification of management measures for marketing authorisation relating to the quality according to risk; and

e improvement of safety measures including provision of package inserts or labels by means of electronic form that updates any relevant information in real time, and improvements in traceability – for example, by means of barcodes.50

50 www.mhlw.go.jp/content/11121000/000463479.pdf.
INTRODUCTION

In Korea, pharmaceutical products are generally regulated by the Pharmaceutical Affairs Act (PA Act) and medical devices by the Medical Devices Act (MD Act) in terms of manufacture, importation, distribution and advertising. The pricing of pharmaceutical products and medical devices is governed by the National Health Insurance Act (NHI Act) and other applicable regulations.

The Ministry of Food and Drug Safety (MFDS) is the main administrative authority to enforce the PA Act and the MD Act, while the Ministry of Health and Welfare (MOHW) is authorised to enforce the NHI Act and the selective provisions of the PA Act and the MD Act. Competition issues arising out of the pharmaceutical and medical device sector are regulated by the Korea Fair Trade Commission (KFTC).

THE REGULATORY REGIME

Classification

The Supreme Court of Korea (the Supreme Court) has held that all substances recognised by or represented to the public as diagnosing, curing, mitigating, treating or preventing diseases in human beings or animals, or exerting a pharmacological action in human beings or animals (except for those that can be instantly recognised as food products), fall under the category of pharmaceutical products, regardless of whether any such recognition or representation is actually true.

The regulatory regime in Korea adopts the following classification of products in the pharmaceutical and medical device sector.

Pharmaceutical products

The PA Act defines pharmaceutical products as:

- products that are not identified as quasi-pharmaceutical products in the substances list issued by the Korean pharmacopoeia;
- any substance used for the purposes of diagnosing, curing, mitigating, treating or preventing human or animal diseases; and
- any substance (other than instruments, apparatuses or cosmetics) used for the purpose of exerting a pharmacological influence on the structures or functions of human beings or animals.
Quasi-pharmaceutical products
Among the following types of products, only those that are officially designated as such by the MFDS pursuant to the PA Act will be recognised as quasi-pharmaceutical products:

a. any fibre or rubber products, or similar products that are used for the purpose of curing, mitigating, treating or preventing human or animal diseases;
b. any products (other than instruments, apparatuses, appliances or other articles) that minimally affect or do not directly act upon the human body; and
c. germicides, insecticides or any products used for sterilisation, killing or prevention of infectious diseases.

Functional foods
Under the Functional Foods for Health Act, functional foods are defined as manufactured food (including processed food) containing 'functional raw materials or ingredients' that are beneficial for the human body.

Medical devices
Medical devices are defined as instruments, apparatuses, appliances or other articles (excluding pharmaceutical products or quasi-pharmaceutical products) that are used, alone or in combination with other products, to:

a. diagnose, treat, alleviate, cure or prevent diseases;
b. diagnose, treat, alleviate or correct injuries or physical disabilities;
c. examine, replace or modify the structure or the function; or
d. contraception.

The MD Act is the governing law for medical devices.

Cosmetics
Substances intended to be applied to the skin for cleansing or beautifying, or applied to the skin or hair to maintain or enhance its condition, but that have minimal effects on bodily functions, are classified as cosmetics. Cosmetics are governed by the Cosmetics Act.

Prescription and over-the-counter drugs
Pharmaceutical products are generally categorised into prescription drugs and over-the-counter (OTC) drugs under Korean laws and regulations. Pharmaceutical drugs that meet any of the following criteria are recognised as OTC drugs by the MFDS in consultation with the MOHW:

a. drugs that are unlikely to be overused or misused, and are expected to be used safely and effectively, even in the absence of a physician's prescription;
b. drugs that can be used for the purpose of treating a disease without relying on the expertise of physicians or dentists; or
c. drugs with minimal side effects to the human body from pharmacological action.

All other pharmaceutical products that are not classified as OTC drugs will fall into the category of prescription drugs.

Prescription drugs may be dispensed by a pharmacist only after an assessment of the patient's condition has been made by a doctor or a dentist and the patient has been
educated about taking the drug by the pharmacist, whereas the dispensing or use of OTC drugs does not require any of these procedures. Prescription drugs and OTC drugs are also distinguishable in terms of their pricing and reimbursement mechanism.

Prescription and OTC drugs were both previously available in pharmacies only. However, since 15 November 2012, a few OTC products (fewer than 20 product types) that are frequently used and designated by the MOHW have been available at convenience stores registered with the relevant local government as a seller of OTCs, subject to requirements as stipulated by the PA Act.

**Controlled substances**

Several prescription medicines that are controlled substances, such as narcotics (e.g., poppies, opium or coca leaves), psychotropic drugs and marijuana, are subject to stringent legal regulations owing to the high risk of misuse or illegal sourcing as opposed to other non-narcotic drugs. Before such controlled substances are imported into Korea or exported to a foreign country, the importing or exporting companies must obtain a licence from the MFDS, and the product itself must have a licence, issued by the MFDS. Naturally, the qualifications are stricter for obtaining a licence to import or export controlled substances than for non-controlled drugs. Once controlled substances are imported or exported, details related to the import or export transactions and commercial sales must be reported to the MFDS. Physicians are allowed to administer (or provide for administration) controlled drugs to a human body to treat an illness or an injury. The administering doctors regarding the administrated substances are required separately to keep a record of the following information: name, address, age, gender and disease of the patient; product name and quantity of the drug administered (or provided); and date of prescription.

**ii Non-clinical studies**

To conduct a non-clinical study, an investigating institution needs to be designated by the MFDS for non-clinical studies to be conducted. For an institution to qualify as a designated investigating institution, it must satisfy certain requirements in terms of personnel, facilities and equipment. All non-clinical studies must comply with MFDS guidelines for good laboratory practice (GLP).

An institution conducting testing on vertebrate animals must be registered with the MFDS as an animal testing facility under the Laboratory Animal Act. The governing legislation for the care of vertebrate animals used for research and testing are the Laboratory Animal Act and the Animal Protection Act.

**iii Clinical trials**

There are no qualifications imposed on a sponsor (the sponsor often hires a contract research organisation to administer the clinical trial), but the organisation undertaking clinical trials must be a qualified general hospital, a specialised hospital or another institution designated by the MFDS. The institution conducting clinical trials must submit a study protocol, an outline of the methods for recruiting subjects (including advertisements), consent forms to be received from recruited subjects and the data collection forms to its internal institutional review board for review. The clinical trials must be conducted in accordance with the standards under the Enforcement Rules of the PA Act (which is the good clinical practice of Korea) regarding various factors, such as the test methods, qualifications of the testing institution and testing supervisor, safety plan, progress report and preservation of relevant
data. To enable the human subjects to give informed consent and to ensure that they do so, the details of the clinical trial, the potential adverse effects on health, and the compensation amount and method must be explained in advance. In 2013, the MFDS first introduced, and has since implemented, the Rules for Compensation of Clinical Trial Victims and Guidelines for Providing Compensation Procedures; these call for setting criteria in these matters, as well as any exceptions, and laying out the process for the application for and assessment of compensation, when regulations for compensating victims of clinical trials are being drawn up by sponsors. The MFDS introduced additional guidelines in 2014, such as the Guidelines for the Operation of the Institutional Review Board, to ensure the safety and efficacy of clinical trials.

iv  Named-patient and compassionate-use procedures

As an exception to the rule that requires imported pharmaceutical products or manufactured or imported medical devices to be authorised prior to its manufacture or import, pre-launch use is permitted in the following circumstances, among others:

a  when the Korean Orphan Drug Centre, a regulatory authority that governs named-patient supply and compassionate use of medicines, directly imports certain products into Korea;

b  when the MFDS determines that certain products are urgently needed for the treatment of patients or the prevention of epidemic; or

c  when the MFDS announces that certain products are necessary for self-treatment or self-aid.

v  Pre-market clearance

Medicines

General procedures

For medicines manufactured in or imported into Korea, each product must have marketing approval from the Minister of the MFDS (product approval) prior to its commercial distribution. For products manufactured in Korea, a manufacturer with the intent to distribute the manufactured products must obtain approval for the manufacture and sale of the product. For products imported into Korea, an importer must obtain an approval for importation. In its review for product approvals, the MFDS mainly considers whether the requirements of safety, efficacy and quality have been satisfied.

Special procedures for follow-on products

Most generic and certain biosimilar pharmaceutical products are exempt from safety and efficacy evaluations, but data on their biological equivalency must be submitted to the MFDS.

Special procedures for accelerated approval of products for unmet medical needs

For orphan drugs, drugs for the treatment of certain lethal diseases (e.g., AIDS, cancer) or incurable diseases, the MFDS may grant accelerated approval and permit the earlier sale of drugs prior to the submission of certain documents (which can be later submitted post-marketing).
Fees
Fees range from 154,220 won to 6,828,150 won, depending on whether the filing is an application for approval or a report, the safety and efficacy evaluations are required, or the evaluations on data for medical product equivalency tests are required.

Requirements for sponsor location
Product approval must be acquired and held by an entity with an address in Korea.

Requirements for appointment of a local agent
A local agent does not need to be appointed. However, because of the address requirement imposed on a sponsor, it is common practice for manufacturers based outside Korea to appoint and authorise a local entity to acquire and hold a product approval on its behalf.

Medical devices
General procedures
The general procedures for the pre-sale approval of medical devices are similar to those for medicines. However, under the amended MD Act, which became effective in July 2015, for certain medical devices with very low risk (classified as Class I medical devices) or low risk (classified as Class II medical devices), the manufacturer or importer will not be required to obtain product approval for each and every product. Instead, it is sufficient to obtain a simple reporting requirement for Class I medical devices, and a product certification from the Medical Device Information and Technology Assistance Centre for Class II medical devices.

Special procedures for follow-on products
Certain Class II follow-on medical devices are exempt from the submission of data for clinical trials and technical documents (this is concluded based on the fact that similar follow-on medical devices were approved for exemption in at least three occurrences). Most follow-on Class II, III and IV medical devices are exempt from the submission of data for clinical trials. However, data for clinical trials and technical documents must be submitted for Class I medical devices.

Special procedures for accelerated approval of products for unmet medical needs
Certain state-of-the-art and rare and in vitro devices, as determined by the MFDS, are entitled to accelerated approval.

Fees
Fees range from 57,000 won to 1,108,000 won, depending on whether the filing is an application for approval or a report and whether the evaluations on data for clinical trials or technical documents are required.

The requirements for the sponsor’s location and the appointment of a local agent are substantially similar as those for medicines.

vi Regulatory incentives
Owing to the recent introduction of the product approval patent linkage system, it is believed that patent protection for original pharmaceutical products in Korea was heightened as
In March 2015, the PA Act was amended to prepare the ground to support a link between the drug approval system and the drug patent system. Under the amended system, if a party that has obtained product approval for a new drug wants its information be placed on the patent list, the party must request the MFDS to do so within 30 days of product approval. Thereafter, once a generic manufacturer submits an application for generic drug approval, the generic manufacturer must notify the relevant patent holder with a detailed statement demonstrating that the listed patent is invalid or the generic manufacturer’s product does not infringe the patent (this only applies to generic manufacturers that seek product approval for the launching of a product during the term of the listed patent and does not apply to generic manufacturers that intend and indicate that the product will be launched after the listed patent has expired). The patent holder may file a legal action against the generic manufacturer if the patent holder believes that the generic drug infringes its patent. The generic product approval will be put on hold for nine months upon the patent holder’s filing of a legal action, which should be submitted within 45 days of the notice from the generic manufacturer.

Under the amended PA Act, the first company to submit an application for a generic drug, and win in a legal action against the patent holder to invalidate the related patent rights, shall be granted an exclusive right to sell the generic product for nine months from the date of the judgment by preventing other competitors of that generic drug from entering the market. The first company will be entitled to recoup the costs it has incurred in legal proceedings through this exclusive right to sell the generic drug for a limited period.

Post-approval controls

The product approval holder must appoint at least one person to be responsible for pharmacovigilance or device vigilance (there are no infrastructure requirements required for post-approval controls) to undertake post-marketing surveillance activities, such as post-approval testing and adverse reaction reporting. If any matter that was reported to the MFDS in the product approval process was altered or modified, the product approval holder must apply for an amendment of the product approval (if the product approval holder is replaced during the transfer of ownership of the product approval through a private transaction, an amendment must be made within one month of the date of the replacement of the product approval holder). Product approval will be valid for five years (this validity period took effect on 1 January 2013) and the product approval holder must apply for reissuance of the approval no later than six months prior to the expiry date of the validity period.

Manufacturing controls

To engage in the manufacture and distribution of pharmaceutical products or medical devices in Korea, several licences must be obtained in advance. The product must receive a licence called a product approval (see Section II.v). Additionally, the companies that are involved in the stages of the manufacture and distribution of the products should be licensed entities by fulfilling the requirements below.

Medicines

Qualifications for a licence to manufacture

A manufacturer should be equipped with the following:

- a manufacturing facility;
- a laboratory to control the quality of ingredients, materials and products;
c a storage facility for ingredients, materials and products; and
d facilities and equipment necessary for maintaining quality and manufacturing products.

In addition, at least one pharmacist or herb pharmacist must be stationed at the manufacturing facility for quality control, subject to certain exceptions.

**Good manufacturing practice**
Manufacturers must act in compliance with the standards of good manufacturing practice (GMP) to ensure that high-quality products are produced. GMP inspections, including review of documents and on-site investigation, are performed by the MFDS.

The MFDS updated its GMP to be in compliance with the quality standards of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme after becoming a member on 1 July 2014.

**Transfer of ownership of manufacturing facilities**
In the event that manufacturing facilities are transferred through a merger or business transfer, the transferee takes on the rights and obligations of the transferor (transferring manufacturer). If an administrative sanction has already been imposed on the transferor, the transferee will also be subject to that sanction for one year from the date of the sanction, but if an administrative sanction has not yet been imposed and is pending, the relevant administrative body may seek to impose a sanction against the transferee. The foregoing does not apply, however, if the sanction or violation at the time of the merger or business transfer was unknown to the transferee.

**Medical devices**
**Qualifications for a licence to manufacture**
The qualifications are substantially similar to those for medicines, but the person stationed at the manufacturing facility for quality control does not necessarily have to be a pharmacist or a herb pharmacist.

**Advertising and promotion**
Advertisements for pharmaceutical products and medical devices are subject to the regulations enforced by the MFDS and to self-regulation carried out by prior review and approval by the Korea Pharmaceutical Manufacturers Association (KPMA, for medicines) and the Korea Medical Devices Industry Association (KMDIA, for medical devices). In general, advertising materials for pharmaceutical products or medical devices must not contain false or exaggerated information regarding the product’s name, manufacturing methods, its effects or results.

**Distributors and wholesalers**
The distribution or wholesale of medical products is subject to the following laws and regulations.

**Medicines**
**Qualifications for a licence to distribute or wholesale**
To distribute pharmaceutical products, a licence issued by the governor of the municipal government must be obtained.
To qualify as a licensee, the distributor or wholesaler must have a sales facility and a minimum storage space of 165 square metres.²

The licensed distributor or wholesaler must employ a pharmacist at the sales facility for the management of sales activities.

**Distribution via the internet**
The distribution of medicines via the internet is prohibited.

**Others**
To prevent unfair trade practices between distributors and healthcare professionals, a distributor or wholesaler is prohibited from, directly or indirectly, selling pharmaceutical products to its affiliates (e.g., an entity or hospital controlling the distributor or wholesaler by possessing 50 per cent or more of its securities, or an executive of the distributor or wholesaler).

**Medical devices**

**Qualifications for a licence to distribute or wholesale**
To distribute or lease medical devices, a report must be filed with the municipal government. A licence is not required.

**Distribution via the internet**
The distribution of medical devices via the internet is permitted.

### Imports and exports

The authorisations required for the import and export of pharmaceutical products and medical devices to and from Korea are set out in the following table.

<table>
<thead>
<tr>
<th></th>
<th>Medicines</th>
<th>Medical devices</th>
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<tbody>
<tr>
<td></td>
<td>Import</td>
<td>Export</td>
</tr>
<tr>
<td><strong>Licence to conduct import or export business</strong></td>
<td>Required*</td>
<td>Not required (but subject to the laws of the importing country)</td>
</tr>
<tr>
<td><strong>Product approval for import or export</strong></td>
<td>Required</td>
<td>Required (but the submission requirement of biological equivalency materials may be exempted)</td>
</tr>
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</table>

* Under the PA Act (effective from 29 September 2015), anyone who intends to engage in the business of importing drugs or quasi-drugs must file a report to the MFDS for the import business, in addition to the product licence for the individual product.

Certain MFDS approvals are required for the import or export of medicines containing ingredients derived from endangered animals or plants pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora.

² However, the minimum space requirement for storage of imported pharmaceutical products, reagents or active ingredients is lower, at 66 square metres. Storage of traditional herbal pharmaceutical products, high-pressure medical gas or radioactive pharmaceutical products is not subject to a minimum space requirement.
III PRICING AND REIMBURSEMENT

At the core of the national health system is insurance under the NHI Act. Any Korean citizen with an income must subscribe to national health insurance and make insurance payments based on his or her level of income. A foreign national residing in Korea who meets certain requirements can become a subscriber, a dependant of a subscriber or a beneficiary of national health insurance.

If the insured party contracts a disease, he or she receives insurance proceeds under the NHI Act until full recovery, regardless of the number of payments he or she has made. The funds administered under the NHI Act consist of a government subsidy and premiums received from the insured.

Generally, the price of medical products is not directly restricted or regulated by law, but the reimbursement prices of medical products are strictly regulated if the costs of the products are reimbursed under the NHI Act. Reimbursement ceilings are negotiated by the medical product producer and the National Health Insurance Service (NHIS). Medical product prices are generally set at the reimbursement ceilings as listed and announced by the MOHW.

The insurance proceeds are reimbursed to the medical institutions and pharmacies that provide medical products to insured patients. The medical institutions and pharmacies:

a. buy medical products from the pharmaceutical companies or medical device companies to treat insured patients;

b. administer or provide these medical products to insured patients, in exchange for a limited amount paid by the insured patient under the NHI Act; and

c. subsequently receive reimbursements in the form of insurance proceeds from the NHIS within the limit set under the NHI Act.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

i Enforcement

The MFDS has the authority to enforce the PA Act and the MD Act, while the MOHW oversees and enforces the PA Act, the MD Act and the NHI Act. The MFDS, the MOHW and the governors of the municipal government have the authority over medical institutions or pharmacies, manufacturers, importers and distributors to order the submission of documents and other necessary information, and to investigate, interrogate personnel or staff and collect necessary items from their places of business, when there are activities or signs that trigger any suspicion of violations of the relevant regulations. The MFDS is authorised to impose the following sanctions in the event of a violation:

a. issue a corrective order to the offending party or parties to immediately cease all prohibited activities;

b. order the disposal or recovery of medical products that are a part of the violation;

c. order the implementation of a recall campaign;

d. suspend operation of the business or cancel a licence or product approval; or

e. impose an administrative fine.

The MFDS is required to refer cases of serious violations to the prosecutors for indictment, criminal investigation and imprisonment or fining of the offending party (in such cases, the offending party’s company may also be subject to a fine).
Administrative and judicial remedies

A decision rendered by healthcare authorities can be appealed through an administrative appeal or administrative litigation.

According to the Administrative Appeals Act, the administrative appeal system allows parties whose legal rights or interests were infringed or who have experienced any injustice by government administrative agencies (i.e., disposition or non-feasance) to file appeals. The objective of the administrative appeal system is to enable the government agencies to self-manage the appeals in an efficient and expeditious manner without having to go through the longer process of administrative litigation. Decisions made in administrative appeals can be appealed again by filing a lawsuit in the administrative court. However, it is not a precondition to have filed an administrative appeal prior to filing an administrative litigation. In cases of infringement of legal rights or interests caused by the illegal actions of administrative agencies, disputes may be settled through administrative litigations directly.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The PA Act, the MD Act and the Medical Service Act, which were amended and became effective on 28 November 2010, prohibit and criminally penalise the givers as well as the takers of economic benefits for the purpose of promoting sales (i.e., illegal rebates). Medicines involved in illegal rebates are subject to the ‘two-strike out rule’ (effective from 2 July 2014), under which a heavier sanction, such as suspension of insurance payments, will be imposed. Punishments are more severe for repeat offenders. For instance, the maximum administrative sanction for a first-time violation is a 12-month suspension of insurance payments, but a second-time offender may be permanently barred from receiving insurance payments for the medicine it deals in, if the amount of the illegal rebates provided in relation to the medicine is 100 million won or more. A third-time offender would be subject to the same sanction regardless of the amount of the illegal rebates provided.

Although the Enforcement Decree for these healthcare laws provides ‘safe harbour provisions’ outlining promotional activities that are exempt from the general prohibition of rebates, the MOHW and the Prosecutor’s Office tend to interpret and enforce the new regulations strictly. In practice, however, voluntary industry codes adopted by industry associations governing promotional activities in the pharmaceutical and medical device sector are often relied on by the authorities in the enforcement of healthcare laws with respect to promotional activities. The KPMA, the Korea Research-Based Pharmaceutical Industry Association (KRPIA) and the KMDIA, which are the NGOs and trade associations in the pharmaceutical and medical device sector, have revised their respective voluntary codes reflecting recent amendments to the PA Act, the MD Act and the Medical Service Act. The KPMA Code, the KRPIA Code and the KMDIA Code (the Codes) are substantively similar and have become the benchmark codes for all companies in the relevant sectors. If the healthcare laws are silent on a particular issue, the MOHW or the Prosecutor’s Office will refer to and follow the rule under the Codes. In other words, it is likely that compliance with the Codes will to some extent determine the legality of conduct.

Further, Korean fair trade laws prohibit private commercial interests from influencing and interfering with physicians’ discretion and professional judgement based on the perception that this conduct unavoidably results in the unfair solicitation of customers away from competitors. The KFTC has in the past reviewed and approved the Codes, and although the Codes are not legally binding, they are considered good practice models, which can fill
in the gaps on issues where the fair trade laws are silent. If the fair trade laws are silent on a particular subject, the KFTC will refer to the applicable rules of the Codes in determining healthcare violations in acts related to that subject.

The PA Act and the MD Act have been further amended (effective from 28 June 2017) and now impose on manufacturers, importers, wholesalers and distributors of pharmaceutical products or medical devices the obligation to keep records of any economic benefit provided to healthcare professionals. These records must be prepared within three months of the end of each fiscal year and must be maintained (with their supporting materials) for five years. These ‘expense reports’ must be submitted to the MOHW upon the regulator’s request.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Claims for compensation by persons injured by defective medicine or medical devices can be made based on the Product Liability Act. Prior to the enactment of the Product Liability Act on 12 January 2000, claims for damages from defective pharmaceutical products and medical devices were solely based on general tort or contract principles, in which liability is predicated on negligence. As a result, the burden to prove the existence of the defect and the injury, the causation of the defect and the injury, and the intentional misconduct or negligence on the part of the manufacturer, were all borne by the claimant. Furthermore, since claims based on a breach of contract can be made only when a contractual relationship exists between the parties, consumers and patients were generally barred from bringing claims against manufacturers or importers because of the lack of contractual relationship. However, the Product Liability Act imposes strict liability on the manufacturers and importers of defective products, which lifts the burden of proving the manufacturer’s intentional misconduct or negligence from the injured party. Moreover, Korean courts tend to further relieve the burden of proving the defect of the product and the injury-defect causation in product liability cases considering the difficulties customers typically face in establishing the existence of a product defect or the causation between the defect and the injury; and the fact that product manufacturers are in a better position than customers to have extensive knowledge about the product.

The Product Liability Act is also distinguished from the general principles of contract in that the plaintiff does not necessarily have to be in privity to a contract to file a claim. Product liability claims can be brought against manufacturers, which include persons engaged in the business of manufacturing, processing or importing a product, and persons who represent or misrepresent themselves to be those engaged in this business by putting their name, trade name, trademark or any other identification on a product. The PA Act (effective from 19 December 2014) was amended to enable the MFDS to impose charges against manufacturers, product approval holders and importers of pharmaceutical products dealing with certain medicines for potential adverse drug events (ADEs), to raise funds as compensation for victims of ADEs.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

During an investigation in 2011, the KFTC found that a multinational originator and a domestic generic manufacturer had been working in collusion to induce generic entry delay by agreeing on a pay-for-delay settlement during a patent dispute. The KFTC reviewed the
pay-for-delay settlement agreement, applying the legal theory of cartels, and determined that
the arrangement was a market allocation arrangement (i.e., withholding generic entry from
the relevant market and, thus, allocating the entire relevant market to the originator) and
an arrangement interfering with the business activities of another company. The defendants
appealed the case to the Supreme Court, but the Supreme Court upheld the KFTC’s view
that a pay-for-delay settlement potentially constituted a violation of competition laws.

This case may be an indication that the KFTC may be leaning towards applying higher
scrutiny to collusive behaviour in the pharmaceutical sector in the future. Accordingly, if
parties enter into a settlement agreement of a patent dispute that is likely to cause undue
delay to one of the parties in the entry of a market, and thereby impair competition in the
relevant market, that agreement is likely to be viewed as a violation of competition laws.
The KFTC has recently commenced an investigation into pay-for-delay arrangements in the
pharmaceutical sector.

Furthermore, the KFTC has been investigating (illegal) rebates in the medical device
sector, which has resulted in its probe into nine companies (including KMDIA) in 2013
alone. However, it appears that there is no other result from these investigations except minor
dispositions (i.e., corrective orders) for two companies as a result of the provision of small
amounts of rebate to healthcare professionals.

ii  Transactional issues

In May 2014, the KFTC abolished its Guideline on Fair Trade Practices in the Pharmaceutical
Sector, as it determined that there were other existing guidelines that were sufficient for the
purpose of regulating unfair trade practices in the pharmaceutical sector.

VIII  ANTI-CORRUPTION LAW

The Prohibition of Improper Solicitation and Receipt of Money or Valuables, more
commonly known as the Kim Young-Ran Act, became effective on 28 September 2016. This
Act prohibits improper solicitation, and provision and receipt of money or valuables between
any person and public officials. Accordingly, this Act will apply to all healthcare professionals:

a  of national and public university hospitals;
b  who hold faculty positions at private university hospitals; and
c  who are members of committees advising the government.

Under the Kim Young-Ran Act, public officials shall not receive, request or be promised any
money or valuables worth more than 1 million won at a time or more than 3 million won
during a fiscal year from one person, regardless of whether the money or valuables are related
to their duties or not. No money or valuables, even if worth less than 1 million won, should
be provided or received if they are provided or received in relation to their duties. Certain
exceptions are set out by the presidential decree to the Kim Young-Ran Act.

IX  CURRENT DEVELOPMENTS

As mentioned previously, healthcare professionals who receive illegal rebates are subject
to sanctions. Until April 2013, the MOHW only imposed administrative sanctions (e.g.,
suspension of a licence) on healthcare professionals who received economic benefits worth
3 million won or more; however, the MOHW has been implementing stronger enforcement since May 2013 by imposing sanctions on healthcare professionals regardless of the amount of the economic benefits received.

The MOHW is also seeking to expand insurance cover for orphan drugs to ease patients’ accessibility to such drugs. The MOHW plans to permit insurance payments even in the absence of the efficiency studies that are required for insurance cover, citing the difficulty of conducting such studies because of a limited number of patients. The MOHW will make references to practices in France, Germany, Italy, Japan, Switzerland, the United Kingdom and the United States, and in lieu of the studies when permitting insurance payments in respect of orphan drugs.

The PA Act and the MD Act will be further amended, effective from June 2017. The amended Acts will enforce tracking responsibilities on manufacturers and importers of pharmaceutical products or medical devices, and an obligation to keep records of any economic benefit provided to healthcare professionals. These records must be prepared within three months of the end of every fiscal year and maintained (with their supporting materials) for five years. These reports must be submitted to the MOHW upon the MOHW’s request.

Under the newly amended PA Act, manufacturers and importers of pharmaceutical products or quasi-drug products must list each and every ingredient of the product on its package. This requirement is applicable to any product newly manufactured or imported after 3 December 2017.

Under the newly amended MD Act, manufacturers, importers and distributors of medical devices must submit details of their product supply to the MFDS. The effective date for this obligation will be set out in the Enforcement Rule of the MD Act, which has not yet been announced.
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 REGION

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

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1 Felipe Coronel is founding partner at Latin Lex Consulting and Latin Lex International.
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

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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 in vitro and 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:

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\text{... products of biotechnological origin [that] are similar in structure, function, and clinical use as their '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
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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.\(^6\)

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.

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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.7

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.8 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

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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.9 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.10

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

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9 Medicine price control in Brazil has its legal basis in Law 10.742, dated 6 October 2003.
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 American 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:

- laboratory sales price (LSP): freely established by the producer;
- 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
- 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 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.

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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,\textsuperscript{15} 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\textsuperscript{16} 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,\textsuperscript{17} 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.

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\textsuperscript{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.
\textsuperscript{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.
\textsuperscript{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
\end{flushleft}
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.
I INTRODUCTION

Article 4 of the Mexican Constitution considers health as a human right, so the government is obliged to guarantee it to Mexican citizens, primarily by providing access to public health services such as public hospitals; and having a health law legal framework that sets the basis to provide safe and effective health products, services and treatments.

This legal framework is designed based on risk analysis of the health supplies, consumer products and services in direct contact with human health. The higher the risk, the higher the regulation and controls by the government.

The General Health Law (GHL) is the main legal instrument that organises and sets the basis of health regulation in Mexico. Article 17 bis for the GHL provides that medical products, food, beverages and other health-related products should be regulated and surveyed by the Federal Commission for the Protection Against Sanitary Risks (COFEPRIS), an autonomous administrative government agency.

The universal coverage of public health services has been a priority for Mexico's government for the past couple of decades, and the government is the biggest buyer of drugs, medical devices and health supplies in the country. The General Health Council (GHC) is in charge of the National Formulary and the Mexican Social Security Institute (responsible for the annual consolidated public bid), which are the other two major public stakeholders in the life sciences business in Mexico besides COFEPRIS.

After the GHL, Mexico has several secondary regulations, the most relevant being:

a. the Rules for Health Supplies (RHS), which cover the regulatory regime and classification of medicines and medical devices, and other health products and facilities;

b. the Rules for the Control of Health Products and Services, which focus on sanitary surveillance;

c. the Rules for Health Advertisement (RHA);

d. the Rules for Clinical Research (RCR);

e. the Mexican Pharmacopeia that specify test methods and requirements for pharmaceutical substances; and

f. a variety of Mexican Official Standards (NOMs) covering specific technical issues such as manufacturing best practices, post-marketing controls, surveillance and labelling rules, among others.

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II THE REGULATORY REGIME

Medicines and medical devices, among other health-related products, are regulated and controlled by COFEPRIS. It also creates policy and regulation, and is in charge of most of health authorisations, including pre-market clearance, health licences, good manufacturing practices certificates, and surveillance with regard to and compliance with the health regulations. The GHL and the RHS are the two main legal instruments for the health law regulatory regime.

Mexico’s legal framework has a legal definition for almost every product related to human health. However, if there is a product that does not fit clearly into a category, the classification of the product can be ruled by COFEPRIS filing a Ruling Request providing the following necessary information: formula, ingredients, pharmacological properties, therapeutic claims, labelling, literature for health professionals and advertisement of the product.

i Classification

The Mexican regulatory regimen classifies and regulates health products by risk analysis criteria, organised as follows.

Medical products

Medicines (new drugs, generic drugs, biologics, biotechnologics, orphan drugs and vitamins) are the most regulated products within the wider regulatory framework, requiring mandatory pre-market clearance, the strictest assessment by COFEPRIS and the longest time frames. It is relevant to mention that medicines have a 0 per cent value added tax rate in Mexico.

Medical devices (medical equipment, prosthesis, osthesis, diagnostics agents, dental supplies, healing supplies, surgical materials and hygiene products), also need a mandatory pre-market clearance, however, since 2014 COFEPRIS has been working on simplifying the process, requirements and implementing a fast-track approval for approximately 100 products considered low risk. Also in 2014, COFEPRIS deregulated about 2,224 products that are no longer consider medical devices because of the minimal risk they represent.

Consumer goods

Food, beverages, dietary supplements, cosmetics and cleaning products do not need pre-market clearance from the authority, but it is important to note that these products need to comply with several Rules and Mexican Official Standards regarding labelling and best manufacturing practices (no certification is needed, just compliance with the standards).

Two particular situations are worth pointing out:

a The tax and importation implications of classifying a product as food or as a dietary supplement. While food has a 0 per cent value added tax rate, dietary supplements have a 16 per cent value added tax rate. This can cause complications because tax and customs authorities may have different criteria to the importer or manufacturer for classifying the product, and this can be avoided or solved by a Ruling Request by COFEPRIS.

b COFEPRIS takes special care with dietary supplements, publishing a list of content limits for certain substances and a list of prohibited ingredients. This makes dietary supplements in the Mexican market a much more complex issue than in other jurisdictions.
Alcohol and tobacco, as products considered to present a high risk to public health, are treated differently, with a more extensive regulatory framework, and very strict controls and surveillance to avoid counterfeiting and smuggling, as well as to guarantee compliance with labelling and advertisement regulations.

**Controlled substances**

Facilities require a licence to produce, manage, store and distribute controlled substances, which include active substances for medicines and diagnostic agents, and toxic substances for industrial use.

**Chemicals**

Pesticides and fertilisers do need pre-market clearance by COFEPRIS, however, favourable opinion of the Ministries of Agriculture, Livestock and Fishery, and the Ministry of the Environment and Natural Resources is required, which usually takes longer than the terms set by the law.

**ii Non-clinical studies**

Non-clinical studies are regulated by the RCR Chapter VII and the Mexican Official Standard NOM-062-ZOO (governed by the Minister of Agriculture, Livestock and Fishery) that regulates the technical specification for the production, care and use of laboratory animals. These studies are required to comply with good laboratory practices and secure procurement of animals, storage specifications, feeding, care and conditions to minimise the suffering of animals.

Non-clinical trial should be coherent with the study model, performed in a comparative way either with placebos or the gold standards. *In vivo* and *in vivo* models must allow the characterisation of the safety of the product, with toxicity, teratogenicity and mutability tests to determine the safety and pharmacology of the product.

**iii Clinical trials**

Clinical trials are regulated by the GHL, the RCR, Mexican Official Standards NOM-012-SSA3 for technical aspects to conduct health research in humans, NOM-220-SSA1 regarding the implementation of the pharmacovigilance, NOM-059-SSA1 regarding good manufacturing practice for medicines, the Guidelines for the integration and operation of ethics committees for research and the Ethics Code of the Pharmaceutical Industry.

According to international standards, the process and authorisation of clinical trials in Mexico should:

- be conducted in a licensed health institution;
- be led by a head investigator;
- be provided with non-clinical data backup;
- have the approval and installation of ethics, research and biosecurity committees;
- guarantee consent and legal and personal security for the subjects of study;
- inform reports of adverse reactions;
- organise follow-up meetings with the authority to inform relevant information; and
- import permits of the medicines used in the trial.
Clinical trials must evidence the full pharmacokinetic and pharmacodynamic profile of the product to prove its safety and efficiency.

COFEPRIS accepts non-clinical and clinical trials performed abroad if they comply with Mexican regulation, which is harmonised with international best practices, and in very rare cases the New Molecules Committee will request studies to be performed on members of the Mexican population.

COFEPRIS has certified academic and health institutions to function as third authorised parties to conduct clinical trials and help expedite the process of authorisation when the trials are performed in Mexico.

iv Named-patient and compassionate use procedures

The regulatory framework demands a pre-market clearance for manufacturing, import, distribution and marketing of medicines and medical devices. However, if a patient has been prescribed a product that does not have pre-market clearance in Mexico, COFEPRIS can authorise the import of it in two cases: for personal medical use; and for diseases of low prevalence, judged on a case-by-case basis.

v Pre-market clearance

Medicines and medical devices both need pre-market clearance granted by filing a dossier containing the legal and technical information of the product to COFEPRIS. Even though the processes for both are similar, medicines have a more complex pathway. In both cases, to apply for a pre-market clearance a Mexican legal entity should appear as legally responsible before COFEPRIS to track and respond to any kind of liability.

Medicines

New drugs

New drugs and vaccines should submit:

a administrative and legal information;

b quality and good manufacturing practices information;

c preclinical trials; and

d clinical trials.

Manufacturers of new drugs should attend the New Molecules Committee to present their case. Here it will be determined whether the product requires specific regulatory treatment, or the agency should ask for particular tests or scientific literature; for example, it may be the case that the committee asks that the trials be performed in Mexico – an exception to the rule. In the case of biotechnologies, the applicant also needs to present its case before the biotechnologies subcommittee to analyse the particularities of the product.

Generic drugs

Generic drugs should submit:

a administrative and legal information;

b quality or good manufacturing practices information; and

c bioequivalence information.
Orphan drugs

Orphan drugs have a different kind of authorisation process and they do not obtain a pre-market clearance, but recognition as an orphan drug. For an orphan drug dossier the following should be submitted:

- administrative and legal information;
- quality or good manufacturing practices information;
- preclinical trials and clinical trials that are reviewed case by case, as complications may appear with low prevalence diseases; and
- recognition as an orphan drug from a recognised foreign entity.

Medicines dossiers

Medicines dossiers can be filed by:

- the conventional application at COFEPRIS – submitting the dossier directly to COFEPRIS;
- a third authorised party application – a private entity certified by COFEPRIS that reviews and assesses the dossier before the submission to COFEPRIS and issues a report; when the dossier complies with the regulatory requirements it is submitted for a fast-track authorisation process; or
- the equivalence application – the applicant submits a pre-market clearance from a recognised foreign entity as part of the dossier to fulfil the compatible requirements, and this has a fast-track authorisation process.

Medical devices

A medical devices dossier should contain administrative and legal information, and quality or good manufacturing practices information. Filing an application follows the same pathway options mentioned for medicines.

vi Regulatory incentives

From 2011 to 2018, COFEPRIS made a significant effort to simplify the regulation process, accelerating the implementation of updates to regulations and the creation of new ones by:

- eliminating the prior local manufacturing plant requirement to apply for a pre-market clearance for medicines;
- the implementation of a fast-track authorisation process as the equivalent application for medical devices and the third authorised party applications;
- the deregulation of more than 2,000 medical devices;
- the issue of the Biotechnologies Mexican Official Standard NOM-257-SSA1; and
- the issue of the Pharmacovigilance and Technovigilance Mexican Official Standard NOM-220-SSA1.

Linkage and data exclusivity

Article 47 bis of the Industrial Property Law Rules and Article 167 bis of the RHS regulates the linkage provisions in Mexico. A generic drug pre-market clearance application must include evidence that the application does not violate a patent. When the dossier does not prove this, COFEPRIS must consult the Mexican Institute for Industrial Property about a
patent ownership or licence before granting a pre-market clearance for a generic drug, to protect industrial property rights. Linkage is applicable for substances and active ingredients, but not for manufacturing process or formulation.

Articles 82 and 86 bis of the Industrial Property Law and Article 167 bis of the RHS regulate the data exclusivity provisions in Mexico, referring the time frame of its protection to the commitments of international treaties Mexico has signed.

Linkage and data exclusivity grant a reasonable degree of legal certainty, however, there are some grey areas about when and how this protection applies, as Mexican legislation does not provide a fixed number of years for data exclusivity protection. There are a lot of opportunities to improve the regulatory framework.

Mexican regulation does not have market exclusivity or patent extension.

vii Post-approval controls

Pre-market clearances for medicines and medical devices are valid for five years, with the possibility of filing a renewal application every five years indefinitely, as long as the regulatory requirements are fulfilled. At any time during which a pre-market clearance is valid, COFEPRIS retains the legal power to vary or revoke this authorisation.

Article 380 of the GHL establishes that a pre-market clearance can be revoked if the product represents a risk to human health, any of the product characteristics has changed from the ones authorised, or the holder failed to comply with any of the applicable regulations or obligations set forth in the relevant authorisation.

While a pre-market clearance is valid, the holder may apply for the revocation or a variation of his or her authorisation. It can be a variation of the legal and administrative information (e.g., corporate name) or a technical variation (e.g., process or formula). Technical variations are much more complicated to review as they may mean changes in the active ingredients or the manufacturing site, which would extend the time frame for approval several months longer than established in the RHS.

NOM-220-SSA1 on pharmacovigilance and technovigilance systems obliges the holder of an authorisation, the health institutions and the health professionals that use the product to report any adverse events to COFEPRIS. If the potential risk of the product is proved, the Risk Analysis Department of COFEPRIS may issue a health alert and the Surveillance Department may initiate a recall process.

The pharmacovigilance and technovigilance systems are also a requirement for the application of a pre-market clearance, so the systems and responsible officer exists and is appointed by the holder of the authorisation from day one.

In some cases, if the New Molecules Committee determines during the assessment of the pre-market clearance application, a product may be obliged to perform a Phase IV clinical trial, also known as pharmacovigilance studies. This obligation is included in writing when the authorisation is issued.

viii Manufacturing controls

Both medicines and medical devices need a sanitary officer to be responsible for the facility and products before COFEPRIS. This officer must be a health professional with a licence to practise (e.g., a chemist).

Medicines manufacturers are obliged to have a health licence issued by COFEPRIS to manufacture medicines in Mexico. To obtain this licence it is mandatory to have previously obtained a good manufacturing practices (GMP) certificate. The manufacturing plants
should have a quality management plan that satisfies the standards for the facilities and manufacturing process set in Mexican Official NOM-059-SSA1 of good manufacturing practices of medicines, then the plant must ask for an inspection visit by COFEPRIS, and if it fulfils the regulatory requirements, the agency issues the GMP certificate. After the issuance of the GMP certificate the plant can continue with the application for the licence.

Medical devices require a notice of operation instead of a licence, where the plant should appoint its sanitary officer. But having a GMP certificate is mandatory in compliance with the Mexican Official NOM-241-SSA1 on good manufacturing practices of medical devices, following the same procedure mentioned for medicines.

ix Advertising and promotion
The advertising of medicines and medical devices is regulated by the RHA. The main requirements for advertising medicines and medical devices are: (1) the information should not be misleading; (2) the information provided should be substantiated; and (3) the information should be consistent with the terms authorised in the pre-market clearance.

The pre-market clearance for each medicine indicates whether the product has authorisation to be advertised to the general public or if its advertisement is limited to health professionals. This advertisement authorisation is based on the classification made by the risk analysis of the product in the GHL. While over-the-counter medicines (OTCs) can be advertised to the general public, prescription medicines are limited to advertisements targeted only at health professionals.

Medical devices pre-market clearance also indicates whether the product has authorisation to be advertised to the general public or if its advertisement is limited to health professionals. In this case, the general rule is that the authority indicates that medical devices advertisement is limited to health professionals, except if at the moment of filing the pre-market clearance application the applicant requests to be authorised to advertise the product to the general public and includes evidence that proves the advertisement does not present a risk to public health.

Promotional activities are regulated by the RHA and by internal industry regulations, the Code of Ethics of the Pharmaceutical Industry and the Code of Good Promotional Practices of the Pharmaceutical Industry.

Advertisement to the general public requires a permit granted by COFEPRIS, while for advertisement to health professionals, only notice needs to be filed before COFEPRIS. Promotional activities also only require a notice.

x Distributors and wholesalers
The distribution and wholesale of medicines and medical devices requires the filing of an operation notice and the appointment of a sanitary officer to be responsible before COFEPRIS, with the qualifications mentioned above. Only in the case of controlled substances and biologics is a health licence required. This notice of operation has indefinite validity and can be subject to variations as requested by the holder.

xi Classification of products
Article 226 of the GHL classifies medicines as follows:
• prescription medicines that require barcoded medical prescription or a special permit from the Health Ministry (e.g., controlled substances);
• prescription medicines that require leaving the prescription at the pharmacy and recording the transaction in the pharmacy control books;
• prescription medicines where the prescription can be refilled three times, and is then left at the pharmacy. The prescription needs to be sealed and recorded in the control book for each refill;
• prescription medicines that can be refilled as many times as the doctor indicates in the prescription;
• medicines that do not require prescription, but their marketing is limited to pharmacies only; and
• medicines that do not require prescription and can be sold in commercial establishments other than pharmacies (e.g., OTCs).

Article 83 of the RHS classifies medical devices as follows:
• products generally known in medical practice, whose security and efficiency is proved and that generally do not enter the body;
• products generally known in medical practice that may have some variations and stay up to 30 days inside the human body; and
• innovative or recently designed products in medical practices or products that stay inside the human body for more than 30 days.

xii Import and export
The Ministry of Economy and the Ministry of Health issued a joint resolution indicating the classification and tariff code of merchandise and products whose import or export is subject to health regulation. This resolution specifies the legal requirements for each product: (1) no importation permit, only pre-market clearance; (2) only importation permit, no pre-market clearance; and (3) both importation permit and pre-market clearance.

There are five types of import permits:

a for commercial purposes;
b for personal use and low prevalence diseases;
c for research or academic purposes;
d temporary maquila importation; and
e temporary importation for conventions.

The importer of a medical product must be expressed in the pre-market clearance and recorded in the National Importers Registry.

Generally exports do not required a permit, except for some biologics such as tissues and blood, and controlled substances. To promote exports, COFEPRIS also issues certificates of free sale and special GMP for exportation purposes.

xiii Controlled substances
As risk level is the main criterion of health regulation in Mexico, controlled substances are highly regulated with regard to the traceability of the substances.

Manufacturing facilities require a health licence and mandatory visit from COFEPRIS to guarantee the safety and traceability of the substances. Transportation, storage and retail is required to be recorded in auditable books, and acquisition, imports and exports require special permits from the authority.
xiv Enforcement

The COFEPRIS Surveillance Department is in charge of the regulatory enforcement, which it carries out through inspection visits. There are two kind of visits: ordinary visits, which are scheduled surveillance visits on facilities selected by lottery to keep a watch on the industry; and extraordinary visits, which are actioned by a health alert from a pharmacovigilance or technovigilance report or a complaint from a consumer or competitor.

These procedures comprise four stages: (1) the inspection visit to collect information and evidence of potential regulatory violations, stated in inspection minutes, which may include the imposition of safety measure from COFEPRIS such as product seize; (2) the assessment of the inspection minute and first resolution, confirmation of safety measures if applicable and ordering corrective actions; (3) response by the subject of the inspection with the corrective actions; and (4) final assessment of the authority where it considers the violations and corrective actions to apply a sanction if considered necessary.

III PRICING AND REIMBURSEMENT

Mexico’s economic model is an open market, however, the pricing for the private market has a system of maximum price limits for medical products. Article 9 of the Federal Competition Law (FCL) and Article 31 of the GHL indicates that the Ministry of Economy, with the assistance of the Ministry of Health, will fix the maximum prices permitted for medical products. These limits are determined with information provided by the industry, and should be printed in medical products labels. This obligation is supervised by the Consumer Protection Agency.

Pricing for the public market works in a different way. The Ministry of Health has a Price Negotiator Commission (NC) that coordinates and negotiates on behalf of all federal public buyers as a unified body the prices of medical products with the industry on an annual basis. The NC’s purpose is to consolidate the federal government’s need to procure savings through a large-scale negotiation, however, this is also a maximum price limit system since the real purchase prices are determined at public bids, which are generally subject to lower prices resulting from discounts offered by the bidders with the intention to win the public bids and be awarded with the contracts.

Mexico’s health system does not work by reimbursement, but by a public procurement model. Mexico’s procurement system is regulated by the Federal Law of Procurement, Leases and Services for the Public Sector (FLPLS). The FLPLS, implemented by the buying entity and supervised by the Anticorruption Ministry, established three processes for public procurement: (1) national and international public bids; (2) at least three bidders’ invitations (e.g., applicable when the bidders are government entities or public universities); and (3) direct awards (e.g., patent products).

As commented in the introduction, to participate in the public procurement process the products are required to be listed in the National Formulary issued by the GHC and in some cases by other entities such a the army or the Mexican Social Security Institute.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

There are three stages for legal remedies to challenge a resolution from a health authority:

- A reconsideration remedy also known as administrative appeal. This remedy is filed before the same authority that issued the challenged resolution.
A nullity trial, filed before the Federal Court for Administrative Law, which now has a specialised chamber for intellectual property rights and a specialised chamber for regulatory cases. This evolution is creating judicial professionals with experience, knowledge and understanding, able to solve complex medicines and medical devices cases.

An amparo trial before a Federal District Court or before a Federal Collegiate Court. If the Mexican Supreme Court considers that a case is highly relevant for the country and involves constitutional matters, it can attract the amparo trial.

V FINANCIAL RELATIONSHIP WITH PRESCRIBERS AND PAYERS

The National Chamber of the Pharmaceutical Industry and the Mexican Association of Innovative Medical Devices Industries have issued internal ethics codes to regulate a healthy relationship between the industry and prescribers and payers to prevent any kind of influence and promote transparency and responsible prescription. These codes are the Promotion Good Practices Code and the Interaction with Healthcare Professionals Code.

In addition, in the case of prescribers and payers from the public health system, it is important to consider the Administrative Responsibility Law for Public Officers, as any kind of influence to prescribe or pay a product or treatment may be considered an act of corruption.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

There is no specific legal framework for special liability or compensation systems in Mexico. However, damages and medical assistance can be demanded by a civil claim.

The clinical trials regulations commented on above in Section II.ii establish that health institutions and sponsors should be responsible and assist if a participant in a clinical trial suffers a disease or medical condition because of the clinical trial. This regulation also establishes that the budget for clinical trials should include a budget heading in case medical assistance and damages payment is necessary.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

In recent years the Mexican competition agency has increased its activity in this market, even though the number of investigations and trials is not significant. There are a few cases with relevant public and media impact regarding the distribution of medicines, medical devices and health services with collusion of participants to partition the public market into regions for local public bids.

At the moment there are no pharmaceutical or medical devices companies involved in these kinds of investigations, distributor and health service companies being the main target. However, the competition agency has requested information from pharmaceutical companies to understand and allocate risks in the market to increase the agency roll.
ii Transactional issues

Life sciences is a highly regulated sector in Mexico, so regulatory due diligence has particular relevance as the health authorisations of the company have great impact on the value of the deal, and the level of compliance with the health regulation can help measure the level of risk of the transaction.

It is important to distinguish between transfer of shares and transfer of assets. Transfer of shares has minimal or no implications for government contracts, administrative procedures and authorisations by COFEPRIS, as long as there are no changes in corporate names. But transfer of assets and changes in corporate names implies the transfer of all regulatory authorisations involved in the deal. This requires filing individual requests to modify the terms of each authorisation of products or facilities, etc.

This means that the regulatory strategy is essential to plan the time frame of a transaction. It is highly recommended to inform COFEPRIS if the regulatory transfer has a significant volume and involves the agency in a conjunct plan to transfer the assets or change the names in the regulatory authorisations.

Regarding the transfer of assets and regulatory authorisation, intellectual property should be taken into account, as depending on the nature of the operation, patents or licence agreements could be requested by the authorities.

VIII CURRENT DEVELOPMENTS

The major current development in Mexico’s life sciences sector is the legalisation of cannabis for medical and industrial use. This started in April 2017 with a legal reform to the Federal Criminal Code to decriminalise the production, distribution, marketing and use of cannabis for medical use and scientific research purposes, and adjunct legal reform to the GHL to eliminate the prohibition of cannabis, and changing its classification from a controlled substance with no therapeutic use to a controlled substance with proven therapeutic use.

In October 2018, COFEPRIS finally issued the Guidelines for the Regulation and Control of Cannabis and its Substances for Medical and Scientific Use (the Cannabis Guidelines). The Cannabis Guidelines open two new possibilities in Mexico: (1) the use of cannabis for medical or scientific research under an authorised research protocol; and (2) the pre-market clearance of a variety of products with cannabis.

Through the Guidelines, COFEPRIS can authorise the production, distribution, import and marketing of products with cannabis with a limit of 1 per cent of tetrahydrocannabinol (THC). There are two classifications of products: (1) new drugs with cannabis; and (2) products with cannabis for industrial use, including food, beverages, dietary supplements and cosmetics.

To apply for a pre-market clearance for a new drugs with cannabis, the solicitor needs to follow the regular filing process for new drugs pre-market clearance application. However, these applications are on hold, as the Cannabis Guidelines establish a requirement for the research protocols authorisation to be recorded at the National Cannabis Research Registry, which has yet to be created.

The authorisation for products with cannabis for industrial use is a much simpler procedure that requires a sanitary evaluation where COFEPRIS makes a product assessment and classification by only reviewing the label, intended use, formula and analysis certificates that confirm the products do not exceed the THC percentage permitted.
This is a big regulatory breakthrough that opens new possibilities and business opportunities. However, the federal government’s new administration has already filed a legislative project to legalise the use of cannabis in a much broader sense, including for recreational use, with the creation of a Cannabis Special Agency to regulate and control it, so it is expected that cannabis regulation will change in the near future.
I INTRODUCTION

Norway is a party to the Agreement establishing the European Economic Area (the EEA Agreement), the purpose of which, essentially, is to enable the European Free Trade Association (EFTA) states – Norway, Iceland and Liechtenstein – to participate in the single market of the European Union. By implication, all EU legislation concerning the single market, in particular rules on free movement, competition law, state aid and relevant secondary legislation, including within the medical field, applies for all practical purposes as if Norway were an EU Member State.

The competent authority in Norway in relation to medicines is the Norwegian Medicines Agency (NoMA), which is subordinate to the Ministry of Health and Care Services. NoMA is entrusted with all tasks related to assessment of medicines, administration of the pharmaceutical distribution chain, pharmacoeconomics, supervision and provision of medical information to prescribers, the industry and the general public.


NoMA is also responsible as competent authority for medical devices. NoMA thus has administrative and advisory responsibilities related to the relevant medical devices legislation, in addition to supervisory authority over manufacturers, distributors and notified bodies. NoMA primarily derives its powers from the Act on Medical Devices of 1995 (the Medical Devices Act) and the Regulation on Medical Devices of 2005 (the Medical Devices Regulation), issued pursuant to the Medical Devices Act and implementing relevant secondary EU legislation, including Directive 90/385/EEC, Directive 93/42/EEC, Directive 98/79/EC, Regulation (EU) 2017/745 and Regulation (EU) 2017/746.

All major international pharmaceutical manufacturers are represented in Norway. At the distribution level, there are primarily three major wholesalers providing a full range of products to the market – each of them vertically integrated with its own pharmacy chain. There is a small number of independent wholesalers and pharmacies. In general, medicines are only dispensed by retail pharmacies and hospital pharmacies. Grocery stores, petrol stations, etc., are allowed to distribute a restricted list of over-the-counter (OTC) products.
Medical devices are sold in a variety of ways – to hospitals, private clinics, pharmacies, through pharmacies directly to patients, etc. – depending on the nature of the product. For the sale of medical devices, in particular to Norwegian hospitals, having a sales organisation in Norway, or cooperating with a local distributor or agent, is often necessary to provide customer service and know-how in relation to local public procurement procedures.

II THE REGULATORY REGIME

i Classification

A substance, drug or preparation is classified as a medicine pursuant to the Act on Medicinal Products if it either (1) purports to be suitable to prevent, heal or alleviate disease, disease symptoms or pain, or modify physiological functions in human beings or animals; or (2) can be used or given to human beings or animals to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action, or to detect disease. The definition of medicines comprises prescription, OTC, herbal, plant-based and homeopathic medicines.

Notably, products may be included in the definition simply by being presented as having a certain effect (the first alternative), even if it is not a conventional medicine. In borderline cases, the assessment will normally take into account factors such as product name, packaging, administration mode, claims and end user. Similar products that are particularly susceptible to being covered by the definition include food supplements, cosmetics, feed, biocides and medical devices. Whether a product is included in the definition of medicines pursuant to the second alternative is normally based on an overall assessment of relevant factors, such as the product’s composition, pharmacological characteristics, administration mode and the risk it poses in use.

Medical devices are defined as any equipment, apparatus, assistive device, material or any other object used alone or in combination, including with necessary software, on human beings to diagnose, prevent, monitor, treat or alleviate disease, injury or disability; examine, replace or amend anatomy or a physiological process; or prevent pregnancy. Borderline cases often concern the class of risk rather than how they are defined as medical devices. NoMA cooperates with relevant European authorities in borderline cases.

ii Non-clinical studies

Non-clinical studies are subject to the general requirements in relation to research as embodied in the Act on Medical and Health Scientific Research of 2008 and the Act on Research Ethics of 2017 – to the extent that they involve testing on human biological material, individuals’ health information or in other ways involve human beings. If so, prior approval from the relevant regional health scientific research ethics committee (the Ethics Committee) is required. Research involving surplus embryos or cloning must further observe requirements and restrictions embodied in the Act on Biotechnology of 2003.

Non-clinical studies involving research on animals require prior approval from the Norwegian Food Safety Authority pursuant to the Regulation on the Use of Animals in Research of 2015. Research activities must comply with the requirements embodied in the regulation and must safeguard animal welfare.
Clinical trials are also subject to the general requirements in relation to research, as mentioned in Section II.ii – in addition to specific requirements laid down in the Regulation on Clinical Trials of 2009 as regards medicines, and the Medical Devices Regulation as regards medical devices.

All clinical trials for medicines require additional prior approval from NoMA, whereas clinical trials for medical devices require additional prior approval from NoMA when the device is not already CE-marked or when it is to be used outside the scope for which it is CE-marked.

It is generally required that all clinical trials are conducted in accordance with good clinical practices and the Declaration of Helsinki – Ethical Principles for Medical Research involving Human Subjects 1964. This implies, *inter alia*, that clinical trials must be scientifically based and governed by ethical principles. Subjects may only be enrolled based on prior and informed written consent. Special provisions apply to minor subjects and subjects who do not have the ability to give consent, or whose ability to give consent is reduced.

Subjects must be insured in relation to all types of clinical trials. In many situations, this requirement may be met by way of mandatory insurance schemes, such as the Norwegian Drug Liability Insurance for medicines and the Norwegian System of Patient Injury Compensation (NPE) for medical devices (see Section VI). Adverse effects and incidents must be reported to NoMA.

It is a requirement that the sponsor of the clinical trial, or the producer of the medical device, is domiciled in the EEA or has an appointed representative in the EEA.

Medicines without marketing authorisations (MAs) in Norway may, under certain circumstances and by way of exemption, be dispensed to patients.

Prescribers may apply to NoMA for an exemption of this kind for individual patients. A number of conditions must be fulfilled, in particular that use of the medicinal product in question is medically justifiable, for example, because no authorised medicine meets the individual’s medical need.

NoMA may also approve use for a group of patients of non-authorised medicines in the context of compassionate use programmes, provided certain conditions are fulfilled, including that the programme only concerns patients with life-threatening, long-lasting, recurring or seriously disabling diseases, and that the relevant patients cannot be included in clinical trials and will not benefit from treatment with authorised medicines. It is for the manufacturer and the prescriber to decide on pricing. Medicines shall be dispensed to patients free of charge. Reporting obligations apply to, *inter alia*, adverse effects and amendments to the protocol for the programme.

Commercial distribution of medicines in Norway generally requires prior approval in the form of an MA from NoMA. Prescription medicines further need price approval from NoMA prior to being marketed.

There are four procedures available for obtaining an MA in Norway: centralised procedure; decentralised procedure; mutual recognition procedure; and national procedure.
When an MA is first granted by another EEA Member State or the European Commission with effect also for Norway, a national MA issued by NoMA is nonetheless necessary. Special rules and procedures apply for herbal, plant-based and homeopathic medicines.

Generic products follow a somewhat simplified procedure in as much as they may rely on the toxicological, pharmacological and clinical documentation of a patented product – provided that patent protection, regulatory market protection and regulatory data protection periods have all expired. By contrast, it is necessary to document bioequivalence.

It is a requirement that the MA holder either resides within the EEA or has appointed a representative residing within the EEA.

The first MA is generally valid for a period of five years, after which it needs renewal. The second, renewed MA is normally perpetual.

For commercial distribution of medical devices in Norway, it is required that the manufacturer demonstrates compliance with all fundamental requirements applicable to the product in question, also known as ‘declaration of conformity’, and that the product bears a CE mark to evidence compliance. Applicable requirements depend on risk assessment and classification of the product in a certain risk class. Further, manufacturers or their representatives must, if they have a Norwegian business address, register themselves and the medical devices they market in the Norwegian Register for Medical Devices.

vi Regulatory incentives

Patents may be granted for medicines and medical devices for 20 years from the date of filing, as provided in the Patents Act.

Norwegian law concerning supplementary protection certificates (SPCs) is harmonised with EU directives. SPCs may be obtained for medicines in Norway. The duration of an SPC is limited to a maximum of five years without the possibility of extension.

Norway implemented Regulation (EC) No. 1901/2006 on medicinal products for paediatric use in 2017. Once paediatric studies have been performed according to an approved, implemented paediatric trial protocol, the holder may be given a six-month extension of the supplementary protection for the medicinal product.

An original medicine has automatic data and market exclusivity based on its MA for the first application in the EEA. This protection is a time-limited right to prevent others from basing its application for an MA on the original medicine producer’s submitted documentation. If an MA was applied for the reference product in Norway after 1 November 2005 but before 12 January 2010, the document and market protection is 10 years. If an MA was applied for the reference product in Norway after 12 January 2010 or in the EEA after 1 November 2005, the reference product enjoys data protection for eight years, and market protection for 10 years. The protection may be extended by one year if an MA is applied for regarding a new indication of significant clinical importance during the document protection period (i.e., the first eight years).

It follows from Section 10 of the Act on Medicinal Products that, in special cases, exemptions to the requirement for an MA may be given. The exemption may be used for fast-track use of specific medicines (e.g., in situations of urgency), but the exemption is not much used in practice.

Medical devices may be protected through the Patent Act, but there is no SPC.

According to Section 47(1) of the Patent Act, a compulsory licence for exploitation of a patent may be obtained when it is deemed necessary for ‘important public interests’.
The provision applies in extraordinary situations, for example where there is the threat of an epidemic and the situation may only be prevented or improved through the exploitation of the invention.

vii Post-approval controls

Post-approval control requirements in Norway for medicines are largely harmonised with Directive 2001/83 and subsequent amendments thereto. The MA holder is obliged to implement and manage a pharmacovigilance system and to employ, at all times, a sufficiently qualified person who is responsible for system and risk management, as further specified in the Regulation on Medicinal Products. The qualified person must be domiciled and work within the EEA and must be reported to NoMA. All suspected adverse effects must be registered, and suspected serious adverse effects must be reported to the EudraVigilance database. Periodic safety reports must be submitted to the Periodic Safety Update Report repository at intervals stated in the MA, and NoMA must be notified of variations and amendments to the documentation or product information in accordance with Regulation (EC) No. 124/2008. Transfer of an MA from one legal entity to another must be reported to NoMA and must follow a certain procedure.

A medical device manufacturer domiciled outside the EEA is obliged to appoint a representative domiciled within the EEA. Any person who manufactures, distributes, owns or uses medical devices has an obligation to report deviations, errors and failures to NoMA, which also requires that a system for post-market surveillance is established.

viii Manufacturing controls

Manufacturing of medicines and any other activities involving packaging, repackaging, labelling, relabelling and release, generally require a manufacturing licence from NoMA. An exception is made, if certain conditions are met, for simple preparation or packaging of medicines in pharmacies, hospitals and other health institutions.

Manufacturing must take place in compliance with the EU Good Manufacturing Practice guidelines. Thus, certain requirements regarding, inter alia, having suitable production facilities, suitable production equipment and a sufficiently qualified person approved by NoMA, must be met. Requirements under the Regulation on Manufacturing and Import of Medicinal Products are harmonised with Directive 2003/94/EC.

ix Advertising and promotion

Advertising of medicines is regulated in the Act and Regulation on Medicinal Products and is permitted only for drugs that have been granted an MA. Advertising of medicinal products to the public is only allowed for OTC products and then only if examination or treatment by a doctor, dentist or veterinary surgeon is not a prerequisite. Prescription products may, therefore, only be advertised to healthcare professionals.

Information in the marketing material must be true, accurate, relevant and not misleading. Advertising or promoting a product that is not classified as a medicine but is recommended as a means of preventing, healing or alleviating illness, sickness symptoms or pain or affecting physiological functions, is prohibited. The purpose is to prevent undocumented claims about medical efficacy in advertising of products that are not medicines.
In addition, a Code of Conduct, compiled by the Norwegian Association of Pharmaceutical Manufacturers, applies to any kind of communication between manufacturers, suppliers and healthcare professionals or the public. It is based on the code adopted by the European Confederation of Pharmaceutical Industries and Associations (EFPIA).

The Medical Devices Act does not contain specific regulations on advertising and promotion but, as a general principle, all claims used in advertising and promotion should be true, accurate, relevant and not misleading, and the producers must be able to substantiate the claims.

x Distributors and wholesalers

The import, purchase, receipt, storage, delivery, distribution, sale and export of medicines are considered wholesale activities and require a wholesale licence issued by NoMA. Regular pharmacy activities are not defined as wholesale.

The Wholesaler Regulation of 1993 sets out the detailed requirements to be met by wholesalers. This includes requirements for good distribution practice (GDP), issued by the European Commission. In addition to suitable premises and equipment, there is a requirement of competence for the person who is responsible for the wholesale business of pharmaceuticals. Wholesalers must be able to deliver drugs within 24 or 48 hours anywhere in the country.

Wholesalers may sell medicines directly to nursing homes, professional end users of veterinary drugs and hospitals.

As a main rule, only pharmacies may sell medicines directly to consumers. A licence is required to own and run a pharmacy. Nonetheless, the Regulation on Sale etc. of Certain Non-Prescription Medicines Outside Pharmacies of 2003 (the LUA Regulation) allowed for the sale of OTC products from outlets other than pharmacies.

As of 1 January 2016, Norwegian pharmacies that are registered and approved by NoMA have been allowed to sell prescription and OTC products online.

xi Classification of products

To determine whether the Act on Medicinal Products applies to a given product or substance, it is necessary to classify it.

For medicines, there are strict requirements regarding quality, safety and efficacy. Moreover, special rules apply to import and sale. A number of products are similar to medicines and particularly susceptible to being defined as medicines, typically supplements, feed, cosmetics and medical devices. See Section II.x.

Norwegian legislation on classification of medicines is harmonised with EU legislation and implemented into the Regulation on Medicinal Products. NoMA has the authority to decide whether a substance is a medicine in borderline cases (see Section II.i). With legal basis in the LUA Regulation, NoMA has issued a list of OTC products that can be sold outside pharmacies, as addressed in Section II.x.

Pursuant to the Medical Devices Act and Regulation, medical devices are classified as active implantable medical devices, in vitro medical devices or other medical devices. In vitro medical devices are subclassified in List A, List B and self-test products. Other medical devices are subclassified in one of four risk classes (see Section II.x).
Norway

xii  Imports and exports
The import and export of medicines generally require a licence issued by NoMA. Imports from the EEA to Norway and export activities are defined as wholesaler activities pursuant to the Wholesaler Regulation and will, in the first instance, require a wholesaler licence issued by NoMA (see Section II.xi). Some exceptions apply to holders of manufacturing licences. First, a manufacturing licence issued by NoMA includes the right to engage in, *inter alia*, import and export activities in relation to the medicines covered by the manufacturing licence. Second, holders of manufacturing licences issued in another EEA country may import medicines to Norway that are covered by the manufacturing licence, simply by notifying NoMA.

As of 1 October 2015, significant restrictions have applied to imports of medicines by private persons. Only OTC products may be imported and only from another EEA country for personal consumption and only on certain conditions, including that the medicine has a valid MA in Norway and that the imported quantity does not exceed three months’ consumption. Whether conditions are fulfilled, for example, whether a medicine is an OTC product, depends on the assessment in Norway.

Imports to Norway directly from countries outside the EEA generally require a manufacturing licence, implying that medicines must be subjected to full inspection prior to release of the products for marketing in Norway. This again implies that the importer must engage a sufficiently qualified person to undertake necessary inspections and to release medicines for sale. Wholesalers with a wholesaler licence may escape the requirement for a manufacturing licence in the case of imports from a country outside the EEA, provided that the exporting country is a member of the Pharmaceutical Inspection Co-operation Scheme or has entered into a mutual recognition agreement with Norway. Medicines manufactured outside the EEA, but released in another EEA country, may be imported without new inspection and new release in Norway.

The Medical Devices Act and Regulation do not require specific import and export licences.

xiii  Controlled substances
Manufacturers, wholesalers and others who handle medicines classified as narcotics or psychotropic substances need a manufacturing, import or wholesale licence (as the case may be) that specifically includes the substance in question. Further, imports or exports of a controlled substance require a special licence (drug certificate) for each shipment. The processing time for issuing a drug certificate is up to seven working days after NoMA receives the application.

Transport, storage and handling of controlled substances shall be conducted in a safe and secure manner and in compliance with the Wholesaler Regulation and the Regulation of Manufacture and Importation of Pharmaceuticals of 2004. Businesses that import or export controlled substances shall keep records of the last quarterly importation and exportation of the substances that require certificates, and of any certificates that are not used.

xiv  Enforcement
NoMA is the national administrative and supervisory body for medicines. It is responsible for monitoring and enforcing the Act on Medicinal Products. NoMA, *inter alia*, supervises clinical trials, manufacturers, importers, wholesalers and pharmacies, and the advertising of medicines. It also monitors controlled substances, including narcotics. NoMA may demand all information necessary for its supervision and decision-making.
The Council for Drug Information is a self-policing body established by the pharmaceutical industry. The Council shall ensure that all drug information and marketing to healthcare professionals and the public are in accordance with the Code of Conduct mentioned in Section II.ix. The Council acts on delegated authority from NoMA. Anyone who holds an MA is obliged to send a copy of all written advertising, regardless of the platform used, to the Council. The Council for Drug Information may issue coercive fines of up to 300,000 kroner for violations of the Code of Conduct.

In the case of repeated violations of advertising rules, NoMA may impose a ban on advertising for individual medicines.

At the outset, NoMA is responsible for the enforcement of the legislation relating to medical devices. For electromedical devices, the Directorate for Civil Protection is responsible for supervision and enforcement. Both supervisory authorities may obtain the information necessary and may require the person who produces, imports or markets a medical device to submit samples needed to carry out their investigations. If the medical devices potentially endanger public health, patients, users or any other persons’ health or safety, or the necessary documentation is not obtainable, the supervisory authority shall take all necessary measures to withdraw the equipment from the market, prohibit or restrict the sales or use of it, and may also issue coercive fines.

III PRICING AND REIMBURSEMENT

The rules for determining, controlling and adjusting the prices of pharmaceuticals are found in Chapter 12 of the Regulation on Medicinal Products. NoMA provides detailed guidelines for pricing.

Non-prescription medicines and veterinary medicines are not subject to price regulations.

NoMA stipulates maximum sales prices to pharmacies (AIP) for prescription products for human use. AIP is set as the average of the three lowest market prices for the product in a variety of reference countries. Reference countries included in price comparison are Austria, Belgium, Great Britain, Denmark, Finland, Germany, Ireland, the Netherlands and Sweden. There are exceptions to the main rule, for example if the price turns out to be exceptionally low. AIP may be subject to adjustment in the case of changed circumstances or new information.

Maximum sales prices that the pharmacies may charge the patient equals AIP plus a certain maximum gross profit, which is also determined by NoMA.

A ‘step price scheme’ was introduced in 2005 to reduce governmental and patient medicine costs. In the step price system, the price of a medicine is reduced in stages, with fixed cut rates once the medicine’s patent protection expires; it becomes subject to generic competition and is included in NoMA’s list of interchangeable medicines. The starting point for calculating the step price is the maximum AIP for the original product the moment the first competing generic equivalent is launched.

The National Insurance Scheme reimburses costs for medicines and medical devices used outside institutions according to the National Insurance Act of 1997. The purpose is to ensure access to effective and essential medicines irrespective of users’ financial situations. Reimbursements are either made through the general reimbursement scheme for pre-approved products or based on individual applications.
The holder of an MA may apply for pre-approved reimbursement, which means that the practitioner may prescribe medicines at reimbursed prices directly to the patient. Generally, this is considered favourable for distribution purposes. For medicines included in NoMA’s list of interchangeable medicines, the National Insurance Scheme reimburses the maximum step price for medicines included in the substitution group. Reimbursement may be granted for an indication not covered by the MA, if at least one product within the substitution group has an MA for the indication in question. However, this does not apply if the indication in question is subject to patent or document protection.

If a patient needs a medicine or medical device that is not part of the reimbursement scheme, the patient, or the doctor on behalf of the patient, may apply for individual reimbursement.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES
Generally, under Norwegian administrative law, a party may file a complaint if it believes that a decision by a relevant authority is wrong or may even make an appeal to its superior public authority. Decisions made by NoMA may thus be appealed to the Ministry of Health and Care Services. The deadline for a complaint is, as a general rule, three weeks. A negative decision from the Ministry of Health and Care Services may subsequently be tried by the courts, if challenged by a party with legal interest.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS
As mentioned in Section II.ix, a Code of Conduct, issued by the Norwegian Association of Pharmaceutical Manufacturers, based on the code adopted by EFPIA, applies to any kind of communication between manufacturers or suppliers and healthcare professionals or the public, including the requirement for information and documentation and rules on hidden marketing, promotion in hospitals, gifts, payment of expenses and use of health professionals as consultants. In addition, a number of bilateral agreements concerning interaction have been entered into between the Norwegian Association of Pharmaceutical Manufacturers and certain healthcare personnel organisations.

For medical devices, interaction between the industry and healthcare personnel is generally regulated by relevant organisations’ ethical codes or guidelines and bilateral agreements.

In addition, the Act on Health Personnel generally prohibits healthcare professionals from receiving gifts in this capacity.

Although interaction is largely governed by soft law – with varying sanctions being relevant – deviations from the various rules could be relevant in relation to assessments pursuant to the general rules on anti-corruption, as set out in the Norwegian Penal Code of 2003.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS
Liability for injuries caused by medicines is governed by the special liability regime embodied in Chapter 3 of the Product Liability Act, establishing the Drug Liability Insurance, which pays compensation to patients who have suffered injuries caused by medicines. To finance the Drug Liability Insurance, all manufacturers of medicines marketed or on clinical trial
in Norway are mandatory members of, and must pay an insurance premium to, the Drug Liability Association. If a manufacturer is not a member itself, the relevant importer must be instead. Insurance premiums must be paid. Liability is not contingent upon fault being established, but a causal link between the injury and use of the medicine in question must be demonstrated. The right to compensation may, in certain cases, lapse, for example because of unforeseeable use contrary to given instructions. Claims must be submitted to the NPE, which investigates and assesses the claim on behalf of the Drug Liability Insurance and decides whether compensation should be paid and, if so, what the amount should be. If the NPE rejects the claim, the injured person may normally bring a civil action against the Drug Liability Insurance. Notably, the patient maintains the right to file a claim directly against the manufacturer or importer. If deemed liable, it is nonetheless the Drug Liability Insurance that pays compensation.

Liability for injuries caused by medical devices is governed by the general regime under the Product Liability Act, which essentially stipulates that the injury must have been caused by a product that has a safety defect and therefore does not comply with the safety standard that could reasonably be expected. Again, existence of a causal link is a prerequisite for liability; fault of the manufacturer is not.

Product liability for medicines and medical devices must be in conjunction with – and to some extent overlap – the scheme for compensation of patients who have suffered an injury while receiving healthcare services in public or private healthcare institutions. The system is embodied in the Patient Injury Act of 2001, which also establishes the NPE as being responsible for all case-handling in relation to such claims. The general condition for the right to compensation is that the injury has been caused by failures, for example malpractice or technical failures, in the course of the provision of healthcare, including participation in clinical trials. It is not a requirement that an error has been made. The NPE may, in principle, claim regress and invoke product liability against manufacturers, if the injury is caused by a medicine or a medical device rather than by the provision of healthcare as such. Rejection of claims may be appealed to the Patients’ Injury Compensation Board. If also rejected there, the patient may bring a civil action against the Patients’ Injury Compensation Board or, in principle, the manufacturer.

VII TRANSACTIONAL AND COMPETITION ISSUES

The Competition Act of 2004 is identical to the provisions of Articles 53 and 54 of the EEA Agreement and Articles 101 and 102 of the Treaty on the Functioning of the European Union. It thus prohibits agreements and cooperation distorting or restricting competition and abuse of a dominant position. The provisions of the Competition Act are enforced by the Norwegian Competition Authority, which may also enforce Articles 53 and 54 of the EEA Agreement in Norway. The latter is enforced in parallel by the EFTA Surveillance Authority (ESA) in Iceland, Norway and Liechtenstein.

To our knowledge, there have been no major cases in the life sciences sector concerning infringements of the aforesaid prohibitions on or involving the Norwegian market in recent years, but the Norwegian Competition Authority consistently supports political initiatives aimed at enhancing price competition on medicines.

Both the Norwegian Competition Act, through its regulations, and the EEA Agreement contain merger control regimes mirroring the merger control regime embodied in Regulation (EC) No. 139/2004, implying that above certain turnover thresholds, a
mandatory pre-merger notification system applies. While the ESA and the EU Commission have exclusive competence over mergers with an EFTA or EU dimension respectively, it is, in practice, the EU Commission that handles all relevant cases, since mergers with only an EFTA dimension are very rare. The ESA and the Norwegian Competition Authority handle cases that concern the Norwegian market only. Whether it is one or the other depends on which turnover thresholds are fulfilled. The criterion for prohibiting mergers according to the Norwegian Competition Act is that the transaction constitutes ‘a substantial impediment to effective competition’. We are not aware of transactions in the life sciences sector in recent years that have been prohibited, but some have only been approved subject to remedies.

VIII CURRENT DEVELOPMENTS

The Norwegian Ministry Health and Care Services has proposed to introduce administrative fines as an alternative sanction for infringements of certain key obligations in the Norwegian pharmacy and medicines regulations. An administrative fine is an administrative reaction to illegal conduct. It may be imposed even after the illegal conduct has been terminated. Existing sanctions include warnings, varying degrees of prohibition against certain activities, and punishment in the form of fines or imprisonment. Administrative fines may be contested before the ordinary courts. It is proposed that NoMA shall be able to issue administrative fines to legal entities for the following infringements, even if no physical person is identified as responsible for the infringement:

- non-fulfilment of requirements of certain necessary licences, such as ownership and operating licences for pharmacies, and wholesaler and import licences in the distribution chain;
- non-fulfilment of the requirement for a pharmaceutical manufacturer to ensure updated and correct information about marketed products; and
- non-fulfilment of the requirement for a manufacturer to report interruptions in supply.

Notably, in June 2018, NoMA was given powers to issue administrative fines for any infringement of the Norwegian rules on advertisement for medicinal products. This indicates a general trend to strengthen the enforcement of legislation related to medicines.
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.

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.

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1 María del Carmen Alvarado Bayo is a partner and Ricardo De Vettor Pinillos is a senior associate at Rodrigo, Elías & Medrano Abogados.
2 ‘Drugstore’ is defined as a pharmaceutical establishment dedicated to the import, export, trading, storing, quality control or distribution of pharmaceutical goods, medical devices or sanitary products.
3 La Dirección General de Medicamentos Insumos y Drogas (Digemid) was created by Legislative Decree No. 584 of 18 April 1990.
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 countries4 (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) 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 and Ireland.
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, 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.

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. In August 2018, Supreme Decree No. 021-SA-2018 was enacted. It approved the GMP Manual applicable to local and foreign laboratories of pharmaceutical products (including products under investigation for clinical trials) and will enter into force in August 2019.

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.

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.01 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

5 Approved by Ministerial Resolution No. 413-2015-MINSA on 1 July 2015.
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., 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, horizontal collusive practices and vertical collusive practices.

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 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.

VIII CURRENT DEVELOPMENTS

In May 2018, the Ministry of Health published a draft of the Regulations of Law No. 30681 that regulates the production, importation and commercialisation of cannabis for medical

6 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.

7 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.

8 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.
purposes. The Law is already effective but is inapplicable in practice without the Regulations. Although comments to the published draft Regulations were welcomed until August 2018, the draft has not yet been approved. It is expected that the Regulations will be enacted by mid 2019.

On 15 September 2018, Supreme Decree No. 024-2018-SA – Rules on interchangeability of medicines was enacted. It will become effective in March 2019, and intends to guarantee the efficacy, safety and quality of generic drugs (multi-source pharmaceutical products), provided that they prove to be therapeutic equivalents of the reference product.
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). 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). In the recently adopted draft law, NHF was empowered with new prerogatives to better fight with misuse of the public funding in the medical sector.

THE REGULATORY REGIME

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 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 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 full years following the end of the study and should be made available to the ORMP upon request.
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.

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 2020. The draft amendment of the PhL is ready and should be made available soon.

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:

a   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;

b   medicinal products containing the same active ingredients, dose and form as products that have already obtained MAs in Poland; and

c   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 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, officinal 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 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 new 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).

Classification of products

Under the PhL there are the following categories of dispensing medicinal products:

- those dispensed over-the-counter without a physician’s prescription (OTCs);
- those dispensed on a physician’s prescription;
- those dispensed on a physician’s prescription for restricted use;
- those dispensed on a physician’s prescription, containing narcotic agents or psychotropic substances defined in separate regulations; and
- 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 of some products listed as being in danger of shortages (the list is compiled on the basis of product availability data gathered from the market by the MPI and is published by the MoH). A parallel exporter must file a notification to the MPI 30 days prior to the export of any listed products. The MPI may then issue an objection to the export. If such object 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 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 and the marketing of medical devices. 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 covered by an application must meet the following requirements at the moment the application for reimbursement is filed:

- it must have a valid MA or remain on the market as specified in the PhL;
- it must actually be available on the market (the evidence thereof must be attached to the application); and
- it must be granted an international article number (or EAN) or another code equivalent to an EAN.

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.

### IV 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.

### 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.\(^4\) 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.

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\(^2\) The specific categories are listed in the ARM.

\(^3\) Different levels of payment are possible.

\(^4\) 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.
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 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 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 is the creation of a special fund for adverse post-vaccinal reactions.

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 amendments to the PhL. The PhL is currently subject to a number of legislative works – for example, aiming for implementation of the EU Falsified Medicines Directive and counteracting illegal export from Poland of reimbursed medicinal products. Whereas some of the provisions of the draft law resulted from misconduct by the entrepreneurs operating on the pharmaceutical market in Poland and were justified, others were so detached from the business reality of the pharmaceutical sector that they caused strong criticisms and a wave of comments or requests for change. This has caused delays in adopting draft amendments that have been processed in parallel, including national regulations implementing the Falsified Medicines Directive and delegated regulation of the Commission No. 2016/161.

The draft Act on openness in public life is of less focus now. However, many entrepreneurs still express concerns relating to the possibility of their trade secrets being disclosed as a result of the application of this Act. The most sensitive issue is the possibility of disclosure of the data exchanged during the course of reimbursement price negotiations with MoH, the reimbursement decision itself and the appendix thereof relating to the risk-sharing schemes or the content of agreements between pharmaceutical companies and its contractors. Recently the MoH promised to exclude the aforementioned from the application of the draft law; however, the draft is still not adopted in its final shape.

The big challenge for the Polish legislator, but also for the pharmaceutical companies, could be the application of Regulation (EU) No. 536/2014 on Clinical Trials in 2020. 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 draft law is awaiting its enactment.

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).
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 other things, the marketing authorisation, manufacture, import, export, marketing, labelling, promotion and pharmacovigilance of medicines; it transposes 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

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1 Francisca Paulouro is an of counsel and Inês Caldas de Almeida 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 IIa

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\(^7\) 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.
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. 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.

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. In the same year, the provisions of Directive 2011/62/EU 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, 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 pharmacovigilance 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 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

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.
Distributors and wholesalers

Wholesale distribution of medicines is subject to prior authorisation from Infarmed, the only exception being for holders of manufacturing authorisations in relation to the products covered by those authorisations (similarly to what happens under the Directive).

The granting of such an 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. Until 2013, the technical director had to exercise the functions of this role exclusively and could not perform those functions for more than one company, even if the wholesale distribution premises were the same. Currently, a technical director 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 medicines was approved, closely following Commission Guideline 2013/C 343/01.

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.

In 2013, to address shortages of medicinal products on the Portuguese market, mainly resulting from parallel exports to other EU Member States, the Medicines Act was amended, granting Infarmed powers to list the medicines of which it requires notification prior to exportation (within and outside the European Union). In 2015, Infarmed published a regulation setting out the terms applicable to the notification and to the medicines covered (a list that has been regularly updated), and wholesalers are currently under an obligation to notify in advance all sales of medicines included on this list made to countries outside Portugal. In addition, marketing authorisation holders, wholesalers and pharmacies must notify Infarmed, once a month, of the quantities of certain listed medicinal products that are sold, dispensed, exported or subject to intra-community commerce. The compatibility of this regime with principles of EU law has always been far from clear. In 2016, the European Commission initiated a procedure against Portugal, determining, in its reasoned opinion, that Portugal should suppress unjustified and disproportionate notification obligations because they constitute an obstacle to the free movement of goods within the European Union. To comply with the terms of the reasoned opinion, Infarmed revised its rules in 2017. Although the regime of prior notification was maintained, clear and transparent criteria for the inclusion of medicines on the list in question, and for the list’s revision, were implemented. 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.

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19 Infarmed Resolution No. 524/2017 of 14 June 2017.
The regime governing the brokering of medicinal products under the Medicines Act follows closely that of Directive 2011/62/EU, 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). 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.

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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 No. 33/2018, which came into force on 1 August 2018. ‘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 No. 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.

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).

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.

22 Law No. 33/2018 of July 18.
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.

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:

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;

b an unprecedented concentration of powers within Infarmed; and

c flexibility on applicable rules, considering that several matters are referred to governmental and Infarmed regulations, thus facilitating the swift change of provisions.

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, 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.

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.

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

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25 Ministerial Order No. 246/2015 of 14 August.
26 Ministerial Order No. 284/2016 of 4 November.
27 Ministerial Order No. 92-E/2017, of 3 March.
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 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.

29 Infarmed Resolution No. 80/CD/2017 of 24 October 2017.
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. 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 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,

31 id.
33 Law No. 19/2012 of 8 May 2012.
distorting or restricting competition in the Portuguese market. Competition rules apply to pharmaceutical companies whenever possible, 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.

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 a distinction could be established between the relevant market for the medicine and the relevant market for the wholesale distribution of the medicine;

b 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;

c 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;

d a refusal to deal may also be considered a discrimination; and

e the effects of the refusal to deal on consumer welfare may be disregarded as long as the wholesale distribution market remains competitive.

During 2018, the PCA continued to engage in a nationwide awareness campaign on the need to fight bid rigging, with a focus on awarding authorities. As a result, an increased number of investigations launched by the PCA may be expected, namely regarding the conditions under which public hospitals are supplied.
VIII CURRENT DEVELOPMENTS

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. The recently approved Major Planning Options for 2019\(^{34}\) establish as priorities the continuity of the policies on price revision of medicines, re-evaluation of reimbursed medicines and the increase in the quota of biosimilars and generics. As regards the quota of biosimilars and generics, the State Budget Law for 2019 provides that the government should take further measures to encourage the use of generics with a view to increasing their market share to the level of 30 per cent.

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. The full extent of the changes that this will produce is unknown as yet and will very much depend on the upcoming implementing regulation.

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\(^{34}\) Law No. 70/2018, of 31 December 2018.
Chapter 24

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 property (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.

As of 1 January 2018, the Federal Law of 29 July 2017 on amending certain legislative acts of the Russian Federation on issues of applying information technologies in healthcare systems (the Telemedicine Law) entered into effect.

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

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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:

- capable of contact with the human or animal body, or penetrating into the organs and tissues of the human or animal body;
- 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
- 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.  

Medicines fall into two categories:

- 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
- 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:

- 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;
- 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
- 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

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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:

- details of the drug, its safety and risks;
- the terms of participation;
- what the patient should do in the event of side effects;
- insurance conditions; and
- 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:

- law enforcement officers;
- military officers (except for trials of drugs developed specifically for use in warfare, emergency situations or other similar circumstances);
- pregnant women (except for trials of drugs intended only for pregnant women);
- orphaned children; and
- imprisoned people.

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.

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11 Regulation of the Russian Government of 3 September 2010, No. 683.
12 Article 43 of the Pharmaceutical Law.
13 Article 44 of the Pharmaceutical Law.
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;

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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:

- **a** orphan medicines;
- **b** the first three medicinal products for registration in Russia as generic products; and
- **c** medicines for use exclusively by minors.

The fast-track procedure does not apply to:

- **a** biosimilar medicines;
- **b** original medicines (except for orphan medicines);
- **c** generic medicines, except for:
  - **•** the first three medicinal products for registration in Russia as generic products; and
  - **•** medicines for use exclusively by minors;
- **d** new combinations of previously registered medicines; and
- **e** 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

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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.
Regulatory incentives

Patent protection

Pharmaceutical products may be protected by a substance patent, a process patent or a use patent.\(^\text{19}\) 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, the principle is followed 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.\(^\text{20}\) Furthermore, if the generic MA is filed a significant amount of 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.\(^\text{21}\)

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.\(^\text{22}\)

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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.\(^{23}\)

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).\(^{24}\) Non-compliance with the term results in the MoH dismissing a generic drug application.\(^{25}\)

vii Post-approval controls

The MoH and Roszdravnadzor are competent for monitoring the safety of drugs.\(^{26}\) There are specific rules on monitoring safety, as well as guidelines introduced by the Roszdravnadzor with regard to in-house monitoring of drugs safety.\(^{27}\)

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.\(^{28}\)

The MA may be revoked in the following cases: \(^{29}\)

\begin{itemize}
  \item[a] if, as result of state safety monitoring, it is evident that a risk to health exists;
  \item[b] a voluntary revocation application is filed;
  \item[c] if an MA was issued for five years, but upon expiry of that term no confirmation of state registration exists;
  \item[d] 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;
  \item[e] if an MA is issued for a trade name that has already been registered for another drug with a different combination of active ingredients;
  \item[f] if one and the same drug has been registered under various trade names;
  \item[g] if a court renders a decision on infringement of IP rights during commercialisation;
  \item[h] if the drug is not commercialised within three years;
\end{itemize}

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\(^{23}\) Article 1363 of the Russian Civil Code.

\(^{24}\) Article 18 of the Pharmaceutical Law.

\(^{25}\) Resolution of the 9th Commercial Appeal Court of 16 June 2017 on Case No. A40-657/17.

\(^{26}\) Articles 5, 9 and 64 of the Pharmaceutical Law.

\(^{27}\) Order of the Roszdravnadzor of 15 February 2017 No. 1071; Order of the MoH of 26 August 2010 No. 757n; Guidelines approved by Roszdravnadzor on 5 October 2009.

\(^{28}\) Article 18 of the Pharmaceutical Law.

\(^{29}\) Article 32 of the Pharmaceutical Law.
when there has been a failure to comply with pharmacovigilance obligations; or

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.\(^\text{30}\)

The manufacturing procedure should comply with the rules of good manufacturing practice approved by the Ministry of Industry and Commerce,\(^\text{31}\) 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.

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)\(^\text{32}\) and specific restrictions and prohibitions,\(^\text{33}\) under which it should not:

- be addressed to minors;
- cite specific cases of cure or improvement of health (not applied to advertising intended only for medical professionals in specialist publications or events);
- use expressions of gratitude by specific individuals (not applied to advertising intended only for medical professionals in specialist publications or events);
- invoke the results of obligatory clinical trials or examinations as evidence of any advantages of the drug;
- contain the assertion that consumers have certain diseases or health problems;
- give the impression that a healthy person should use the drug (not applied to advertising of preventive drugs);
- give the impression that by using the drug, it is not necessary to consult a doctor;
- guarantee favourable effects of the drug, its safety and effectiveness, and the absence of side effects;
- imply that the drug is a biologically active additive or food supplement or any other product that is not a medicine; and
- imply that safety or effectiveness of the drug is explained by its natural origin.

\(^{30}\) Article 45 of the Pharmaceutical Law.
\(^{31}\) Order of the Russian Ministry of Industry and Commerce of 14 June 2013, No. 916.
\(^{32}\) Article 5 of the Advertising Law; Chapter 2.1 of the Competition Law.
\(^{33}\) 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

**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).35

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 2015.36

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.37

**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.38 There is also a limit on the total number of medicines that may be covered by one prescription.39 Classification of a drug as a prescription drug affects its advertising in that it is only allowed if aimed at professionals.

**xii Imports and exports**

The import of drugs into Russia is regulated in detail by the government40 within the framework provided by the Pharmaceutical Law.41

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34 Articles 74 and 75 of the Healthcare Law.
37 Article 5 of the Pharmaceutical Law.
38 Order of the Russian MoH of 20 December 2012, No. 1175n.
40 Regulation of the Russian Government of 29 September 2010, No. 771.
41 Article 47 of the Pharmaceutical Law.
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.42

**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.43

**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 government44 and the list of drugs is approved annually. The prices for these listed drugs are subject to state registration.45

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.46

### 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.47

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42 Article 47 of the Pharmaceutical Law.
44 Article 60 of the Pharmaceutical Law.
45 Articles 61 and 62 of the Pharmaceutical Law.
46 Article 63 of the Pharmaceutical Law.
47 Chapter 24 of the Russian Commercial Procedure Code.
V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

The following restrictions and prohibitions are imposed on prescribers in their relations with medical representatives:48

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.49

In addition, commercialisation of substandard (off-grade) medicines may give rise to criminal liability.50

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Patent-related agreements are exempted from antitrust control,51 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.

48 Article 74 of the Healthcare Law.
49 Article 69 of the Pharmaceutical Law.
50 Article 238.1 of the Russian Criminal Code.
51 Section 4, Articles 10 and 11 of the Competition Law.
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.\textsuperscript{52}

\textbf{ii} \hspace{1em} \textbf{Transactional issues}

Corporate transactions, including mergers and acquisitions and strategic partnerships, are subject to general antitrust control based on the economic criteria.\textsuperscript{53}

\section*{VIII CURRENT DEVELOPMENTS}

The entry into effect of the Telemedicine Law drew the attention of IT and life sciences companies in 2018. Further practical developments on the launch of telemedicine services are expected, 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 January 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).

Further, the adoption of nationally recognised good practices will result in more effective control by the regulators. Regulatory and legislative trends aimed at increasing the level of localisation regarding the manufacture of pharmaceuticals in Russia have also gained attention.

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, and has increased the criteria that must be met by some forms of advertising to be considered valid.

\textsuperscript{52} Resolution of the 9th Commercial Appellate Court of 6 October 2014 No. 09AP-34696/2014; Case No. A40-42997/2014.

\textsuperscript{53} Chapter 8 of the Competition Law.
Chapter 25

SINGAPORE

Melanie Ho and Chang Man Phing

I  INTRODUCTION

The life sciences industry in Singapore is regulated by the Health Sciences Authority (HSA), 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. In particular, the Ethical Code and Ethical Guidelines (ECEG) set ethical benchmarks for medical practitioners. The ECEG was revised in 2016 and came into force on 1 January 2017 (ECEG 2016).

Human biomedical research is regulated by the Human Biomedical Research Act (HBRA) and subsidiary legislation, namely, the Human Biomedical Research Regulations 2017, the Human Biomedical Research (Restricted Research) Regulations 2017, and the Human Biomedical Research (Exemption) Regulations 2018. 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 and the relevant subsidiary legislation of the MA and HPA.

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

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 Registered medical practitioners refer to doctors registered under the Medical Registration Act (Chapter 174).
4 Act No. 29 of 2015.
5 Act No. 26 of 2012.
6 Health Products (Clinical Trials) Regulations 2016 and Medicines (Clinical Trials) Regulations 2016.
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, including traditional medicines, homeopathic medicines and quasi-medicinal products). The Poisons Act regulates specific substances (excluding use in medicines supplied by medical practitioners), whereas the Sale of Drugs Act regulates the sale of any substance or mixture of substances used as a medicine.

### 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.; medical devices used for the diagnosis, prevention, monitoring, treatment or alleviation of disease not through pharmacological, immunological or metabolic means; cosmetic products used on the external parts of the human body to clean, perfume, change appearance, etc.; therapeutic products used for a therapeutic, preventive, palliative or diagnostic purpose that is constituted by certain specified chemical and biological active ingredients, etc.; complementary health products, including Chinese proprietary medicines and traditional medicines.

Food and supplements of a food nature (including food-based complementary health products) are under the purview of the Agri-Food and Veterinary Authority (AVA) 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 AVA, depending on whether the product appears to be part of a daily diet, taken as supplement to a diet, or taken for medicinal purposes.

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), 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

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8 The Schedule (Poisons List) to and Section 7 of the Poisons Act.
9 Medicines Act, Section 3.
10 Paragraph 1 of the First Schedule to the HPA.
11 Paragraph 2 of the First Schedule to the HPA.
12 Paragraph 3 of the First Schedule to the HPA.
15 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.
performed in the context of a formal and approved clinical trial. 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.

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 will continue to be 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. In the third phase, which commenced on 1 November 2017, provisions on the regulation of human biomedical research took effect. These include the taking of consent, and the constitution of institutional review boards (IRBs) in relevant research institutions as part of the system of ‘self-accountability’ for reviewing research proposals.

In the next phase (the fourth phase), provisions on the regulation of human tissue research have been targeted to be brought into force in the first half of 2019. These are expected to include regulations pertaining to the duties of tissue banks, restrictions on disclosure of information on tissue donors, among other things. 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 ethics or are contrary to public interest.

Subsidiary legislation regulating human biomedical research includes the Human Biomedical Research Regulations 2017 and the Human Biomedical Research (Restricted Research) Regulations 2017. 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

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16 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.
18 Section 32 of HBRA. See also Human Organ Transplant Act (Chapter 131A) and Public Prosecutor v. Tang Wee Sung [2008] SGDC 262.
19 Sections 6–31, 65 and 68, and the Third, Fourth and Fifth Schedules to the HBRA.
20 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.
22 Sections 34–36, 37–39 and 64 of the HBRA.
23 Section 42(1)(b) of HBRA.
24 Section 42(1)(d) of HBRA.
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 AVA. 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 establish an Institutional Animal Care and Use Committee to oversee and evaluate the animal care and use programmes of an institution.

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.

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

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25 Fourth Schedule to the HBRA.
26 Third Schedule to the HBRA.
27 BAC’s Ethics Guidelines (June 2015) at Paragraphs 2.3–2.17.
28 Section 7 of Human Cloning and Other Prohibited Practices Act.
29 Section 31 read with the Fourth Schedule to the HBRA and Regulations 3 and 4 of the Human Biomedical Research (Restricted Research) Regulations 2017.
30 Human oocytes include those obtained from excised ovarian tissue.
31 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.
32 Rule 7(1) of Animal & Birds (Care and Use of Animals for Scientific Purposes) Rules.
33 Clinical Trials Guidance: Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC) (May 2017) – Determination of whether a clinical trial requires a CTA, CTN or CTC at Paragraph 1.2.1.
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. Under the ECEG 2016, doctors may offer innovative therapy to patients in desperate or dire situations, and where conventional therapy is unhelpful. Patients’ informed consent must be obtained; failing to do so can result in the doctor being struck off

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34 Clinical Trials Guidance: Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC) (May 2017) – Determination of whether a clinical trial requires a CTA, CTN or CTC at Paragraph 1.2.2.; See also Section 18 of the MA, and the Medicines (Clinical Trials) Regulations 2016.

35 Regulation 4(1) of Medicines (Clinical Trials) Regulations 2016 and Regulation 4(1) of Health Products (Clinical Trials) Regulations 2016.

36 Regulation 9(2) of Medicines (Clinical Trials) Regulations 2016.

37 Clinical Trials Guidance: Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC) (May 2017) – Determination of whether a clinical trial requires a CTA, CTN or CTC at Paragraph 1.3.2.

38 Clinical Trials Guidance: Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC) (May 2017) – Determination of whether a clinical trial requires a CTA, CTN or CTC at Paragraph 1.3.2.


41 Pang Ah San v. Singapore Medical Council [2014] 1 SLR 1094 (SGHC) at [26].

42 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.

43 SMC Handbook on Medical Ethics 2016 at B6.1.
the Singapore Register of Medical Practitioners. 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.

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.

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, 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. However, prior approval from the HSA must be sought. 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.

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.

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.

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45 ECEG 2016 at Guideline B8.
47 Regulation 51 of the Health Products (Therapeutic Products) Regulations 2016.
48 A registered medical practitioner under the Medical Registration Act (Chapter 174) and a registered dentist under the Dental Registration Act (Chapter 76).
49 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.
50 Therapeutic Products Guidance – Import and Supply of an Unregistered Therapeutic Product for Patients’ Use (November 2016) at Paragraph 2.2.
51 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.
Depending on whether the NDA or GDA has been previously evaluated and approved, as well as the subcategory of the NDA or GDA,\textsuperscript{52} 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;\textsuperscript{53} 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.\textsuperscript{54}

There were several notable amendments to the HP(MD)R that 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.\textsuperscript{55} An abridged evaluation process for registration has been provided for the other three classes, to allow faster market access.\textsuperscript{56} 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,\textsuperscript{57} and where the supply of medical devices is intended for charitable purposes.\textsuperscript{58} The category of implantable medical devices has been expanded to include orthopaedic, neurological, breast, intraocular and cardiovascular implants.\textsuperscript{59} In another amendment, wellness devices have been expressly excluded from the HP(MD)R.\textsuperscript{60}

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\textsuperscript{61} prior to their placement on

\textsuperscript{52} 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).

\textsuperscript{53} ‘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.

\textsuperscript{54} Third Schedule to the Health Products (Medical Devices) Regulations 2010; Medical Device Guidance – Guidance on Medical Device Product Registration (June 2018) at Paragraph 2.

\textsuperscript{55} Regulation 10b of the Health Products (Medical Devices) Regulations 2010.

\textsuperscript{56} Regulation 26 of the Health Products (Medical Devices) Regulations 2010.

\textsuperscript{57} Regulation 3B of the Health Products (Medical Devices) Regulations 2010.

\textsuperscript{58} Regulation 3C of the Health Products (Medical Devices) Regulations 2010.

\textsuperscript{59} Fifth Schedule to the Health Products (Medical Devices) Regulations 2010.

\textsuperscript{60} Order 5 of the Health Products (Exemptions) (Amendment) Order 2018.

\textsuperscript{61} Regulation 25 of the Health Products (Medical Devices) Regulations 2010.
the Singapore market. Requirements under all applicable legislation\textsuperscript{62} 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.\textsuperscript{63}

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.\textsuperscript{64} 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.\textsuperscript{65} Instead, the HSA must be notified before the supply or sale of the cosmetic product.\textsuperscript{66} 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.\textsuperscript{67} 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.\textsuperscript{68}

**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.\textsuperscript{69}

\textsuperscript{62} For example, the Private Hospitals and Medical Clinics Act (Chapter 248), Medical Registration Act (Chapter 174), Dental Registration Act (Chapter 76), Radiation Protection Act (Chapter 262), etc. See www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Medical_Devices/Overview.html.


\textsuperscript{64} Article 1(1) of the ASEAN Agreement on Medical Device Directive.

\textsuperscript{65} Guidelines on the Control of Cosmetic Products (Revised December 2018) at Paragraph 1.

\textsuperscript{66} Guidelines on the Control of Cosmetic Products (Revised December 2018) at Paragraph 5.

\textsuperscript{67} See www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Cosmetic_Products/Overview.html.

\textsuperscript{68} Guidelines on the Control of Cosmetic Products (Revised December 2018) at Paragraphs 5 and 10.

\textsuperscript{69} See www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Complementary_Health_Products/TM.html.
**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.70

**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.71 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.72

The HP(TP)R73 and MA74 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 2018.75 R&D expenditure 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.77

**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.78

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70 Section 5 of Medicines Act.
71 Guidance on Registration of Biosimilar Products (November 2016).
72 Section 36A of the Patents Act.
73 Regulation 26(1) of the Health Product (Therapeutic Products) Regulations.
74 Section 19A of the Medicines Act.
75 See https://www.iras.gov.sg/irashome/Schemes/Businesses/Productivity-and-Innovation-Credit-Scheme/.
76 R&D expenditure also encompasses staff costs and consumables. See Part 4 of IRAS Research and Development (R&D) Claim Form.
77 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’.
78 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.
Under the HPA and MA, 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. 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.

**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.

As with other health products, the HSA has the power to suspend, cancel or reclassify the registration of cosmetic products, as set out above.

### 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. 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 or Cooperation Scheme Guide to Good Manufacturing Practice for Medicinal Products. 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.
Cosmetic products manufactured in Singapore must comply with Appendix VI of the ASEAN Cosmetic Documents entitled ‘ASEAN Guidelines for Cosmetic Good Manufacturing Practice’.

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.\(^88\)

Unlike medicinal products, prior approval from the HSA is not required for advertisements relating to therapeutic products.\(^89\) 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.\(^90\)

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.\(^91\)

With regard to cosmetic products, advertisements cannot include claims that they have therapeutic benefits or can be used for therapeutic purposes,\(^92\) nor can they create an erroneous impression regarding the formulation, composition, quality or safety of the product.\(^93\)

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 the public into believing that any of the services are medically endorsed’.\(^94\) 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.\(^95\)

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\(^96\) or wholesale

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88 Section 50 of the Medicines Act.
89 Explanatory Guidance to the Health Products (Advertisement of Therapeutic Products) Regulations 2016 (November 2016) at Paragraph 2.2.
90 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.
91 Regulation 19 of the Health Products (Medical Device) Regulations 2010.
93 Regulation 9(b) of the Health Products (Cosmetic Products – ASEAN Cosmetics Directive) Regulations 2007.
94 ECEG 2016 at Guideline I2(4).
95 ECEG 2016 at Guideline I2(5).
96 See https://www.hsa.gov.sg/content/hsa/en/Health_Products_Registration/Manufacturing_Importation_Distribution/Overview/Audit_and_Licensing_Of_Importers_Wholesale_Dealers_and_Exporters.html.
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.

## 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.

## 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

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98 Guidance notes on duties of responsible persons named in the importer's licence and wholesaler's licence 2016 at Paragraph 4. For duties and responsibilities of responsible persons, see Regulation 39 of the Health Products (Therapeutic Products) Regulations 2016.

99 Guidance on Licensing for Manufacturers, Importers and Wholesalers of Medical Devices (August 2018) at Paragraph 5.2.

100 See www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Western_Medicines/Reclassified_Medicines.html.

101 Regulation 11 of the Health Products (Therapeutic Products) Regulations 2018.

102 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.

103 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.
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.

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.

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104 Regulation 39 of the Health Products (Therapeutic Products) Regulations 2016.
105 Guidance on Licensing for Manufacturers, Importers and Wholesalers of Medical Devices (August 2018) at Paragraph 5.2.
107 Part II of the Medicines Act.
108 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.
109 As defined in the First Schedule to the Misuse of Drugs Act.
110 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.
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.112

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.113

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),114 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).115 Subsidised drugs cover up to 90 per cent of the total volume of public medication prescriptions and are reviewed and updated regularly by the MOH.116 Subsidies are also provided for medical devices, such as implants.117 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.118 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.119

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112 Section 49 of the Health Products Act.
113 Section 12 of the Private Hospitals and Medical Clinics Act (Chapter 248).
114 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, administrated 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.
115 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.
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.\textsuperscript{120}

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.\textsuperscript{121}

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 PAYERS

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.\textsuperscript{122}

The ECEG 2016 also provides guidance to doctors in relation to issues of financial conflicts of interest.\textsuperscript{123} 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 the ECEG 2016.\textsuperscript{124} 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).\textsuperscript{125}

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.\textsuperscript{126} The rationale is to ensure that the patient’s interests would take priority over

\textsuperscript{121} Section 28 of the Health Products Act.
\textsuperscript{122} SAPI Code of Marketing Practices (2016).
\textsuperscript{123} Guideline H3(1)-(5) of the ECEG 2016.
\textsuperscript{124} Guideline H3(5) of the ECEG 2016.
\textsuperscript{125} See \textit{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.
\textsuperscript{126} 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
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.

If done on a large scale, the termination of contracts with TPAs may result in wider implications for the healthcare sector. For doctors, there may be a substantial loss of patient referrals from the TPAs. Patients who rely on the subsidised rates when visiting doctors on the TPA panel may now need to change healthcare providers or pay their existing doctor’s new non-subsidised rates. In turn, this may increase the patient load of the public healthcare sector as private-paying patients may now have to switch to government-run polyclinics for subsidised rates to reduce their medical expenses.

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 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.

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

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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.  
127 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.
128 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.  
129 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 companies on 11 April 2017, and Joint Advisory on Fees Paid to Managed Care and Third-Party Administrator (TPA) Companies on 23 June 2017 by Academy of Medicine, Singapore, College of Family Physicians, Singapore, and Singapore Medical Association.
130 ECEG 2016 Guideline I1.
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.\(^{131}\) Although rare, class actions are possible.\(^{132}\)

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.\(^ {133}\)

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.\(^ {134}\)

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 with the aim of publishing a public consultation report.\(^ {135}\) The

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\(^{131}\) For example, Section 14 of the Sale of Goods Act (Chapter 393) or Section 6 of the Consumer Protection (Fair Trading) Act (Chapter 52A).

\(^{132}\) Under Order 15, Rule 12 of the Rules of Court of Singapore.


\(^{135}\) 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.

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MOH is currently reviewing the use of pre-implantation genetic screening (PGS) and its ethical implications, having commenced a three-year pilot programme in the first half of 2017 to assess its clinical effectiveness at improving in vitro fertilisation (IVF) cycle outcomes by screening for chromosomal abnormalities in embryos created through IVF.\footnote{See www.moh.gov.sg/content/moh_web/home/pressRoom/Parliamentary_QA/2016/pre-implantation-genetic-screening--pgs-.html and https://www.nuh.com.sg/wbn/spot/u3007/ Patients%20and%20Visitors/Newsroom/Media%20Articles/2016/Nov_2016/TODAY_Pg18_ ThreeHospitalsOfferEmbryoScreeningTechniquePilotStudy%20_15Nov16.pdf.}

A recent High Court judgment\footnote{UKM v. Attorney-General [2018] SGHCF 18.} has prompted governmental reviews of the status of surrogacy in Singapore.\footnote{See https://www.straitstimes.com/singapore/parliament-authorities-looking-at-adoption-laws-and-surrogacy-does-not-support-gay.} 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.\footnote{Regulation 18(1) read with Second Schedule to the Private Hospitals and Medical Clinics Regulations.}

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.\footnote{MOH, Fee Benchmarks for Private Sector Surgeon Fees (As of 13 November 2018).} While the benchmarks are not intended to be a fee cap,\footnote{Fee Benchmarks Advisory Committee Report (9 November 2018).} doctors who charge above the benchmarks are expected to explain to patients and other stakeholders why their charges exceed the benchmarks.\footnote{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_2017122241b0a3be9c8c4d65b2ac0bfa0aa81bf.pdf.}

The current PHMCA is to be replaced with a new Healthcare Services Act (HSA),\footnote{See https://www.moh.gov.sg/hcsa/about-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 are issued based on the types of services provided, such as hospital services, long-term residential care services, and non-premises based services, among others.

The intended HSA will also make it mandatory for licensed hospitals and medical clinics under the HSA 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 will be contributed to the NEHR.\footnote{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_2017122241b0a3be9c8c4d65b2ac0bfa0aa81bf.pdf.}
Enactment of the new HSA is targeted for 2019, and the Ministry of Health intends to implement it in three phases: Phase 1 (from December 2019), Phase 2 (from June 2020) and Phase 3 (from December 2020). However, since the draft Healthcare Services Bill was first published in January 2018, Singapore has seen its worst cyberattack occur 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 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. There may be further amendments to the draft Bill following this data breach incident.

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147 Wong Partnership LLP represented MOH Holdings Private Limited in the inquiry.
I INTRODUCTION

The South African pharmaceutical environment is highly regulated. Recent amendments to the Medicines and Related Substances Act 101 of 1965 (the Medicines Act) brought about the replacement of the Medicines Control Council – the regulatory body responsible for the pharmaceutical industry, which reported to the National Department of Health (the Department of Health) – with the newly established South African Health Products Regulatory Authority (the Authority).

The Authority has a broader mandate than its predecessor, including the regulation of complementary and alternative medicines (CAMs) and medical devices. Being an independent organ of the state, the Authority levies fees in respect of applications for licensing and the registration of medicines.

II THE REGULATORY REGIME

i Classification

In terms of the Medicines Act, the term ‘medicine’ is broadly defined to include a substance (or mixture of substances) used, manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease or for restoring, correcting or modifying any somatic or psychic, or organic function in humans, and which includes any veterinary medicine.2

The term ‘complementary medicine’ is broadly defined to include a substance (or mixture of substances) that originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substances determined by the Authority and is used, manufactured or sold for use in maintaining, complementing or assisting the physical or mental state; or in the diagnosis, treatment, mitigation, modification, alleviation or prevention of disease or illness or the symptoms or signs thereof or abnormal physical or mental state of a human or an animal.3

CAMs are classified into sub-categories based on whether they constitute discipline-specific medicines (with such disciplines as may be determined by the Authority) or health supplements.

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1 Vaughn Harrison is a partner, Mandi Krebs is a senior associate and Abrianne Marais is an associate at Hogan Lovells (South Africa) Inc.
2 Section 1 of the Medicines Act.
3 Regulation 1 of the General Regulations, as amended, to the Medicines Act.
The term ‘medical device’ is broadly defined in the Medicines Act to mean any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, including certain hazardous substances intended by the manufacturer to be used, alone or in combination, for humans or animals, for one or more of the following purposes such as the diagnosis, prevention, monitoring, treatment or alleviation of disease or injury, the investigation, replacement, modification or support of the anatomy or of a physiological process; supporting or sustaining life; control of conception; disinfection of medical devices; or providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body; and that does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human or animal body, but that may be assisted in its intended function by such means.

The Foodstuffs, Cosmetics and Disinfectants Act 54 of 1972 (the Foodstuffs Act) defines a ‘foodstuff’ as any article or substance (except a medicine as defined in the Medicines Act) ordinarily eaten or drunk by a person or purporting to be suitable, or manufactured or sold, for human consumption, and includes any part or ingredient of any such article or substance, or any substance used or intended or destined to be used as a part or ingredient of any such article or substance.4

Consequently, if a product is a medicine, as contemplated in the Medicines Act, by definition it cannot be a foodstuff. Foodstuffs are not subject to any registration process in South Africa, however, the labels of all foodstuffs must comply with the provisions of the relevant labelling regulations,5 as well as any guidelines published thereunder.

ii Non-clinical studies

The National Health Research Ethics Council, which was established under the National Health Act 61 of 2003 (the National Health Act) is, inter alia, authorised and mandated to set norms and standards with respect to research conducted on animal and human subjects.6

In terms of the General Regulations to the Medicines Act, as amended (the General Regulations), persons desiring to initiate or conduct a clinical study are required to apply to the Authority, in the prescribed form, for authorisation to conduct such a clinical study.7

Other legislation, guidelines and standards that must be taken into account when clinical studies are initiated and conducted include the Animals Protection Act 71 of 1962, the South African Medical Research Council’s (SAMRC) Guidelines for Ethics of Medical Research: Use of Animals in Research and Training, and the South African Bureau of Standards’ South African National Standard for the Care and Use of Animals for Scientific Purposes.

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4 Section 1 of the Foodstuffs Act.
5 Labelling of Foodstuffs must comply with the provisions of the Regulations relating to the Labelling and Advertising of Foodstuffs (1 March 2010) as published under the Foodstuffs Act. Draft Regulations relating to the Labelling and Advertising of Foodstuffs (Draft Labelling Regulations) were published for comment on 29 May 2014. The Draft Labelling Regulations contain provisions regarding functional claims, and specify the manner in which such claims may be included on the label of a foodstuff.
6 Section 72(6) of the National Health Act.
7 Regulation 30 of the General Regulations.
iii Clinical studies

No person may conduct a clinical study without the authorisation of the Authority.\(^8\)

Clinical studies in respect of living persons must comply with the provisions set forth in the following:

a the National Health Act and the Medicines Act, and the regulations thereto; and

b regulations, guidelines on ethics and professional standards and other norms and standards set by institutions such as the Department of Health, SAMRC and relevant Research Ethics Committees (RECs) such as the National Health Research Ethics Council, in respect of procedural and substantive matters.

In terms of the General Regulations, persons desiring to initiate or conduct a clinical study are required to apply to the Authority, in the prescribed form, for authorisation to conduct such a clinical study.\(^9\) Such application must include, as a minimum, the clinical study protocol, the investigator’s brochure, details regarding the investigators, supporting documents regarding the qualifications of the investigators, study insurance, professional indemnity insurance, participant information forms, informed consent documents and the approval by the relevant REC.\(^10\)

All clinical studies must be conducted in accordance with guidelines for good clinical practice as may be determined by the Authority from time to time.

The person authorised by the Authority to conduct the clinical study is further required to submit milestone and special reports to the Authority.\(^11\) Notwithstanding the latter, the principal investigator is also required to inform the Authority of any suspected adverse events, or safety concerns, occurring as a result of the use of any medicine during the conduct of a clinical study.\(^12\)

iv Named-patient and compassionate use procedure

Access to unregistered pharmaceutical products may be achieved by means of submitting an application to the Authority in terms of Section 21 of the Medicines Act.

Although the Authority is empowered to authorise the supply of an unregistered medicine, this power is only exercised in emergency situations, in which case the requesting entity will be required to record the names of those persons to which the unregistered medicine is being supplied.

Section 21 Applications are generally made on a named-patient basis and must be initiated by the patient’s treating physician. The Section 21 Applications must be on in the prescribed form and, \textit{inter alia}, set out details regarding the unregistered medicine. A duly completed and witnessed informed consent document is also required.\(^13\)

The person under whose supervision the unregistered medicine is prescribed, is required to submit a progress report to the Authority no later than six months after the commencement of the use of the unregistered medicine, or earlier if requested.

\(^8\) Regulation 30(5) of the General Regulations.
\(^9\) Regulation 30 of the General Regulations.
\(^10\) Regulation 30(2) of the General Regulations.
\(^11\) ibid.
\(^12\) Regulation 30(7) of the General Regulations.
\(^13\) ibid.
In addition, reporting in respect of the outcome of the treatment, as well as any adverse drug reaction, is required. A further progress report must be submitted to the Authority within 30 days after the completion or termination of the use of the unregistered medicine.  

In the case of unregistered biological medicines, the Authority may require that:

a. the number of samples of every batch, together with one copy of the protocol in respect of the testing of the bulk batch and filling batch and one copy of the certificate of release issued by the competent authority in the country in which the biological medicine was manufactured, be submitted to the Authority as a batch release condition; and

b. at least the number of samples of every batch, together with one copy of the protocol in respect of the testing of the bulk batch and filling batch of the biological medicine manufactured in South Africa, be submitted to the National Control Laboratory of the Authority, as a batch release condition.

v Pre-market clearance

The Medicines Act provides that, save for certain limited exceptions, no person shall sell any medicine that is subject to registration by virtue of a declaration published, unless it is registered.

The definition of ‘sell’ includes to import, offer or supply or dispose of a medicine to any person whether for a consideration or otherwise.

In principle, and in respect of a specific product, if the product falls within the broad definition of a medicine it will be subject to compulsory registration in terms of the Medicines Act if it is in a class or category of medicines that has been called up to registration by the Authority in terms of Section 14(2).

In terms of the Medicines Act, every application for the registration of a medicine, medical device or in vitro diagnostic (IVD) devices shall be submitted to the Authority in the prescribed form and shall be accompanied by the prescribed particulars, samples of the relevant medicines and the prescribed registration fee.

If the Authority is satisfied that the medicine is suitable for the purpose for which it is intended, complies with the prescribed requirements, and is safe, efficacious and of good quality, the Authority is required to issue the applicant with a certificate of registration in respect of the relevant medicine. Regard must also be had to the General Regulations and the forms and guidelines issued and revised from time to time by the Authority.

In South Africa, these registration certificates are not publicly available documents.

As regards the renewal of registration certificates, strictly speaking, the Medicines Act provides that the registration of medicines is valid for a period of five years, however, practically speaking, the pharmaceutical industry does not attend to the five-yearly renewal of any medicine registrations.

In recent years, CAMs have been called up by the Authority and are now subject to registration in accordance with the provisions of the Medicines Act. As such, the manufacturers, distributors, importers and exporters of CAMs are equally required to be licensed in accordance with the Medicines Act.

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14 Regulation 29(3) of the General Regulations.
15 Section 15(1) of the Medicines Act.
16 Section 15(3) of the Medicines Act.
Subject to certain exceptions, medical devices were previously not heavily regulated in South Africa. Prescriptive requirements for medical devices were not in force and advertisers and marketers of medical devices had few legislative and regulatory formalities to comply with.

As of December 2016, the local regulatory framework governing medical devices underwent a substantial legislative change, requiring, *inter alia*, the registration of medical devices, the licensing of manufacturers, wholesalers and distributors of medical devices and further providing guidelines regarding the advertising and labelling of medical devices.

The primary purpose of the Regulations Relating to Medical Devices and In Vitro Diagnostic Medical Devices (the Device Regulations) is to provide for the registration of medical and IVD devices, including matters related thereto.

### vi Regulatory incentives

There is no connection between the regulatory approval process for medicines and the patent and intellectual property protection regime in South Africa.

South Africa currently has a deposit-based patent filing system with no examination and opposition. Accordingly, and provided that the prescribed formal requirement for the lodging of a patent is complied with, such application will be granted.

The Cabinet of South Africa recently adopted and published a new intellectual property policy that, *inter alia*, addresses proposed reforms to the intellectual property regime in South Africa.

It is envisaged that government will leverage off of the flexibilities allowed in terms of the Trade-Related Aspects of Intellectual Property Rights rules of the World Trade Organization and for the purpose of promoting public health, local manufacturing, research and development, transfer of technology and socio-economic development.

This includes the introduction of a system of substantive search and examination (SSE) for patents to replace the current depository system in respect of certain fields of technology, with pharmaceuticals being identified as prime candidates. It is envisaged that SSE will benefit patent holders by granting rigorously assessed rights and ensuring that market exclusivity is only granted when appropriate. In addition, it is also envisaged that new patentability criteria will be adopted to address South Africa’s public health and environmental concerns, as well as industrial policy objectives.

### vii Post-approval controls

Persons that have applied for the registration of medicine and persons that are holders of certificates of registration (HCRs) with regard to medicines are required to inform the Authority of new or existing quality, safety or efficacy concerns related to any medicine or scheduled substance, including but not limited to any adverse drug reactions (ADRs). In addition, such persons are required to maintain or have access to records of the reports and case reports made.

More generally, HCRs are required to have an appropriate pharmacovigilance system, which they must adequately maintain.

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18 Regulation 40 of the General Regulations.
19 The Authority in its Post-marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa Guideline.
The Authority in its Post-marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa guideline sets out the framework that HCRs are required to follow in terms of reporting any ADRs. This guideline also addresses the management of safety data during post-registration and post-marketing clinical trials.

It is generally advisable that a suitably qualified pharmacovigilance officer be nominated by the responsible pharmacist.\textsuperscript{20}

Certificates of registration may be transferred from the existing HCRs to any other appropriately licensed person, subject to an application being made in the prescribed form and the same being granted by the Authority.\textsuperscript{21}

\noindent \textbf{viii \ Manufacturing controls}

Guidelines are issued by the Authority from time to time, which relate to various matters including good manufacturing practices (GMP) or good distribution practices (GDP). All pharmaceutical manufacturers and wholesalers are required to comply with such guidelines.

The Department of Health further requires that premises licences be held by the relevant pharmaceutical manufacturer or wholesaler. Such a licence may be withdrawn in the event of any contravention of the provisions of the Medicines Act or the Pharmacy Act 53 of 1974 (the Pharmacy Act), or a failure to comply with GMP or GDP.

Manufacturers of medical devices must ensure that they have adequate quality management systems in place, with ISO 13485:2016 being the benchmark. The benefit of this is that manufacturers can decide whether or not they wish to have a quality management system for each of their sites or just one system that will apply to multiple sites.

\noindent \textbf{ix \ Advertising and promotion}

The advertising to the public of medicines listed per Schedule 2 or above is prohibited in terms of the General Regulations.

In addition, Regulation 21 of the Device Regulations provides that only Class A or Class B medical devices may be advertised to the ‘public or a lay person’. In terms of the Device Regulations, Class A refers to medical devices that are classified as ‘low risk’, and Class B refers to medical devices that are classified as ‘low–moderate risk’.

Advertisement is defined in the Medicines Act as, \textit{inter alia}, as any written, pictorial, visual or other descriptive matter or verbal statement or reference that is intended to promote the sale of a product.

Furthermore, the advertising and promotion of medicines and medical devices to healthcare professionals and the public is regulated in terms of the South African Code of Marketing Practice for Health Products (the Code), a voluntary marketing code that is intended to signify the industry's commitment to ensure that the marketing of health products is carried out in a responsible, ethical and professional manner.

The enforcement of the Code has been entrusted to a Marketing Code Authority and enforcement is generally based on the principle of self-regulation through the handling of complaints raised.

\textsuperscript{20} ibid.
\textsuperscript{21} Section 15B of the Medicines Act.
Distributors and wholesalers

Section 22C(6) of the Medicines Act provides that no manufacturer, wholesaler or distributor may manufacture, import, export, act as a wholesaler of or distribute, as the case may be, any medicine, scheduled substance or medical device, unless licensed.

In respect of a pharmaceutical manufacturer licence, this may include a licence to import or export medicines, or to act as a wholesaler of medicines.

Guidelines have been issued by the Authority, which are revised from time to time and relate to various matters including GMP and GDP. All pharmaceutical manufacturers and wholesalers are required to comply with such guidelines.

In addition, a pharmaceutical manufacturer or wholesaler must be licensed and recorded as a manufacturing or wholesale pharmacy, as the case may be, with the South African Pharmacy Council (the Pharmacy Council), and must further be recorded as a pharmacy owner.

Additional requirements of the Pharmacy Council include the appointment of a dedicated responsible pharmacist who is required to continually and personally supervise the operations of the relevant manufacturing or wholesale pharmacy.

The Department of Health further requires that premises licences be held by the relevant pharmaceutical manufacturer or wholesaler. Such a licence may be withdrawn in the event of any contravention of the provisions of the Medicines Act or the Pharmacy Act, or the failure to comply with GMP or GDP.

The Device Regulations provide, *inter alia*, for the following:

a. the process for the application by a manufacturer, wholesaler or distributor of medical and IVD devices for a manufacturer, distributor or wholesaler licence. The Device Regulations go further to indicate the period of validity of a licence and provide for the renewal thereof; and

b. details regarding the application process for the registration of medical and IVD devices as well as the classification thereof.

Notwithstanding the above, the Authority has not yet called up medical devices for registration; however, the Authority has initiated the licensing process for parties engaging in medical devices-related manufacturing, distribution and wholesale activities.

Applicants are required to appoint an ‘authorised person’, and the Device Regulations provide that such person needs to be ‘suitably qualified’ when it comes to the medical device or categories of medical devices held, imported or manufactured by the relevant applicant. If an applicant has multiple sites of manufacture and distribution, an application must be submitted per site, with an authorised representative appointed in respect of each site.

Classification of products

There are four basic categories of medicines, and each category is further subdivided into a number of listed pharmacological classes.

The four categories are:

a. Category A: medicines that are intended for use in humans and that are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine;

b. Category B: medicines intended for use in humans and animals that cannot normally be administered without further manipulation;
c Category C: medicines intended for veterinary use that are, without further manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine; and

d Category D: complementary medicines intended for use in humans and animals that are, without further manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine.22

In terms of the Medicines Act, substances are further classified in terms of a scheduling system from Schedule 0 through Schedule 8, the latter being the most highly controlled.

xii Imports and exports

No person may import or export any Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substance, unless a permit has been issued by Director-General of the Department of Health in the prescribed manner.23

xiii Controlled substances

Schedule 0 medicines may be sold to the public in an ‘open shop’.24 This means that sales of such medicines are not restricted to pharmacies, whereas medicines of Schedule 1 and above may only be sold to the public in a pharmacy. Medicines of Schedule 3 and above require the prescription of a medical practitioner or another applicable healthcare professional.

xiv Enforcement

The Medicines Act, the regulations thereto and the National Health Act set out their own list of offences and penalties, and include both monetary penalties and criminal offences. In addition the Authority has wide powers that include the authority to launch inspections, request documents and information, and revoke and suspend registrations and licences.

III PRICING AND REIMBURSEMENT

i Transparent pricing

A transparent pricing system, which includes a single exit price regime for medicines and scheduled substances, was introduced within the framework of the Medicines Act in 2004.

A pharmaceutical manufacturer, importer, distributor or wholesaler may not charge any fee or amount other than the single exit price (SEP) in respect of the sale of a medicine or scheduled substance to a person other than the state.

Maximum allowable price increases are set by the Minister of Health on an annual basis. The extent to which the SEP of a medicine may be increased is determined by factors such as the increases in the average Consumer Price Index for the preceding year, the increase

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22 Regulation 9 of the General Regulation.
23 Section 22A(11) of the Medicines Act.
24 The concept of an ‘open shop’ is included in Section 22A(3) of the Medicines Act; however, the term is undefined.
in the average Producer Price Index for the preceding year, changes in the rates of foreign exchange, purchasing power parity and the need to ensure the availability, affordability and quality of medicines and scheduled substances in South Africa.25

ii Benchmark pricing systems

The Department of Health has indicated its intention to price medicines according to an international benchmarking system that will essentially require the SEP of a particular medicine or scheduled substance to match the lowest price at which it is sold in a selected basket of countries, including South Africa.

Although proposed regulations relating to this benchmarking methodology were published during 2014, the regulations have not yet been finalised and have thus not yet come into force. It has, however, been industry practice for pharmaceutical companies to include, together with their applications for single exit pricing approval, information relating to the benchmark pricing of medicines and scheduled substances, in several other jurisdictions, including Australia, Canada, New Zealand and Spain.

iii Logistics fees

Presently, any logistics fees payable to wholesalers and distributors is determined by agreement between the provider of logistical services and the relevant pharmaceutical manufacturer or importer.

On 18 September 2012, the Minister of Health, on the recommendation of the Department of Health’s pricing committee, published draft regulations that, once in force, would provide for a capped logistics fee. However, these regulations have yet to be published in final form.

iv Incentives

The Medicines Act prohibits the supply of any medicine or medical device according to a bonus system, rebate system or any other incentive scheme (Prohibited Activities).

Although no definitions in respect of these Prohibited Activities have been included in the Medicines Act, considerable guidance as to the meaning thereof has previously been sought from a number of court decisions. However, on 1 December 2017, the Minister of Health published proposed regulations that are intended to provide further guidance regarding the Prohibited Activities included in the Medicine Act.

More specifically, the proposed regulations provide proposed definitions for each of the three Prohibited Activities, and further propose penalties for the transgression thereof.

v Health technology assessments

In respect of medical devices, health technology assessments (HTAs) are well established in South Africa and are often required by private healthcare organisations and medical schemes when assessing new technologies with regard to efficacy and cost.

Previously, it has been suggested that the Department of Health may consider directly establishing an HTA agency that will be independent and will undertake HTAs to support the key policy reforms in respect of health and medical care.

25 National Health Insurance Policy (Notice 627 of 30 June 2017).
However, and subsequent to the proposed implementation of the NHI scheme (detailed below), it is contemplated that an HTA Ministerial Advisory Committee will be established to advise the Minister of Health in respect of HTA, and which will serve as a precursor to an HTA Agency that will regularly review the available range of health interventions and technology, by using the best available evidence on cost-effectiveness, and allocative, productive and technical efficiency.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The Promotion of Administrative Justice Act 3 of 2000 (PAJA) aims to promote the right to administrative action that is lawful, reasonable and procedurally fair. PAJA and the public law jurisprudence that have been developed over many years allow for a framework in which administrative action by the state and certain statutory bodies such as the Authority may be challenged.

However, the internal appeals process provided for in terms of the Medicines Act, and the regulations thereto, must be exhausted before the procedures and remedies available under PAJA may be pursued.

The Medicines Act does provide for the Minister of Health to confirm, set aside or vary a decision of the Director-General of Health, and in the case of the decisions by the Authority, such decisions may be considered by an appeal committee to be convened by the Minister of Health on request.

V FINANCIAL RELATIONSHIP WITH PRESCRIBERS AND PAYERS

The Health Professions Act 56 of 1974 (the Health Professions Act) and the various guidelines published by the Health Professions Council of South Africa, established under the Health Professions Act, are aimed at setting and maintaining excellent standards of ethical and professional practice by healthcare providers, and this includes the following restrictions:

a a healthcare practitioner may not participate in the manufacture for commercial purposes, or in the sale, advertising or promotion of any medicine or medical device;
b a healthcare practitioner may not participate in any other activity that amounts to selling medicine or medical devices to the public or keeping an open shop or pharmacy; and
c a healthcare practitioner shall not engage in or advocate the preferential use or prescription of any medicine or medical device that, save for the valuable consideration he or she may derive from such preferential use or prescription, would not be clinically appropriate or the most cost-effective option.26

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Consumer Protection Act

In terms of the Consumer Protection Act (CPA), strict liability is imposed on all persons in a supply chain, for example, manufacturers, importers, distributors and retailers, in respect

26 Ethical and Professional Rules of the Health Professions Council of South Africa – Booklet 2.
of harm caused wholly or partly as a consequence of supplying any unsafe goods, a product
failure, defect or hazard in any goods, or inadequate instructions or warnings provided to
the consumer pertaining to any hazard arising from or associated with the use of any goods.

Liability arises irrespective of whether the harm resulted from any negligence on the part
of the manufacturer, importer, distributor or retailer, as the case may be, and it is therefore
important that provision is made for suitable guarantees, warranties and indemnities between
all parties in the supply chain, including the manufacturers, importers and distributors.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

On 5 July 2018, the Competition Commission of South Africa (Commission) published
its provisional findings and recommendations (the Provisional Report) in respect of an
investigation held into the private healthcare market known as the Health Market Inquiry
(HMI).

The HMI is focused primarily on determining the factors that presently, and allegedly,
distort and lessen competition in the private healthcare sector, which encompasses numerous
interrelated markets, and is aimed at improving competition and increasing transparency to
allow for value purchasing.

The Commission has been tasked to make recommendations that support the
achievement of accessible, affordable, high-quality and innovative private healthcare in
South Africa, and following the publication of the Provisional Report, has requested that
stakeholders engage with them and make submissions in relation to the Provisional Report. These submissions are still being considered, and as at the time of writing, the final report of the Commission has yet to be published.

Going forward, it is expected that the Commission’s recommendations will materially
influence the continued debate regarding the future regulatory structure of both the private
and public healthcare sectors in South Africa, and will have far-reaching implications for all
stakeholders including healthcare practitioners, healthcare establishments, businesses in the
pharmaceutical and medical devices industries, healthcare funders, medical scheme members,
and industry and statutory bodies.

VIII CURRENT DEVELOPMENTS

During 2018, the South African Cabinet approved the highly anticipated National Health
Insurance Bill (the NHI Bill). The aim of the NHI scheme is to establish a single-payer and
single-purchaser fund for all patients in South Africa.

It is intended that the NHI Bill will apply to public and private health establishments,
which include institutions, facilities, buildings or places, whether for profit or not, that are
operated or designed to provide in-patient or outpatient treatment, diagnostic or therapeutic
interventions, nursing, or rehabilitative, palliative, convalescent, preventative or other health
services.

It is proposed that the NHI scheme will be funded by means of cross-subsidisation of
medical services. Currently, the reserves held by medical schemes are equivalent to 33 per
cent, notwithstanding that statutorily the reserves required are 25 per cent.

In addition to the NHI Bill, the Cabinet approved the draft Medical Schemes
Amendment Bill in 2018. This amendment bill proposes doing away with prescribed
minimum benefits and replacing them with ‘basic benefits’, but little guidance has been provided as to what this constitutes. Currently, medical schemes are required to cover the costs related to the diagnosis, care and treatment of those receiving prescribed minimum benefits. It can, however, be stated that much interaction will be required between the public and private sectors to finally modify, align, implement and fund the above-mentioned and proposed healthcare reforms.
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 20 December 2018, 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.

Manufracturers 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.

viii 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 itself to be authorised and further 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.

ix 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 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).

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.
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.

x 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.

xi 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, medicines for hospital diagnosis to be prescribed by a specialist and medicines under special medical supervision).

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. Nonetheless, given the special structure of the drugs market in Spain, the Spanish Competition Authority (CNMC) launched a study on the market in March 2017 for wholesale distribution and marketing of medicines in Spain, in order to complement the recommendations provided on the study launched in 2015 regarding the retail market. The resulting report would address preliminary potential regulatory and competition restrictions arising from the functioning and structure of the market and the exercise of the distribution activity.

Regarding proceedings before the CNMC in this sector, in August 2018 (Resolution on File S/DC/0608/17), the CNMC finally considered that the double-price scheme imposed by some pharmaceutical companies, which implied fixing different prices to retailers, depending on whether the drugs were sold in Spain or abroad, does not entail an infringement of competition law.

ii Transactional issues

The pharma sector in Spain experienced important transactions during 2018, especially regarding M&A. The CNMC authorised the first phase of the acquisition of the sole control of at least 10 life sciences companies that develop healthcare activities or are related to the manufacture of medicinal products, medical devices or wholesale distribution.
VIII CURRENT DEVELOPMENTS

The main development that took place in 2018 was the entry into force of the Regulation (EU) 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and its implementation in Spain by means of Organic Law 3/2018 of 5 December, on protection of personal data and safeguard of digital rights. This law has an important impact on the life science sector since it provides for a simplified regulation regarding the processing of health-related data, including a set of measures oriented to foster biomedical research based on the reutilisation of health-related data for investigational purposes without obtaining new specific consent of the patient. Besides, this regulation opens the door to the use of big data within the healthcare sector, establishing the conditions to allow access to health-related data contained in clinical and patient records.

Finally, the protection of competition within public procurement is also in the spotlight. Law 9/2017, of 8 November, on Public Procurement implementing the European Procurement Directives (2014 Concession Contracts Directive, 2014 Public Contract Directive and 2014 Utilities Contracts Directive) governing the public procurement of medicines established a framework to foster competition and to increase the participation of small and medium-sized enterprises, promoting sustainability in the national economy. In this line, during 2018, the CNMC implemented an action plan oriented to avoid bid rigging and has also created a special economic unit expressly dedicated to detect collusion in public tenders, acting *ex officio*. 

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SWEDEN

Chapter 28

I INTRODUCTION

Healthcare in Sweden is the shared responsibility of the state, 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 innovation leader, according to the European Innovation Scoreboard.

Being an EU Member State, Sweden’s legal framework on medicinal products and medical devices is 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.

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 Ordinance 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

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1 Camilla Appelgren and Odd Swarting are partners at Calissendorff Swarting Advokatbyrå.
2 SFS 2015:315.
3 SFS 2015:458.
4 SFS 1993:584.
5 SFS 1993:876.
a transitional period of three years after entry into force for the regulation on medical devices (in spring 2020), and five years after entry into force for the regulation on *in vitro* diagnostic medical devices (in spring 2022).

### 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:

- any substance or combination of substances having properties for treating or preventing diseases in human beings; or
- 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:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process; or
- 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 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

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\(^7\) SFS 1988:534.

\(^8\) SFS 2003:460.
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 Regulation and the Patient Data Act, 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 LVFS 2008:1 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 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.

10 SFS 2008:355.
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 disproportionally 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,\(^{11}\) 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\(^{12}\) is also applicable.

The Medicinal Products Act and the MPAs provision published in the MPAs Code of Statutes\(^{13}\) 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.

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 12 February 2018.

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\(^{11}\) SFS 2008:486.

\(^{12}\) SFS 2010:696.

\(^{13}\) LVFS 2009:6.
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 they are 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,\(^\text{14}\) the Ordinance on Trading in Medicinal Products\(^\text{15}\) 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, 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.

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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 enters 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\(^{16}\) 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,\(^{17}\) 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.

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.

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\(^{16}\) SFS 1968:64.

\(^{17}\) SFS 1992:860.
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 2,300 kronor (as of 1 January 2019).

The TLV, which is an expert state agency, decides to what extent a medicinal product shall be reimbursed, according to the Pharmaceutical Benefits Act.\textsuperscript{18} 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 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. Even if the patient has a prescription for a specific medicinal product, and as long as the prescribing

\textsuperscript{18} SFS 2002:160.
doctor has not opposed substitution for medical reasons in writing, the pharmacy must offer the product with the lowest price. 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.

\(^\text{19}\) SFS 1971:291.
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 agreement came into force on 1 January 2014.

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 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,23 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.

22 SFS 1972:207.
23 SFS 2010:659.
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. 24 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).

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.

24  SFS 2008:579.
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. 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 inquiry’s findings include the presentation of several proposals for major changes in the allocation of responsibilities between the state, the county councils and regions in relation to funding, subsidy and pricing of medicines, in general resulting in increased financing and cost responsibilities for the county councils and regions. Also among the inquiry’s proposals is one for the introduction of a new, regional joint authority, and one for the dismantling of the frameworks for three-party deliberations between the TLV, county councils and pharmaceutical companies. The inquiry also includes proposals for special financing of new, innovative treatments such as cell and gene therapies.

The Swedish government established the public inquiry with the task of investigating and analysing the pharmacy market, 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.

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 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.

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In 2015, the government commissioned an inquiry to investigate how public funding of privately provided welfare services can be designed to ensure equality, quality, economic efficiency and transparency. A key proposal presented in a report from the inquiry included limiting profits in, for example, privately owned for-profit health and social care businesses by restricting operating profits in relation to the working capital at a rate based on the government borrowing rate plus 7 percentage units. The inquiry and its proposals have been the subject of massive debate in Sweden. In January 2018, the government presented a bill to the parliament, which included the profit limitation proposal with regard to social care services but did not include the healthcare sector. In June 2018, the parliament voted down the bill.
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 been revised (the amended provisions came into force on 1 January 2019). 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.

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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, \textit{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 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.

\(^{2}\) 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 of the 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.
\(^{9}\) Article 11 paragraph 2 lit. a (1) and (2) TPA; Articles 3 et seq. of the Ordinance on the Requirements Regarding the Marketing Authorisation of Medicinal Products (AMZV).
Clinical trials are mainly governed by Articles 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).\(^{14}\)

### Named-patient and compassionate use procedures

In Switzerland, there are two main possibilities to use non-authorised medicines. Swissmedic may authorise a medical professional to 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.\(^{16}\)

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10 Article 54 paragraph 1 and 2 lit. b TPA.
11 Article 45 paragraph 1 HRA; Articles 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 Articles 4 et seq., Articles 19 et seq., Article 46 and Article 56 HRA; Articles 3 et seq., Articles 10 et seq., Articles 37 et seq. and Articles 64 et seq. KlinV.
15 Article 49 of the 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; Articles 52 et seq. AMBV.
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.\textsuperscript{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.\textsuperscript{18}

\textbf{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.\textsuperscript{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.\textsuperscript{20}

The marketing authorisation is issued for five years. Its renewal is generally unlimited in terms of time.\textsuperscript{21}

A simplified procedure ensures fast access to certain categories of medicines:

\hspace{1em}a medicines with known active pharmaceutical ingredients;

\hspace{1em}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;

\hspace{1em}c 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;

\hspace{1em}d 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;

\hspace{1em}e complementary medicines;

\hspace{1em}f herbal medicines;

\hspace{1em}g medicines prepared by a hospital pharmacy or in the hospital’s own radiopharmaceutical unit for the needs of the hospital;

\hspace{1em}h medicines prepared by the army and used in the context of the coordinated army medical corps;

\hspace{1em}i important medicines for rare diseases; and

\textsuperscript{17} Article 71c paragraph 1 in conjunction with Article 71a paragraph 1 lit. a and b KVV.

\textsuperscript{18} Article 71d paragraph 1 and 2 KVV.

\textsuperscript{19} Article 9 paragraph 1 and Article 45 TPA.

\textsuperscript{20} Article 10 paragraph 1 TPA. See also Article 11 and Article 16 et seq. TPA.

\textsuperscript{21} Article 16 paragraph 2 and Article 16b paragraph 2 TPA.
v 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:

a authorisation of a medicine with a new active substance: 80,000 Swiss francs;

b authorisation of a medicine with a known active substance: 50,000 Swiss francs;
c authorisation of a herbal medicine with a new active substance: 30,000 Swiss francs;
d authorisation of a medicine in the simplified procedure: 100 to 80,000 Swiss francs;
e renewal of an existing authorisation and change into authorisation unlimited in time: 500 Swiss francs; and

f 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

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

22 Articles 14 et seq. TPA.
23 Article 15 TPA.
24 Article 4 paragraph 1, Article 9 lit. a and annexes 1 and 2 of the Ordinance of the Swiss Agency for Therapeutic Products on its fees.
25 Articles 45 et seq. TPA; Articles 4, 6 and 9 et seq. MepV.
26 Articles 140a et seq. of the Federal Act on Patents for Inventions (PatG).
27 Articles 11a et seq. TPA; Article 30 of the Ordinance on Medicinal Products (VAM).
Medicines for paediatric use benefit from a six-month extension of the supplementary protection certificate, subject to certain conditions.\textsuperscript{28} Patent-protected medicines may be manufactured and exported to developing countries to combat public health problems, subject to certain conditions (compulsory licences).\textsuperscript{29}

\textbf{vii} \hspace{1em} \textbf{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.\textsuperscript{30}

The marketing authorisation is transferable.\textsuperscript{31} The rules regarding amendments to approvals (known as variations) have been largely harmonised with EU law.\textsuperscript{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.\textsuperscript{33}

\textbf{viii} \hspace{1em} \textbf{Manufacturing controls}

Manufacturers of medicines require a licence from Swissmedic, whereas manufacturers of medical devices are not required to obtain such a licence.\textsuperscript{34}

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}

\textbf{ix} \hspace{1em} \textbf{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.

\textsuperscript{28} Articles 140n et seq. PatG.
\textsuperscript{29} Article 40d PatG.
\textsuperscript{30} Article 59 TPA.
\textsuperscript{31} Article 10 VAM.
\textsuperscript{32} Articles 21 et seq. VAM; Articles 22a et seq. AMZV.
\textsuperscript{33} Article 16a TPA; Articles 11 and 13 VAM.
\textsuperscript{34} Article 5 paragraph 1 lit. a TPA.
\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.
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.\(^\text{38}\)

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.\(^\text{39}\)

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.\(^\text{40}\)

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.\(^\text{41}\)

The infringement of the regulations on the advertising of medicines may entail criminal sanctions.\(^\text{42}\)

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 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.\(^\text{43}\)

**x 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.\(^\text{44}\)
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 in a pharmacy, a drugstore or another retail trade establishment 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{xii 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 pharmacists. 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}

\textbf{xiii 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.\textsuperscript{54}

The licence is unlimited in time in principle, and specifies in particular the qualified person, the authorised activities and the business locations.\textsuperscript{55}

\begin{flushright}
\textsuperscript{45} Article 4 paragraph 1 lit. e TPA; Articles 24 et seq. AMBV.  \\
\textsuperscript{46} Articles 40 and 42 AMBV.  \\
\textsuperscript{47} Article 30 TPA.  \\
\textsuperscript{48} Article 27 TPA.  \\
\textsuperscript{49} Articles 23 et seq. TPA; Articles 40 et seq. VAM.  \\
\textsuperscript{50} Articles 41 et seq. VAM.  \\
\textsuperscript{51} Article 45 VAM.  \\
\textsuperscript{52} Articles 43 et seq. VAM.  \\
\textsuperscript{53} Article 88 VAM.  \\
\textsuperscript{54} Article 18 TPA; Articles 11 et seq. and Articles 21 et seq. AMBV.  \\
\textsuperscript{55} Articles 40 and 42 AMBV.
\end{flushright}
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.\(^{56}\)

The import of medicines is generally limited to medicines that have been authorised or that are not subject to authorisation.\(^{57}\) 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.\(^{58}\)

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.\(^{59}\)

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.\(^{60}\)

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.\(^{61}\)

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.

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.\(^ {62}\)

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

\(^{56}\) 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.
\(^{62}\) Article 32 KVG.
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 specialties is reviewed every three years.63

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.64

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.65

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.66

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYORS

The TPA states that it is prohibited to grant, offer or promise material benefits to persons who prescribe or dispense medicines or to the organisations that employ them, and for such persons or organisations to solicit or accept such material benefits. However, material benefits of modest value and that are related to medical or pharmaceutical practice, as well as commercially and economically justified discounts that directly reflect on the price are permitted.67

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.68

The Pharma Code and the Pharma Cooperation Code contain further provisions regarding the relationship between the pharmaceutical industry and prescribers. 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. So far, such disclosure obligations only exist in self-regulatory codes, as no such statutory obligations exist.

63 Articles 65b and 65d KVV; Articles 34a bis et seq. of the 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.
67 Article 33 TPA.
68 Article 56 paragraph 3 KVG.
The TPA has also been revised with regard to this topic, but the accordant ordinance has not been completed yet. These will not come into force before January 2020.

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.69

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 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.70 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.71

69 Article 40 lit. h of the Federal Act on the Medical Profession.
71 Decision of the Federal Administrative Court B-843/2015 of 19 December 2017, consid. 6.
ii Transactional 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 TPA, the majority of which came into force on 1 January 2019, brought several improvements to the marketing authorisation process of medicines. It has made it faster and less costly for some medicines to be authorised and offers better data protection. It supports paediatric indications as well as orphan indications. The re-classification, especially the unwanted upscaling of certain medicines to the prescription category B, could lead to appeals, since prescription medicines may not be advertised to the public in Switzerland. Whether current ordinance law in this regard correctly reflects the TPA is still not decided either.

Medical devices regulations shall be harmonised with the new specific EU regulations. Negotiations between Switzerland and the EU are ongoing and are viewed in light of the general exchanges between Switzerland and the EU to develop bilateral treaties.

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, some provisions of the KVV and KLV were altered as from 1 March 2017. In late-2019, 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:

- 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;
- other medicines capable of sufficiently affecting the body and physiological functions of human beings; and
- medicines used in preparing the above-mentioned medicines.

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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. Several meetings were held by the TFDA in 2016 and 2017 to gather comments from the public; a revised draft was approved in late 2017 by the MoHW and the Executive Yuan (the highest administrative body in Taiwan (EY)) and was submitted to the Legislative Yuan (LY) in December 2017. A bill becomes effective after it has passed three readings and has been announced by the president. The draft passed its first reading on 29 December 2017; however, there has been no further progress on the bill to date.

There are no ‘borderline’ cases as regards medicines and medical devices in relation to cosmetics and cosmeceutical products, foods and food additives. Since the MoHW is the sole central authority with competence to enforce the relevant laws, such as the PAA, the Statute for Control of Cosmetic Hygiene, the Food Safety and Sanitation Control Act and the Health Food Control Act, the MoHW reviews all cases and determines the necessary classifications.

With respect to chemicals, toxic chemicals are regulated by the Toxic Chemical Substances Control Act, with the Environmental Protection Administration as the competent central authority, while precursor chemicals are regulated by the Narcotics Prevention and Control Act and the Categories and Regulations Governing Inspection and Declaration of Industrial Precursor Chemicals, with the MoHW and the Industrial Development Bureau as the competent central authorities, depending on whether the chemicals are manufactured for medical or industrial products. There are no borderline cases at the moment.

ii Non-clinical studies
Currently, there are only two Taiwanese regulations related to non-clinical studies: the Good Laboratory Practice for Non-clinical Laboratory Studies (GLP) and the Guideline for the Non-clinical Safety Studies for Medicinal Products (the Guidelines) amended by the MoHW in March 2006 and June 2014, respectively. As indicated in their respective prefaces, the GLP and the Guidelines 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, the GLP and the Guidelines 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 to provide

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2 See more classification details in Section II.v.
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. Where a pharmaceutical firm acting as a sponsor engages an institution and an investigator to conduct clinical trials under the GCP, a clinical trial agreement (CTA) must be executed and any financial support from the sponsor must be specified therein. It is also required under the GCP that the sponsor should be responsible for compensation and insurance for injuries inflicted on the human subjects; however, the institutions and investigators do not have this responsibility. Allocation of liability between institutions or investigators and sponsors is mostly determined in the terms of the CTAs. Although the GCP does not stipulate that the sponsor must be established in Taiwan, in practice, local hospitals prefer to enter into CTAs with sponsors or their clinical research organisations (CRO) established in Taiwan to ensure that, in the case of legal dispute, they can claim against local entities. Safety reporting requirements and mechanisms have also been established to ensure the protection of human subjects’ safety and to ensure that a trial could be terminated as soon as the study is no longer deemed safe. 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 CTA 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. An application must first pass the internal review of the institutional review board or ethics committee of the teaching hospital that is applying. 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. While the legal basis of a project-related importation programme is provided in certain administrative rules, Article 48–2 was added to the amendments to the PAA, effective as of 2 December 2015, to provide a higher-ranking legal basis for project-related importation programmes.

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: the patients’ consent, a treatment plan issued by a healthcare institution, documents providing evidence that the medicaments have obtained marketing approval from the competent sanitation authority of the country where they are manufactured, and safety and efficacy data.
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. If the applicant is an individual, entity, agency or institution, he or she may apply for reimbursement from the MoHW for 80 to 100 per cent of the costs.

### 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 January 2018. One of the most important changes is that a post-marketing risk management plan (RMP) becomes a requirement when filing the application, to ensure the applicant manages risk after marketing approval is granted.

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 RMD was comprehensively amended in September 2014 to restructure the provisions, to simplify the application procedure for medical devices that have already been approved in the United States or EU Member States, and to reflect and clarify the TFDA’s current practice, and was partly amended in March 2017 to simplify or clarify certain documentation requirements.

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; the TFDA welcomes discussion and comments from the public. Additionally, the TFDA has proposed a draft Cell and Genetic Therapy Product Control Act in early 2017, and the EY has proposed a draft Regenerative Medicinal Products Control Act in October 2018; both drafts are still under discussion.

The application fee for registration of NCE, biological medicines or biosimilar products is in the region of NT$600,000. The application fee for registration of other types of medicines and medical devices ranges from NT$15,000 to NT$50,000. 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. Therefore, international pharmaceutical firms usually set up subsidiaries or branches in Taiwan or appoint agents to comply with these requirements.

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. However, there are special regulations for biological medicines and herbal medicines under the RRM, and the RMD specifies that customised medical devices must also meet the requirements set out in the Regulations on Pharmaceutical Toll-Manufacturing and Contract Analysis. For generic products, relevant information and data of bioavailability and bioequivalence (BA/BE) must be submitted. The Guidelines for BA/BE Studies promulgated by the MoHW provide guidance on how such studies should be conducted.

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 date on which these patent linkage-related provisions in the PAA 2017 will become effective is subject to the determination of the EY, since the administrative body will require time to prepare for the implementation of the patent linkage mechanism. The TFDA published draft Enforcement Rules of Patent Linkage in September 2018, but further changes will be made to these draft Enforcement Rules to reflect comments gathered from the public consultation, and thus the implementation date of the patent linkage mechanism is still unknown. 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 PAA provides data exclusivity and study exemption clauses to balance the benefit of brand-name and generic firms. The relevant provisions were amended in the PAA 2017 and the amended provisions have become effective; 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.

An article similar to the Bolar provision was added to the Patent Act of December 2011, which provides that the research and studies conducted for the registration of medicaments in this or other jurisdictions, regardless of whether they were conducted prior to or after an application for registration, will be covered by the study exemption. On the other hand, 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, it is provided under the Patent Act that where there is an invention patent in respect of a medicine or a medicine manufacturing process, if exploitation of that patent would require regulatory approval pursuant to other laws and if regulatory approval could only be obtained after publication of the invention patent, 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. A compulsory licensing mechanism has been included in the Patent Act to help developing countries prevent pandemics and other serious diseases.

vii Post-approval controls

The marketing approval holder must be a company duly registered under the laws of Taiwan and holding a pharmaceutical dealer licence. In addition, the pharmaceutical firm must employ a full-time resident pharmacist as part of its management. For a manufacturer engaged in the manufacturing of biological medicines, a resident technician with a degree in medical science, pharmacy or biology from a domestic or foreign university or college and possessing professional knowledge backed with more than five years of experience in the manufacturing of microbiological and immunological medicines must be employed to supervise the manufacturing. 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. This proposed legislation is the subject of intensive debate within the industry. 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. This Regulation was amended on 21 November 2013 to include pharmaceutical products being subject to the RMP or participating in post-marketing surveillance studies as part of the mandatory reporting category and to provide more detailed procedures for such reporting.

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 any post-approval trials or studies are conducted, they have to comply with the HSRA guidelines. 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 launched an overall inspection of local manufacturers of active pharmaceutical ingredients (APIs) during the period from March to June 2013, to ensure that the ingredients in API products manufactured locally were in compliance with the products’ application and registration data. Thirty-three pharmaceutical products contained ingredients that deviated from their application and registration data so they were suspended from the market for further BA/BE tests. The TFDA intends to conduct such inspections regularly to ensure the safety and efficacy of the pharmaceutical products manufactured locally. In addition, the MoHW issued a ruling on 25 September 2013 requiring that all API factories being established or relocated after 1 July 2014 and all API factories applying for marketing approvals for new APIs after 1 July 2014 must meet the requirements of the GMP; all other API factories had to meet GMP standards by 31 December 2015, the aim being to improve manufacturing quality in Taiwan. 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. Details of this practice will be further regulated and promulgated 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 May 2014, a health awareness advertisement that aimed to bring the public’s attention to a disease caused by a certain virus and the possibility of preventing the disease by use of a vaccine (without mentioning the name of any vaccine) has been investigated jointly by the TFDA and the Department of Health of the Taipei City Government, the competent local authority. The advertisement was ultimately deemed to be a disguised pharmaceutical advertisement to promote the vaccine since there is only one vaccine product registered in Taiwan that is used for preventing the disease. The advertisement was later suspended by the TFDA and the Taipei Department of Health and the vaccine marketing approval holder was fined. This shows the stringent implementation of relevant provisions by local authorities.

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). As a result, the calculation of premiums, based on different classifications of insured persons, was entirely restructured from 1 January 2013; this is also known as second-generation NHI. 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), which was also extensively amended by the NHIA, promulgated by the MoHW in December 2012 and effective on 1 January 2013 to cope with the changes made to the NHI Act; it was subject to minor amendments during the period from August 2013 to March 2017 to clarify certain provisions. 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 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 between the NHIA and marketing approval holder is available under the PB Scheme for newly added medicines and indications. In this respect, the NHIA has published a draft amendment in July 2018 to the PB Scheme to include the managed-entry agreement (MEA) mechanism, which will allow the NHIA and the marketing approval holder more room to negotiate the drug price and budget, and to allocate the risk more reasonably.

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
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 will also implement the Drug Expenditure Target (DET) for the period from 1 January 2013 to 31 December 2015 to improve the transparency and predictability of pricing and reimbursement in the market. The implementation of the DET has been extended until the end of 2019. 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. On 18 December 2015, the NHIA published a draft to relax the criteria of drugs under patent protection; the draft was passed in February 2016 and more drugs now have patent protection under the Price Adjustment Guidelines.

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.

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.
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 2018. 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. Takeda Pharmaceutical Co Ltd (Takeda), a Japanese brand-name company, sued Genovate Biotechnology Co Ltd, a Taiwanese generic company, for patent infringement and sought a preliminary injunction. The preliminary injunction was granted and later became final; thus, Genovate was prevented from selling the drugs. It was subsequently found during litigation that the patent infringement assessment report submitted by Takeda to substantiate its application for a preliminary injunction was
fundamentally erroneous, since the report found that a kind of preparation product could infringe a compound preparation patent. As a brand-name pharmaceutical firm, Takeda ought to have known of the inaccuracy contained in the 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 has been included in the PAA 2017, 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 recent inclusion of patent linkage in the PAA 2017. As the TFDA will have to establish in more detail the implementing regulations for patent linkage, further developments regarding the promulgation of these regulations by the relevant administrative agencies, and their impact on the industries concerned, should be closely monitored.

As to the draft Medical Devices Act, the TFDA intends to separate the medical device-related regulations from the PAA so that there is room to gradually fine tune the regulations in several stages in the future. It is also the view of some scholars that the contents of the draft would not fundamentally or suddenly change current practices in the medical devices industry.
I INTRODUCTION

Established by a policy of the Ministry of Public Health (MOPH), the Food and Drug Administration (FDA) is the principal government regulatory authority for drugs, medical devices, foods, cosmetics, hazardous substances, narcotics and psychotropic substances in Thailand. The FDA controls these products through the following divisions: Bureau of Drug Control, Medical Device Control Division; Bureau of Foods, Cosmetic and Hazardous Substance Control Division; and Narcotics Control Division.\(^1\)

The roles and responsibilities of the FDA can be grouped into five main areas: pre-marketing control, post-marketing control, a surveillance programme for consumers’ safety, consumer education, and technical support and cooperation with other agencies.

The FDA's duties are conducted in accordance with national legislation in the form of specific Acts for each product category. The Acts generally follow a common format and cover the following matters: definitions, specialised committees, officers’ responsibilities, licences, obligations on the licence holder, product classification, advertisement, licence suspension and revocation, penalties and government fees. Under each Act, notifications are issued by the relevant committees or ministers that provide additional guidelines and requirements for operators. These notifications usually provide details of what approvals are needed, the requirements to obtain those approvals, the relevant forms and the implementation date. These notifications serve as updates on changes implemented by the FDA, such as the new e-submission system, which will be discussed in Section II.

The relevant laws also demand that certain issues are decided by committees whose members (experts in their respective fields) will be appointed by the Minister of Public Health. At present, there are seven committees: drugs, medical devices, foods, cosmetics, hazardous substances, narcotics, and psychotropic substances.

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II THE REGULATORY REGIME

i Classification
There are seven Acts that govern specific products, in particular, drugs, medical devices, foods, cosmetics, hazardous substances, narcotics and psychotropic substances. The products (and their variations) governed by each specific Act are laid out in the introductory section of each Act.

The Acts provide for definitions and classifications of products. For example, the Drug Act provides a broad definition of a drug that covers details such as substances recognised in a pharmacopoeia approved by the Minister and intended for use in the diagnosis, treatment, relief, care or prevention of human or animal disease. Once it is clear that a particular product has the characteristics of a drug (and more importantly that it does not have characteristics that are excluded under the Drug Act), there are then further subclassifications (such as modern drugs and herbal drugs).

For medical devices, the Medical Device Act provides clear definitions for medical devices and the main focus for product classification is on the manufacturer's intended use, which must be clearly declared by statements made on the product label or leaflet issued by the manufacturer.

ii Non-clinical studies and animal testing
The Institute of Animals for Scientific Purpose Development, an agency of the National Research Council of Thailand, is the body responsible for the use of animals for scientific purposes. Non-clinical testing on animals is regulated by the Animals for Scientific Purposes Act, BE 2558 (2015).

In addition to the Act, the National Research Council of Thailand has issued Ethical Principles and Guidelines for the Use of Animals. The Guidelines set standards for animal care and management of animal health, and only allow techniques that minimise the stress and pain endured by animals during testing.

iii Clinical trials
There is no specific Thai law governing human clinical trials. However, in practice, clinical trials in Thailand should follow international codes of ethics, such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice (ICH/GCP). In 2000, the FDA translated the ICH/GCP into Thai for ease of reference and to act as guidelines.

To facilitate clinical trials, the FDA has issued a Notification that deals with the importation of drugs for clinical trial purposes. The Notification outlines the requirements for an Ethics Committee to consider requests for importing drugs into Thailand for clinical research. If approved, these drugs are then exempted from the need for drug formula registration with the FDA, until such time as the manufacturer decides to commercially sell or distribute the drug in Thailand.

Research participants must be volunteers and a high level of care has to be used. A research project has first to be approved by the Ethical Review Committee for Research in

4 The Notification of the Food and Drug Administration Re: the Requirement on the Import of Drug into the Kingdom for Clinical Trial, dated 17 September 2561 (2018).
Human Subjects (EC), which is under the purview of the MOPH. The EC has put in place Guidelines and Procedure for Research on Human Subjects; however, these are not enforced by law and most research institutions have their own sets of guidelines and procedures.

The requirement for informed consent is covered by Section 9 of the National Health Act, which requires that volunteers must provide written consent before participating in any medical research. Volunteers can revoke their consent at any time. Informed consent is not limited to a one-off signature on a piece of paper, but is a continuing process.

iv  **Named-patient and compassionate-use procedures**

Unlike some countries, there is no specific legislation or regulation that deals with named-patient production or importation. Neither are there any specific exceptions on product registration for the purposes of named-patient usage stipulated in the Drug Act.

v  **Pre-market clearance**

**Drugs**

Pre-marketing control covers product registration and related licences and permits (such as manufacturing facilities, product quality assurance and advertising).

The pre-marketing control of drugs by the FDA is divided into two main steps. The first step is that the Drug Act requires that those who wish to import, manufacture or sell drugs in Thailand must obtain an appropriate licence.

The second step is for the applicant to apply for the relevant product (formula) registration licence.

The application file is then reviewed in detail by the FDA to check the quality, efficacy and safety of the drug. If the application file is complete, it requires a final signature for approval.

It takes approximately 280 working days for a drug registration licence to be granted, according to the current citizen manual, and the application file must be submitted using the eCTD (electronic Common Technical Dossier) only. The first approval of a new drug is a conditional approval only, which allows the new drug to be sold solely through hospitals and medical clinics, and is subject to at least a two-year safety monitoring programme (SMP). Reports from the SMP during these two years will then be considered when a subsequent application is made for an unconditional approval. If granted, an unconditional approval will also allow the drug to be sold through retail pharmacies.

The dossier requirements for drug applications must follow the Association of Southeast Asian Nations (ASEAN) Harmonisation rules that came into effect on 1 January 2009. This means that under the new rules of the ASEAN Harmonisation on Pharmaceutical Registration, manufacturers wishing to sell their products in ASEAN countries are required to prepare dossiers in a common format in accordance with the ASEAN Common Technical Requirement and the ASEAN Common Technical Dossier.

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5 Section 9 National Health Act, BE 2550 (2007).
6 Section 12 Drug Act, BE 2510 (1967).
Medical devices
Medical devices are categorised into three subcategories (see Section II.xi for product classifications) and each category has its own specific pre-marketing procedures.

As a general first step, a local manufacturing facility requires a manufacturing licence and an importer requires an import licence.

vi Regulatory incentives
Thailand does not have specific laws on data exclusivity for the protection of an originator’s drug registration data from other companies submitting applications to the FDA to register generic versions of the drug in question. There is a Trade Secrets Act of general application under which the MOPH has issued a Regulation. However, this Regulation is of limited use as it does not prevent the FDA from referring to and relying upon an originator’s registration data when considering a subsequent generic application. The scope of this Regulation is limited to pharmacopoeia registration information related to modern drugs that use new kinds of chemical substances that have not ever been approved for registration in Thailand.9

The purpose of the Regulation is to allow an applicant who submits the pharmacopoeia registration information, as part of the drug registration process, to also submit an application requesting that the FDA keep the trade secrets of the pharmacopoeia registration information confidential. If the confidentiality application is approved under the Regulation, the FDA is required to keep the information confidential for five years from the approval date.10

It is important to note that the protection granted under this regulation is limited to the maintenance and safe-keeping of the pharmacopoeia registration information as a trade secret.

Thailand has no special provisions to encourage the development of products for rare diseases and no ‘orphan drug’ programme.

vii Post-approval controls
Post-marketing controls aim to monitor manufacturing facilities and product quality and safety after approval has been granted. The objective is to ensure there is continuing compliance with both previously approved requirements and current standards, legislation and notifications. Occasionally, the FDA randomly selects and spot checks products in the market and tests them to ensure that the ingredients are true to the pre-approved product licence label. The surveillance programme for consumers’ safety works hand in hand with the operators’ required pharmacovigilance to protect consumers from dangerous products.

The FDA uses research and epidemiological data, which includes technical information on adverse events.

Manufacturing facilities that have previously been approved are inspected to ensure continuing compliance with the good manufacturing practices (GMP) certification and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), an extension of the Pharmaceutical Inspection Convention.

Currently there are no laws or regulations regarding the transfer of ownership of medical device licences and a transferee would have to apply for a new licence.

9 Article 3 Ministry of Public Health Regulation governing the Keeping of Trade Secrets of Pharmacopoeia Registration Information, BE 2550 (2007).
10 Article 19 Ministry of Public Health Regulation governing the Keeping of Trade Secrets of Pharmacopoeia Registration Information, BE 2550 (2007).
Post-marketing controls on medical devices involve surveillance of the medical devices to prevent injury that are on the market, and the development of regulatory standards and product improvement. Various sources of information are used for post-marketing surveillance (PMS).

To ensure that Thailand’s PMS procedures and requirements meet ASEAN standards, the MOPH has issued a notification on the procedures for the submission of a Device Defect Report or Adverse Event Report and the ensuing Field Safety Corrective Action Report, which came into effect on 4 November 2016.11

As an ASEAN Member State, Thailand has applied and harmonised its standards in compliance with the ASEAN Consultative Committee for Standards and Quality-Medical Device Product Working Group, which has set up a Post-Marketing Alert System to keep track of medical devices on the market that are unsafe.

viii Manufacturing controls
An entity that intends to manufacture drugs in Thailand must apply for a manufacturing licence from the FDA.12 A factory licence from the Ministry of Industry will have to be obtained before applying for the manufacturing licence. A manufacturer of modern drugs must have at least two pharmacists to manage the operation and monitor drugs at the premises during business hours.13 All manufacturers are required to have GMP certification that complies with the standards of PIC/S.

An entity that intends to manufacture any category of medical device in Thailand must have its business premises inspected and registered with the FDA and obtain a manufacturing licence.14 Additionally, procedures to register or notify each type of medical device is required.

ix Advertising and promotion
Each category of drugs and medical devices has different requirements regarding advertisement and promotion. Some products are more restricted than others when it comes to advertising. For example, specially controlled drugs and dangerous drugs cannot be advertised to the public.15 Several medical devices can only be advertised to healthcare professionals, while other medical devices can be advertised to the general public.16 The specific requirements regarding advertising and promotion are prescribed by the FDA.

There are two fundamental requirements for advertising drugs and medical devices.

First, both drugs and medical devices must meet pre-approval requirements for advertising. Before advertising any drug or medical device by any means, the content and wording that will be used in the advertisement must be submitted to the FDA for approval.17

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12 Section 12 Drug Act, BE 2510 (1967).
13 Section 20 Drug Act, BE 2510 (1967).
14 Section 15 Medical Device Act, BE 2551 (2008).
15 Section 88(6) Drug Act, BE 2510 (1967).
16 Section 4.5 Notification on Guidelines, Procedures and Restrictions on Medical Device Advertising, BE 2553 (2010).
17 Section 88 bis Drug Act, BE 2510 (1967), and Section 57 Medical Device Act, BE 2551 (2008).
Second, the content of advertisements must comply with the conditions set by the FDA and must not contain information that is false, exaggerated, misleading or different from the details as registered with the FDA. An advertisement must not use information that cannot be proven. In the approval process, supporting evidence such as scientific or academic information must be provided.¹⁸

In addition to the main requirements set out in the Drugs Act and the Medical Device Act there are several other laws and regulations of relevance, including the Consumer Protection Act, BE 2522, the Direct Sales and Direct Marketing Act, BE 2545, the Medical Professionals Act, BE 2525, and the ASEAN Harmonisation Guidelines covering topics such as labelling requirements and interaction with medical professionals.

**Distributors and wholesalers**

*Drugs*

To sell drugs, a selling licence relevant to the type of business in question is required from the FDA; this may be a wholesale licence, a retail licence or a pharmacy licence. The main condition is that the seller must have such facilities as are prescribed by the ministerial regulations. A pharmacist must be in attendance during business hours to dispense drugs and to monitor activities.

A selling licence is also required for the sale of certain types of medical devices.

**Classification of products**

The Drug Act generally categorises drugs as modern, traditional, dangerous, specially controlled, household, packaged (other than those categorised as dangerous or specially controlled) and herbal.¹⁹ The Minister of the MOPH, on the advice of the Drugs Committee, has the authority to classify drugs into one of these categories by making an announcement in the Royal Gazette.²⁰

However, in practice, for licensing purposes, the FDA classifies drugs into seven main categories: new, new generic, modern, traditional; herbal, household and orphan. Each category of drugs has different restrictions and requirements.

As is the case with a number of other South East Asian countries, the incidence of self-medication in Thailand is generally more prevalent than in some Western countries. For example, what would commonly be regarded as prescription-only items in certain other jurisdictions are available for purchase in retail pharmacies in Thailand without the need for a doctor’s prescription. Generic substitution is accepted practice.

The Medical Device Act classify medical devices into three categories, each with different restrictions and requirements. The Minister of the MOPH, on the advice of the Medical Devices Committee, has the authority to classify medical devices based on risk and safety to consumers,²¹ and the classifications are subject to change as announced.

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¹⁸ Section 88 Drug Act, BE 2510 (1967), and Section 59 Medical Device Act, BE 2551 (2008).
¹⁹ Section 4 Drug Act, BE 2510 (1967).
²⁰ Sections 76 and 78 Drug Act, BE 2510 (1967).
²¹ Section 6 Medical Device Act, BE 2551 (2008).
xii Imports and exports
An entity that intends to import drugs into Thailand must obtain an import licence from the FDA.22

An entity that intends to import any category of medical device must have its business premises registered with the FDA.23

Under the Drugs Act and the Medical Device Act, there is no requirement for a licence to export drugs or medical devices. However, an export certificate (similar to a free sale certificate) may be required by Thai Customs.

A business in Thailand that wishes to manufacture medical devices in accordance with the quality standards, labelling standards or other details specified by an overseas purchaser, and to export those devices without selling them in Thailand, can apply for a manufacturing-for-export licence that will expedite the application process and make it faster than a normal manufacturing licence application process. The procedures and conditions for obtaining a manufacturing-for-export licence are as prescribed by the FDA.24

xiii Controlled substances
Narcotics and psychotropics are listed under various categories and are either restricted or subject to strict licensing requirements.

xiv Enforcement
Owing to personnel limitations, the enforcement phase is initiated when spot checks in the market reveal that products are not up to standard, or when a complaint is made to the FDA about concerns regarding drugs or medical devices. Some follow-up questions might be asked and proof requested from the complainant to determine the legitimacy of the complaint. The FDA will then take over and begin by gathering preliminary information about the product and the responsible person. The product in question will then be analysed and the results will be compared with the product licence and registrations, and any relevant legislation, to determine infractions. The investigation and inspection procedures applied by the FDA vary from case to case. If necessary, the FDA may enlist the police for assistance. The penalties for infractions are provided in the relevant legislation. Additional enforcement actions required for medical devices are covered above in the post-marketing subsections.

III PRICING AND REIMBURSEMENT
In Thailand, drug reimbursement can be made through three programmes: the Civil Service Welfare System for civil servants and their families, social security for private employees, and the Universal Coverage scheme (UC), which is theoretically available to all other Thai nationals who have identification cards.25 A citizen is legally entitled to participate in only one government programme, but he or she may also have private insurance or be self-insured.

22 Section 12 Drug Act, BE 2510 (1967).
23 Section 15 Medical Device Act, BE 2551 (2008).
24 Section 34 Medical Device Act, BE 2551 (2008).
All three programmes have their own health service benefit package, payment system and funding. For the civil service welfare system, all payments are funded by the Comptroller General’s Department\(^\text{26}\) of the Ministry of Finance. For social security, payments are funded by the Social Security Office\(^\text{27}\) and the UC is funded by the National Health Security Office.\(^\text{28}\) Each programme also uses a different payment system, namely fee-for-service, Diagnosis Related Groups and capitation.\(^\text{29}\) However, in all three programmes, the only drugs that can be reimbursed are those included on the National List of Essential Medicines (NLEM). The NLEM is developed by the National Drug System Development Committee, which includes a number of experts, the majority of whom are selected by the FDA. Drugs outside the NLEM can only be reimbursed when a doctor prescribes such drugs as necessary and required to cure the patient of the sickness.

The Health Intervention and Technology Assessment Program (HITAP) under the MOPH is responsible for conducting economic evaluations to develop the Thai health system and policies (including the drug reimbursement policy), to be more effective through using methods such as pharmaeconomics and surveys of relevant stakeholders, such as healthcare providers, academics and patients.\(^\text{30}\) Apart from HITAP, the Health Systems Research Institute (HSRI), which is also an agency under the MOPH, is developing academic information on health policy to develop cost-effective drug reimbursement, among other issues.\(^\text{31}\)

There is also a median drug price for public hospital drug procurement prescribed by the National Drug System Development Committee.\(^\text{32}\) This median price is one of the mechanisms used to control drug expenditure so that public hospitals can purchase drugs at an appropriate price.\(^\text{33}\) The criteria of median price of the supplies to be purchased by government agencies, including the median price for the purchase of drugs by the public hospitals, is also subject to the criteria and requirements under the Public Procurement and Management of Supplies Act, BE 2560 (2017), which became effective on 23 August 2017.\(^\text{34}\) The Government Pharmaceutical Organization also plays a role in controlling drug prices.\(^\text{35}\)

### IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The Drug Act and the Medical Device Act provide mechanisms for internal review of administrative decisions. Under the Drug Act, if the FDA declines to issue or renew a licence,

\(^\text{26}\) Comptroller General’s Department, ‘Guideline for Civil Service Welfare System for civil servants’.
\(^\text{27}\) Social Security Act, BE 2533 (1990).
\(^\text{28}\) National Health Security Act, BE 2545 (2002).
\(^\text{32}\) National Drug System Development Committee Notification regarding median drug price, BE 2561 (2018).
\(^\text{34}\) Government Gazette Book No. 134, Section 24 Gor, dated 24 February 2017.

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the applicant is entitled to submit a letter seeking an administrative review by the Minister of the MOPH within 30 days of the date of the letter declining the application.\(^{36}\) The Drug Act provides the same mechanism for someone whose licence is suspended or revoked.\(^{37}\)

Similar to the administrative review mechanism provided under the Drug Act, the Medical Device Act provides that if the FDA declines to issue or renew a licence, the applicant is entitled to submit a letter seeking an administrative review by the health minister within 30 days of the date of the letter declining the application.\(^{38}\) A person whose licence is suspended or revoked is also entitled to the same administrative review mechanism.\(^{39}\) The Medical Device Act also provides that after receiving a letter requesting an administrative review, the Minister of the MOPH must render a decision within 120 days.\(^{40}\)

According to both the Drug Act and the Medical Device Act, the Minister of MOPH’s judgment is considered to be final,\(^{41}\) and this will be the end of the appeal under the internal administrative review system. If the petitioner is still not satisfied with the Minister of the MOPH’s judgment, the next step is to bring the dispute to an administrative court, which has the function of addressing disputes caused by acts of the government and its agencies, including the FDA.\(^{42}\)

The Administrative Court Act provides:

*If the law provides for the process or procedure for the redress of the grievance or injury in any particular matter, the filing of an administrative case with respect to such matter may be made only after action has been taken in accordance with such process and procedure and an order has also been given thereunder or no order has been given within a reasonable period of time or within such time as prescribed by law.*\(^{43}\)

Since there is a specific appeal process provided by the Drug Act and the Medical Device Act, the entity will have to complete the appeal process before filing a dispute with an administrative court.

According to the Administrative Court Act, any person who is aggrieved or injured, or who may be aggrieved or injured in consequence of an act by the government and its agencies, can file a case with an administrative court.\(^{44}\) This means that competitors and consumers who are affected by an FDA decision can also file a case with an administrative court.

In addition to the aforementioned mechanisms provided by the law, in practice, a number of disputes relating to non-critical issues are resolved through an informal internal dispute resolution process conducted by an FDA officer. In practice, for non-critical issues, after the submission of the licence application, or before the suspension of each existing licence, the FDA’s official will review the application and related facts and let the business

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\(^{36}\) Section 18 Drug Act, BE 2510 (1967).

\(^{37}\) Section 99 Drug Act, BE 2510 (1967).

\(^{38}\) Section 74 Medical Device Act, BE 2551 (2008).

\(^{39}\) Section 75 Medical Device Act, BE 2551 (2008).

\(^{40}\) Section 76 Medical Device Act, BE 2551 (2008).

\(^{41}\) Section 18 Drug Act, BE 2510 (1967) and Sections 74 and 75 Medical Device Act, BE 2551 (2008).

\(^{42}\) Section 9 Act on Establishment of the Administrative Court and Administrative Court Procedures, BE 2542 (1999).

\(^{43}\) Section 42 Act on Establishment of the Administrative Court and Administrative Court Procedures, BE 2542 (1999).

\(^{44}\) ibid.

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entity know of any issues that may lead to the rejection of the application or suspension of the existing licence, before making any decision. The official will inform the business entity of the problem and ask it to resolve those issues internally.

For critical issues, where criteria cannot be negotiated or resolved, the FDA official will render a decision directly. An entity that wishes to challenge or appeal the decision will then submit a letter seeking an administrative review by the Minister of the MOPH. The classification of critical issues and non-critical issues are listed internally by the FDA official and are subject to the discretion of the official involved.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

Generally, there should not be any financial relationships between prescribers and payers or product suppliers. The procurement of products must be done with hospitals and not through prescribers. In Thailand, most healthcare facilities are government hospitals or hospitals that belong to medical schools that are mostly required to abide by the same set of procurement rules as used by government hospitals.45

Doctors and healthcare professionals who work in government hospitals are deemed to be ‘officials’ under and subject to the Penal Code and the Act Supplementing the Constitution Relating to Prevention and Suppression of Corruption, BE 2561 (2018). Generally, the types of procurement methods that are used in government hospitals are e-market and e-bidding under the general invitation method, the selection method and the specific method. The e-market applies to the procurement of supplies costing in excess of 500,000 baht that do not have specific or complex features, and where the specification of such supplies is provided in the government’s e-catalogue system, while the e-bidding applies to the procurement of supplies costing in excess of 500,000 baht, where specification of such supplies is not provided in the government’s e-catalogue system. The relevant processes must be in accordance with the method specified by the Comptroller General’s Department.46 The selection method requires at least three entrepreneurs who have qualifications as specified by the government agency, all of whom must submit a proposal, unless there are fewer than three entrepreneurs who meet the requirements.47 This method is often used by public hospitals when there are special circumstances or conditions, for example when the article being procured must be a brand name owing to the nature of its use or its technical specifications.48 The specific method applies primarily when supplies are procured that are manufactured, distributed, constructed or serviced in general, the cost is within the financial limit specified by ministerial regulations for single procurement (not exceeding 500,000 baht)49 and there is only one entrepreneur who possesses the qualifications specified by a government agency.50

45 Public Procurement and Management of Supplies Act, BE 2560 (2017).
46 Comptroller General’s Department Regulation on Public Procurement and Management of Supplies Act, BE 2560 (2017).
47 Section 55(2) the Public Procurement and Management of Supplies Act, BE 2560 (2017).
48 Section 56(1)(d) the Public Procurement and Management of Supplies Act, BE 2560 (2017).
49 Section 56(2)(b) the Public Procurement and Management of Supplies Act, BE 2560 (2017) and Section 1 the Minister of Finance Regulation Specifying the Budget for Procurement of Supplies by the Specific Method, the Budget for Procurement of Supplies that a Written Agreement is not required, and the Budget for Procurement of Supplies in appointing the Procurement of Supplies Inspector, BE 2560 (2017).
50 Section 55(3) the Public Procurement and Management of Supplies Act, BE 2560 (2017).
It is common practice that certain discount schemes are required as part of the procurement process adopted by government hospitals. Currently, discounts of this nature are considered to be acceptable within the industry as long as the discount and the payment of the discount in question is made in a transparent manner. Nevertheless, the National Anti-Corruption Commission (NACC) has issued a guidance letter to the secretary general of the Cabinet as a proposal for the Cabinet to consider. One of the criteria is to prohibit government agencies that procure any medical or healthcare supplies from seeking any income (to be payable to a hospital welfare fund) in any form that might be considered a *quid pro quo* from pharmaceutical companies.\(^{51}\) The Cabinet had a conference on 12 September 2017 acknowledging the proposed measures under the NACC guidance letter, and requested that the MOPH be the main agency, alongside the Ministry of Finance and other related agencies, to consider proceeding with the relevant matter. The MOPH also agrees with the NACC guidance letter.\(^{52}\) Failure to comply with these requirements may lead to accusations of non-compliance with government corruption prevention measures and disciplinary sanctions for the government agency.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Thailand does not have any special systems or laws dealing with patients who are injured by drugs or medical devices. In circumstances where an injury is caused by drugs or a medical device, the general principles of tort law and product liability law may apply.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Thailand does not have any specific rules or laws that provide for any settlement or arrangements where there is a patent dispute between the originator and generic manufacturers.

ii Transactional issues

There is no specific law or rules governing commercial arrangements between importers or manufacturers and other business operators in the industry. Any licensing and strategic collaborations, joint ventures or mergers and acquisitions in the life sciences industry will be subject to national laws on the subject matter that apply to other industries or products.

VIII CURRENT DEVELOPMENTS

On 13 November 2018, the Cabinet approved in principle the draft amendment of the Drug Act (the Bill), as proposed by the Ministry of Public Health. The Bill will be sent to the National Legislative Assembly for further review and enactment. Among other matters, the key amendments to the Drug Act as proposed under the Bill include:

a allowing experts (in the form of external organisations, government agencies, or private entities, both in Thailand and overseas) that meet the required qualifications to enrol

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\(^{51}\) The NACC Guidance Letter No. PorChor. 0003/0133, dated 28 June 2017.

\(^{52}\) The Secretariat of the Cabinet Letter No. NorRor 0505/Wor(Lor) 30342, dated 15 September 2017, and the MOPH Letter No. 0217/3382, dated 9 August 2017.
with the FDA to evaluate academic documents, conduct product analyses and audit business premises on behalf of the FDA. The aim of this is to facilitate and accelerate the drug approval process by lessening the workload of the FDA;

b allowing the FDA to use the official fees collected from the experts’ enrolment and the drug approval process for its own operations (including the development of the required systems related to the drug approval process and consumer protection activities), without first having to return the fees to the government treasury;

c requiring the applicant to provide a document showing the patent or petty patent for a drug product that has a patent or petty patent in accordance with the applicable patent laws, or the right to data related to Thai traditional medicinal wisdom for Thai traditional drug products, when applying for a drug registration licence; and

d specifying the period of validity of drug registration licences to be five years from the issue date (instead of having no expiration date). Drug registration licences issued before the Bill becomes effective will remain valid for between five and seven years (depending on the year the drug registration licences were issued).
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.

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.

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.
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 is currently reviewing 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. Although no firm deadlines have been published, these regulations are likely to be promulgated in 2019.

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 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.

Currently, there are four duly licensed organ transplant clinics in the UAE. 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;
- 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;
medications that have been previously registered but have been cancelled by the local agent as a result of lack of market demand; or
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.

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 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.

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.

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.

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:

a. Class I medical devices are considered to be of low risk to patients. A declaration of conformity is usually accepted from the manufacturer.

b. 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.

c. 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.

d. 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.

xiv 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.

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 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 Department of Health – Abu Dhabi (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 and the Medical Malpractice Law (UAE Federal Law No. 10 of 2008, which allows for direct and consequential damages related to medical malpractice), there are no special liability or compensation systems contemplated in applicable law.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

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) 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 unclear at this stage.

I INTRODUCTION

Medicines for human use are regulated primarily by the Human Medicines Regulations 2012 (the Medicines Regulations).² The Medicines Regulations implement Directive 2001/83/EC³ 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 1968⁴ – 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 Device Regulations,⁵ which implement the three EU Medical Devices Directives⁶ into UK law (pending the implementation of Regulation (EU) 2017/745⁷ on Medical Devices, and Regulation (EU) 2017/746⁸ on In Vitro

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4 The Medicines Act 1968 (Chapter 67), as amended.
5 The Medical Devices Regulations 2002 (SI 2002/618), as amended.
Diagnostic Medical Devices, which both entered into force on 25 May 2017 and, following a transition period, are anticipated to apply fully 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 1986\(^9\) implemented Directive 2010/63/EU\(^10\) 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 1999\(^11\) transpose Directive 2004/10/EC\(^12\) 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/EC\(^14\) and 2005/28/EC\(^15\) 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.

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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.
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.

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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:

- the product is needed to treat a life-threatening or seriously debilitating condition, and there is a high unmet need;
- the medicinal product is likely to offer significant advantages over methods currently used in the United Kingdom;
- the potential benefits of the medicinal product outweigh the adverse effects; and
- 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

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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\textsuperscript{18} and Regulation (EC) No. 1901/2006,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.


\textsuperscript{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 has no specific rules governing the distribution or wholesale of medical devices.

**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 1971\(^{22}\) 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 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

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\(^{22}\) The Misuse of Drugs Act 1971 (Chapter 38), as amended.

\(^{23}\) The Misuse of Drugs Regulations 2001 (SI 2001/3998), as amended.
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. 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, National and Social Care 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. 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 participate in the voluntary Pharmaceutical Price Regulation Scheme (PPRS) (for branded medicines), which provides for a system of price controls or rebates negotiated between the ABPI and Department of Health and Social Care. Companies that do not participate in the PPRS must participate in a statutory scheme whereby the Department of Health and Social Care imposes price reductions. 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 Pharmaceutical Price Regulation Scheme

The PPRS is a voluntary arrangement negotiated between the Department of Health and Social Care and the branded pharmaceutical industry represented by the ABPI. The ABPI negotiates the PPRS approximately every five years and agrees a price reduction or payment that participants must deliver during the term of the next scheme. The reduction is based largely on profits companies have generated on NHS sales. Historically, participants were

24 The Consumer Protection Act 1987 (Chapter 43), as amended.
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.
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 most recent PPRS, which took effect on 1 January 2014, companies will be expected to deliver savings by making payments to the government.

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. 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, but 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’,26 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’.27

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

26 Section 31(3) of the Senior Courts Act 1981 (Chapter 54).
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.
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.

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 no national scheme or system to compensate individuals injured by medical devices.

29  The Bribery Act 2010 (Chapter 23).
30  The Vaccine Damages Payments Act 1979 (Chapter 17), as amended.
31  Section 2 of the VDPA.
VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Since the United Kingdom is 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 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. At least three other investigations relating to excessive and unfair prices are in train 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 European Union Court of Justice. The CMA is also investigating a discount scheme that Merck Sharp & Dohme has operated for its product Remicade, among suggestions that it might restrict competition for ‘biosimilar’ versions of infliximab.

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 have been investigated for fixing the prices of opiate drugs. The OFT found that Napp abused its 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.

ii 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.

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 will repeal the European Communities Act 1972 at 11pm on 29 March 2019, 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.

A draft withdrawal agreement (the Draft WA), representing the 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 November 2018. 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 25 November 2018, it was recently rejected in a UK parliamentary vote on 15 January 2019. At time of writing, the exact nature of Brexit 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 Department of Health and Social Care and MHRA have published a series of ‘no Brexit deal’ guidance and proposed contingency planning (available on the UK government website). However, there is now a growing acceptance that potentially affected pharmaceutical companies must move regulatory approvals and adjust pharmaceutical supply chains in preparation for a potential ‘hard’ Brexit. That means the United Kingdom will not join either the EEA or the European Free Trade Association, and the extent to which the United Kingdom continues to participate in the EU regulatory schemes will need to be defined in 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 15,000 and an annual budget in excess of US$5 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 CDER, CBER and CDRH all fall within the Office of Medical Products and Tobacco, which is headed by a deputy commissioner. The Office of Global Regulatory Operations and Policy, also headed

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2 The FDA budget request for fiscal year 2019 states that US$2.5 billion of the total budget of US$5.8 billion will come from user fees.
by a deputy 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 and in several other countries.  

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. 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.

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.

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

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.
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)
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.

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.

iii 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

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7 21 CFR, Part 3.
8 21 CFR, Part 58.
in institutional review boards (IRBs).\textsuperscript{9} 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.\textsuperscript{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).\textsuperscript{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 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,

\textsuperscript{9} 21 CFR, Parts 50, 56.
\textsuperscript{10} 21 CFR, Part 54.
\textsuperscript{11} See generally, 21 CFR, Part 312.
record-keeping and reporting. Studies conducted in accordance with ICH\textsuperscript{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.\textsuperscript{13}

\textbf{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).\textsuperscript{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). Moreover, following enactment of the FDA Safety and Innovation Act (FDASIA) in 2012, the FDA now has express authority to put a device investigation on clinical hold. The FDASIA also provided that the FDA may not disapprove an IDE because the study may not support clearance or approval of the device.\textsuperscript{15} 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.

‘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.

\textsuperscript{12} The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

\textsuperscript{13} See 21 CFR, Section 312.120.

\textsuperscript{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).

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.\textsuperscript{16}

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.\textsuperscript{17} 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 that are collected in accordance with GCP and subject to validation.\textsuperscript{18} 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.\textsuperscript{19}

\textbf{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.

\textbf{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 approval from 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 pharmacy compounding\textsuperscript{20} 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.\textsuperscript{21} 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

\textsuperscript{16} 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).
\textsuperscript{17} 21 CFR, Section 814.15(b).
\textsuperscript{18} 83 Fed Reg 7366 (21 February 2018).
\textsuperscript{19} 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).
\textsuperscript{20} 21 USC, Section 353a.
\textsuperscript{21} \textit{Thompson v. Western States Medical Center}, 535 US 357 (2002).
United States

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 compounding facility 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 requirements 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 PHSAs'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 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.

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22 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.
23 FDA, Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2018).
‘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 by individual laboratories 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 on the guidance and a proposed revised approach 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.

25 21 USC, Section 360j(b).
26 FDA, Guidance for Industry and Food and Drug Administration Staff: Custom Device Exemption (September 2014).
30 21 CFR, Section 809.10(c)(2).
31 FDA, ‘Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Guidance for Industry and Food and Drug Administration Staff’ (November 2013).
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. 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.

32 21 CFR, Parts 330-361.
33 General provisions of the FDCA require that all drug establishments register with the FDA and submit periodic product listings, but the system does not entail FDA review or approval. The registration and listing requirements apply to foreign establishments that export drug products to the United States.
34 Although the FDA has established procedures for inclusion of new active ingredients in the OTC drug monograph process based on history of use in other countries (‘time and extent applications’, or TEAs), those procedures have proved ineffective in practice. In 2014, Congress enacted the Sunscreen Innovation Act, Pub. L. 113-195, which requires the FDA to establish an expedited procedure for inclusion of new active ingredients in OTC sunscreen products, based in part on approval and safe use in other countries, and to consider methods for expediting inclusion of new active ingredients for other OTC drug products.
35 A handful of older prescription drug products remain on the market pending completion of a review of effectiveness of marketed drug products that was initiated in the 1960s (the Drug Efficacy Study Implementation, or DESI). Eventually, the FDA intends to subject these products to NDAs or remove them from the market. In the meantime, the products are marketed subject to the FDA’s enforcement discretion.
36 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).
37 Regulations governing the content and review of NDAs are set out in 21 CFR, Part 314.
Legislation originally enacted in 1992 and known as the Prescription Drug User Fee Act (PDUFA) requires sponsors of original products to pay fees upon the submission and filing 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. 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. 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.

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 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.

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, which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2), which rely

38 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’.
39 For fiscal year 2018, the fees are as follows: for an application containing clinical data, US$2,588,478; for an application that does not contain clinical data, US$1,294,239; and the programme fee, US$309,915.
40 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.
41 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.
42 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).
43 21 USC, Section 355(j).
44 21 USC, Section 355(b)(2).
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).45

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.46 There is a 10-month target for standard review of new applications, and priority review is now also available for certain generic applications.

**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.

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45 The official name of the publication is *Approved Drug Products with Therapeutic Equivalence Determinations*.
46 Application fees for fiscal year 2018 are US$178,799 for new ANDAs; US$55,013 for DMFs; US$44,226 for domestic facilities that manufacture active substances; US$59,226 for foreign facilities that manufacture active substances; US$211,305 for domestic facilities that manufacture finished products; and US$226,305 for foreign facilities that manufacture finished products.
In 2010, Congress enacted legislation establishing an approval process for follow-on versions of biological products, or ‘biosimilars’. Such a product must:

1. be ‘highly similar’ to a reference product ‘notwithstanding minor differences in clinically inactive components’;
2. have no clinically meaningful differences from a reference product in safety, purity or potency;
3. be labelled for a condition of use for which the reference product is approved;
4. have the same route of administration, dosage form and strength as the reference product; and
5. 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 2017, the FDA released draft 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, the FDA Reauthorization Act (FDARA) amended the law to create an independent fee structure for biosimilars under which FDA will set 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 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

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48 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 regulated under the FDCA will transfer to the PHSA. Id. Section 7002(e).
49 FDA, Draft Guidance, Considerations in Demonstrating Interchangeability With a Reference Product (January 2017).
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).50 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. A Special 510(k) can be used when a manufacturer makes certain modifications to its own device. In 2018, the FDA issued draft guidance documents clarifying and expanding the Abbreviated 510(k) and Special 510(k) programmes.51 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 FDA grants the request, the agency will classify the device into class I or class II and authorize 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 clinical 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’ 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.

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 reclassify 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’. Although this language suggests the three activities must occur in chronological

53 FDA, Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (October 2017).
54 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).
56 FDASIA, Section 608 (amending FDCA, Section 513(e)).
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.’

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). 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). 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 superiority to that prior drug, even if the prior drug never had orphan drug exclusivity or it expired.

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.

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 until the period expires.

58 See 21 USC, Sections 360n-360ff; 21 CFR, Part 316.
60 35 USC, Section 156.
61 21 USC, Section 355(j).
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:

- that no patents are listed for the reference product;
- that all listed patents have expired;
- that a patent is listed and has not expired, but the applicant wishes that approval of its product be made effective upon expiry; or
- 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.62

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.63

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 infections caused by ‘qualifying pathogens’ (drug-resistant organisms designated by FDA) 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.64

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62 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.

63 21 USC, Section 355a.

64 21 USC, Section 355f.
**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 it should adopt an ‘umbrella’ exclusivity policy for biologics as it has for drugs.65 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.66 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.67

**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

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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 CIOMS68 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.69 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.70

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.71 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

68 Council for International Organizations of Medical Sciences.
69 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).
70 21 USC, Section 356c, 356i; 21 CFR Section 600.82.
71 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).
a change, but certain changes can be made immediately upon submission.\(^{72}\) Minor changes (e.g., minor editorial changes in labelling) can be notified in annual reports to the NDA or 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 recently released draft guidance addresses this topic for certain biologics.

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.\(^{73}\) 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.\(^ {74}\) 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

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72 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).


74 Some Class I devices are exempt from certain elements of the quality system regulation.
contribute to a death or serious injury.\textsuperscript{75} 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 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.\textsuperscript{76} Importers must complete their reports within 30 days; for user facilities, the deadline is 10 days.\textsuperscript{77} 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.\textsuperscript{78} 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.\textsuperscript{79}

The FDA also requires manufacturers and importers to report certain device 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.\textsuperscript{80} These actions are generally 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’.\textsuperscript{81} In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.\textsuperscript{82}

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.\textsuperscript{83} 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.\textsuperscript{84}

Different frameworks apply to post-approval changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.\textsuperscript{85} 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

\textsuperscript{75} 21 CFR, Section 803.50(a).
\textsuperscript{76} 21 CFR, Section 803.40.
\textsuperscript{77} 21 CFR, Section 803.10.
\textsuperscript{78} FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device Reporting for Manufacturers (November 2016).
\textsuperscript{79} FDA, Guidance for Industry and Food and Drug Administration Staff: Public Notification of Emerging Post-market Medical Device Signals (December 2016).
\textsuperscript{80} 21 CFR, Section 806.2(d) and (i).
\textsuperscript{81} 21 CFR, Section 806.10(a).
\textsuperscript{82} FDA, Distinguishing Medical Device Recalls from Medical Device Enhancements: Guidance for Industry and Food and Drug Administration Staff (October 2014).
\textsuperscript{83} FDCA, Sections 519(e), 522.
\textsuperscript{84} 78 Fed. Reg. 58,786 (24 September 2013).
\textsuperscript{85} See 21 CFR, Section 814.39.
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). These changes 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.\(^{86}\) 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.\(^{87}\)

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.\(^{88}\)

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.\(^{89}\) 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.\(^{90}\) 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 situations’, 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.\(^{91}\) 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.\(^{92}\)

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

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86 21 CFR, Section 807.81(a)(3).
87 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).
88 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Transfer of a Premarket Notification (510(k)) Clearance – Questions and Answers (December 2014).
89 21 USC, Sections 360e(e), 360(j)(5), 360(j)(m)(5).
92 Ivy Sports Medicine, LLC v. Burwell, 767 F.3d 81, 87 (D.C. Cir. 2014).
information on manufacturing facilities, which are normally inspected by the FDA before marketing authorisations are granted. All facilities that manufacture drugs or biologics (including ‘old’ drugs, such as monograph OTCs, for which prior approval is not required) must comply with regulations governing current GMP,\(^\text{93}\) 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.

\section*{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.\(^\text{94}\) PMAs must contain a detailed description of methods, facilities and controls used in manufacturing the device.\(^\text{95}\) 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.\(^\text{96}\) 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).

\section*{Advertising and promotion}

\subsection*{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.\(^\text{97}\)

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

\begin{itemize}
\item \(^\text{93}\) 21 CFR, Parts 210, 211.
\item \(^\text{94}\) 21 CFR, Part 820.
\item \(^\text{95}\) 21 CFR, Section 814.20(b)(4)(v).
\item \(^\text{96}\) 21 CFR, Section 814.39(a)(3).
\item \(^\text{97}\) See 21 CFR, Part 202.
\end{itemize}
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.

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.98

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.99 Decisions by the US Supreme Court in 2011,100 an influential federal court of appeals in 2012,101 and most recently, a federal district court in 2015,102 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.103

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

98 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).
100 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.
101 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.
103 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 and communications with payers. In June 2018, FDA issued revised final versions of the guidance.
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.104 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.105 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.106 Device promotion remains subject to the statutory prohibitions on false and misleading representations, however.107 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.108

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.109 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
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.\textsuperscript{110} For prescription drugs, elements to ensure safe use, established as part of FDA-imposed REMS, can limit use of a product to certain medical specialities 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’.\textsuperscript{111} 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.\textsuperscript{112} 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.\textsuperscript{113}

\textsuperscript{110} 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.

\textsuperscript{111} 21 USC, Section 360j(e).

\textsuperscript{112} 21 USC, Section 381(e).

\textsuperscript{113} 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,\(^{114}\) 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.\(^{115}\)

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.\(^{116}\)

\(^{114}\) 21 USC, Section 801 et seq.

\(^{115}\) 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 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).

\(^{116}\) There is one cannabidiol product approved for sale as a drug in the United States, and it remains a schedule IV 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. On 20 December 2018, the FDA 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, Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the Agency’s Regulation of Products Containing...
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). 117 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. 118 The FDA also has authority to impose civil monetary penalties for certain violations of the FDCA and the PHSA, 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. 119 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.

Pricing and Reimbursement

Reimbursement for prescription drugs in the United States is provided through a mixed system of private and public coverage. More than 60 per cent of all patients have private insurance, often provided through their employer, which covers prescription drugs, 120

Cannabis and Cannabis-Derived Compounds (20 December 2018), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm. Federal enforcement against CBD products has been limited. Aside from federal restrictions, CBD products must also comply with state law. Each state has controlled substance laws, which are not preempted by the CSA. CBD remains a schedule I controlled substance in some states and, other than in the approved drug, is prohibited for sale. Other states restrict CBD products for certain uses, such as CBD intended for use as a dietary supplement or consumption. To date, most states have not systematically enforced against CBD products. States will need to decide how to regulate CBD products as they harmonise their existing regulatory schemes with the Farm Bill’s hemp provisions.

118 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.
119 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 GlaxoSmitKline, 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.
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.}

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 Affordable Care Act (ACA) was enacted in 2010 to provide health cover for those individuals (by some estimates, at least 30 million) who are not covered by other programmes. The ACA established minimum requirements for health insurance programmes, require most individuals to purchase insurance and subsidise 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.\footnote{In the meantime, there is continued focus on prices charged for innovative medicines in the United States, and there is a possibility that measures will be introduced in response to that issue.} The current administration and many members of Congress have undertaken significant efforts to repeal the ACA, and its future is uncertain. In 2018, the penalty for not having health insurance was eliminated, and additional efforts to further dismantle the law are under consideration.
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.123 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.124 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’125) 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.126 Statutory provisions authorising the FDA to require REMS, post-approval studies and labelling changes afford sponsors a right to an informal dispute resolution procedure.127 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.128 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””.129

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).130 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 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.131

123 21 USC, Section 355(d), (e).
124 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.
125 FDA, PDUFA VI Commitment Letter, Section I.E.
126 FDA, Guidance for Industry and Review Staff, Formal Dispute Resolution: Sponsor Appeals Above the Division Level (Nov. 2017).
127 21 USC, Sections 355(o), 355-1.
128 FDCA Section 517A(b).
129 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).
130 5 USC, Section 501 et seq.
131 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
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.\(^\text{132}\) 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.\(^\text{133}\)

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.\(^\text{134}\)

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.\(^\text{135}\) 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. The federal Anti-Kickback Statute\(^\text{136}\) prohibits the provision 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 \textit{qui tam} lawsuits on behalf of the federal government under the False Claims Act.\(^\text{137}\) Such suits may result in penalties equal to three times the cost of unlawful activities to federal healthcare programmes, a portion of which may be awarded to the whistle-blower.

\(^{132}\) 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. Pre-enforcement review is available as to final regulations issued by the FDA. \textit{Abbott Laboratories v. Gardner}, 387 US 136 (1967).


\(^{135}\) 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).

\(^{136}\) 42 USC, Section 1320a-7b.

\(^{137}\) 31 USC, Sections 3729-3733.
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. In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals.

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. 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. 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:

- actual, non-reimbursable expenses for medical care, rehabilitation, custodial care and similar needs;
- lost earnings;
- pain and suffering (capped at US$250,000);
- a US$250,000 payment for a vaccine-related death; and
- reasonable attorneys’ fees.

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.

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138 42 CFR, Section 1001.952.
142 42 USC, Section 300aa-10 et seq.
Section 304 of the Homeland Security Act of 2002\textsuperscript{143} 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\textsuperscript{144} 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.\textsuperscript{145}

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

One of the most contentious legal issues in the US drug approval system involves the interplay between the Hatch-Waxman Act and the US antitrust laws. 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.\textsuperscript{146} And under the Hatch-Waxman Act, 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 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 sought for over a decade to demonstrate that settlements that involve consideration flowing back to the generic company are anticompetitive. In particular, the

\textsuperscript{143} 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.

\textsuperscript{144} 42 USC, Section 247d-6d.

\textsuperscript{145} In December 2014, a PREP Act declaration was issued for designated vaccines under development for the Ebola virus disease.

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.147

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.148 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.149

The Third Circuit rejected the ‘scope of the patent’ standard in a significant 2012 decision, In re K-Dur Antitrust Litigation.150 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 entry or offers some pro-competitive benefit.151 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’.152 The Third Circuit’s explicit rejection of the standard applied by the majority of other courts to consider the issue has 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.153 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

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147 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.


149 See, e.g., In re Tamoxifen Citrate Antitrust Litig, 466 F. 3d at 213.

150 See In re K-Dur Antitrust Litig, 686 F. 3d 197 (3d Cir. 2012).

151 Id. at 219.

152 In re K-Dur Antitrust Litig, 686 F.3d 197, 214 (3d Cir. 2012).

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.154

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.155 Nevertheless, the FTC and private plaintiffs have continued to challenge alleged improper petitioning activity harming generic competition.156

ii 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


155 21 USC, Section 355(q).

the enforcement of patents against generic competitors. Similarly, the recently enacted, and 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 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 August 2017, the FDARA became law. It reauthorised the user fee programmes for prescription drugs, biosimilars, generic drugs and medical devices and also enacted various reforms in the FDA regulation of these medical products. Most significantly, 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 remains in the early stages of implementation. The FDARA also addressed a range of other issues, including reforms to the generic drug approval system and measures related to, for example, orphan drug exclusivity as discussed above.

On 24 October 2018, the President signed the SUPPORT for Patients and Communities Act, legislation intended to stem the opioid crisis in America. This Act broadens several FDA authorities. New section 569D of the FDCA authorises the FDA to initiate a mandatory recall if the FDA ‘determines there is a reasonable probability that a controlled substance would cause serious adverse health consequences or death’. The SUPPORT Act also expanded the FDA’s REMS authorities, enabling 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 expanded the FDA’s authority to require drug-labelling changes: the FDA may now require addition of new information related to reduced effectiveness to drug labelling.

Commissioner Scott Gottlieb has proven to be an active Commissioner. During his tenure, the FDA has published guidance on many timely topics, including ‘suites’ of guidance documents on regenerative medicine regulatory issues. In a statement issued early in his tenure, he 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

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fraudulent stem cell clinics. The agency has continued to take steps aimed at streamlining development and approval of regenerative medicine products, and recently Commissioner Gottlieb again promised ‘brisk activity from the FDA when it comes to some rogue stem cell outfits that are putting patients at risk’. During Commissioner Gottlieb’s tenure, the agency has also increased its focus on competition issues, launching the Drug Competition Action Plan and Biosimilars Action Plan. These programmes are aimed at increasing access to generic and biosimilar drugs by streamlining and incentivising their development.

The regulation of diagnostic tests, including laboratory-developed tests (LDTs), next-generation sequencing (NGS)-based tests and companion diagnostics, continues to evolve in light of rapid technological advancements and an increasing focus on precision medicine. In 2014, the FDA issued draft guidances describing a proposed regulatory framework for LDTs. Although the agency announced in November 2016 that it would not move forward with finalising those guidances, Congress, the agency and other stakeholders are considering the appropriate regulatory framework for LDTs and potential legislation. For example, a discussion draft of the Diagnostic Accuracy and Innovation Act was released by Representatives Buschon and DeGette in March 2017. The FDA issued a Technical Assistance on the discussion draft in August 2018, revising much of the draft legislation and proposing an alternative approach. In December 2018, Representatives Buchon and DeGette released a new discussion draft of the Verifying Accurate, Leading-edge IVCT Development (VALID) Act. In addition, the agency held six public workshops in 2015 and 2016 to discuss its consideration of developing a new, more flexible approach to the regulation of NGS-based tests. In November 2017, the FDA announced a streamlined approach to tumour-profiling NGS-based tests, which would permit test reports to include both companion diagnostic biomarkers and other biomarkers with potential clinical significance, or evidence of clinical significance, but that are not approved companion diagnostic biomarkers. In 2018, the agency finalised two guidance documents that address the use of public genetic variant databases to support a demonstration of clinical validity for NGS-based tests and considerations for the development and validation of NGS-based tests used for diagnosing germ-line diseases. The FDA has also issued draft guidance documents providing recommendations on the co-development of a companion diagnostic with a therapeutic product, developing and

163 FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (April 2018); FDA, Guidance for Industry, Food and Drug Administration Staff: Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) intended to Aid in the Diagnosis of Suspected Germline Diseases (April 2018).
labelling companion diagnostics for a group or class of oncology therapeutic products, and recommendations for investigational \textit{in vitro} diagnostic devices used in clinical trials of therapeutic products.\footnote{164}

Digital health products, including standalone software as a medical device, is an area of significant focus and activity for the FDA. In 2015 and 2016, the agency issued several guidance documents identifying which digital health products, including mobile medical applications, the agency would actively regulate as medical devices and for which categories of products the agency would exercise enforcement discretion.\footnote{165} Subsequently, in December 2016, the 21st Century Cures Act excluded five categories of software functions from the statutory definition of ‘device’. In December 2017, the FDA issued two draft guidance documents addressing how the Act affected the agency’s prior guidance documents and interpreting the scope of the categories excluded from the device definition, including clinical decision support software.\footnote{166} Also in 2017, the FDA announced the development of a pre-certification programme for software as a medical device that would involve the agency pre-certifying software developers who demonstrate a culture of quality and organisational excellence. Pre-certified developers would then qualify to market certain software devices with no pre-market review or to streamline pre-market reviews by the FDA. The FDA launched a pilot pre-certification programme in September 2017 and released several versions of a working model for the programme throughout 2018. Finally, in November 2018, the FDA published a proposed framework for the regulation of ‘prescription drug-use related software’ as promotional labelling for drugs as well as for the inclusion of information regarding prescription drug-use related software in FDA-required labelling for drugs.\footnote{167}

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.

\footnote{164} FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product (July 2016); FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Investigational IVDs Used in Clinical Investigations of Therapeutic Products (December 2017); FDA Draft Guidance for Industry, Food and Drug Administration Staff: Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products (December 2018).

\footnote{165} FDA, Guidance for Industry and Food and Drug Administration Staff: Mobile Medical Applications (February 2015); FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices (February 2015); FDA, Guidance for Industry and Food and Drug Administration Staff: General Wellness: Policy for Low Risk Devices (July 2016).

\footnote{166} FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Changes to Existing Medical Software Policies Resulting from Section 2060 of the 21st Century Cures Act (December 2017); FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Clinical and Patient Decision Support Software (December 2017).

\footnote{167} 83 Fed. Reg. 58574 (20 November 2018).
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) and the Rafael Rangel National Hygiene Institute (INHRR). 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.
**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.

**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.

**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 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;
those that require a prescription, but that prescription can be repeated as many times as stated therein; and

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 73 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.
V 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.

VI 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.

VII 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.
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 might be beneficial for importers and manufacturers of medicines.

On the other hand, as part of Mercosur, Venezuela has incorporated the trade bloc’s regulations into Venezuela’s national legal system, which might allow for greater commercial relations with other member countries, although this possibility has also yet to become a reality.
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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.

INÈS 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.

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, Asia IP, 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

Calissendorff Swarting Advokatbyrå

Camilla Appelgren is a partner at Calissendorff Swarting. 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.

EMIL BJERRUM

_Bech-Bruun Law Firm P/S_

Emil Bjerrum is a senior associate at Bech-Bruun in the life sciences practice group. He specialises in the law relating to life sciences with particular focus on medicinal products and medicinal equipment. Emil in particular advises national and international clients on regulatory aspects and contracts, including on matters pertaining to licence and distribution.
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.

MARCO BLEI  
*Portolano Cavallo*  
Marco’s focus is on intellectual property and information technology in the area of life sciences. During his 15-year career, Marco has advised pharmaceutical, medical devices and other life sciences players in contentious and non-contentious matters. His expertise includes the drafting and negotiation of agreements relating to the development, use and exploitation of intellectual property grants and acquisition agreements; manufacturing, supply, distribution and co-marketing agreements for pharmaceutical companies, as well as contracts relating to clinical trials; assistance in litigation concerning patents, trademarks, design, copyrights and unfair competition; misleading advertisement; and unfair commercial practices. Marco was awarded his law degree by the Università Cattolica del Sacro Cuore in Milan in 2003, subsequently earning his master of laws in intellectual property from King’s College London in 2008. He is a teaching assistant of industrial law at the Milano-Bicocca University. He frequently speaks at conferences and seminars on intellectual property and life sciences and teaches courses on the subject. He regularly publishes articles on IP and life sciences in print and in online magazines.

PETER BOGAERT  
*Covington & Burling LLP*  
Peter Bogaert is managing partner of the Brussels office of Covington & Burling LLP, and has a broad European life sciences practice. He has detailed regulatory expertise under EU and national laws, handles legislative and other policy assignments, and provides strategic advice. He also represents life sciences companies before the European courts in Luxembourg and in local litigation in Belgium. Mr Bogaert’s practice covers pharmaceuticals, biotechnology, medical devices, special foods and feed, cosmetics and other consumer products, and he represents numerous innovative life sciences companies, including start-ups, as well as several industry associations. He is consistently ranked by *PLC* as one of the leading life sciences lawyers globally, and *The Legal 500 EMEA* and *Chambers Europe* note Mr Bogaert’s prominent regulatory pharmaceutical and environmental practice. The 2011 edition of *The Legal 500 EMEA* noted that he is ‘a superb lawyer who is very pleasant to work with’. Mr
Bogaert regularly writes and speaks on life sciences issues. He is a founding member of the Brussels pharma law group.

**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; 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 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 and FDA Reauthorization Act of 2017. 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 and has participated in formal and informal advertising, commercial practices, good manufacturing practices, good clinical practices, drug safety and pharmacovigilance proceedings before the European Medicines Agency, national authorities, courts and self-regulatory bodies.

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.

PRAWEEN CHANTANAKOMES
Baker McKenzie

Mr Chantanakomes is currently active in the corporate and commercial, corporate compliance and healthcare groups. Mr Chantanakomes has been involved in assisting multinational clients with their operations in Thailand. He advises on issues relevant to foreign investors, such as foreign investment laws, mergers and acquisitions and corporate structures. He has also advised on consumer protection law, food, drug and cosmetics law, and natural resources regulations. His specialisation also extends to corporate compliance, anti-bribery and FCPA issues, including participating in investigations in Thailand with respect to these matters, with a special focus on pharmaceutical and healthcare companies.

VOJTĚCH CHLOUPEK
Bird & Bird

Vojtěch Chloupek is a partner at Bird & Bird, where he heads the Czech and Slovak intellectual property and life sciences practices. He provides legal advice to clients primarily in the healthcare, electronics, media, life sciences, telecommunications and information technology sectors. Vojtěch specialises primarily in intellectual property law, although he has also gained significant experience in commercial and regulatory matters, especially in the aforementioned sectors. He frequently represents pharmaceutical clients in patent and other IP matters, and assists clients with regulatory, data protection and commercial issues (including distribution, licensing, advertising and clinical trials).

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 an associate 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. 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.

RICARDO DE VETTOR PINILLOS
Rodrigo, Elías & Medrano Abogados
Mr De Vettor is a senior associate in the intellectual property department at Rodrigo, Elías & 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).

MARTIN DRÆBYE GANTZHORN
Bech-Bruun Law Firm P/S
Martin Dræbye Gantzhorn is a partner at Bech-Bruun, heading the intellectual property and technology practice group, and co-head of Bech-Bruun in the life sciences practice group. He is highly specialised in IP litigation, product liability, and regulatory and transactional life sciences.

ALEXANDRE EINSFELD
Fialdini 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.

**CIARA FARRELL**

*Arthur Cox*

Ciara is a regulatory and compliance specialist advising clients on EU and Irish regulatory matters applicable to medical devices, medicinal products, food law and cosmetics throughout their entire life cycle. This includes assisting clients in classification of their products, establishment of a pathway to authorisation and marketing of their products in the European Union (including related regulatory obligations), pharmacovigilance obligations, promotion and marketing of products, sales agreements, clinical trial agreements, adverse event reporting, product withdrawals, data privacy obligations, conduct of compliance and anti-bribery investigations, and regulatory due diligence. She also challenges national authority and EU institution decisions concerning classification and marketing of medicinal products and medical devices.

Ciara assists life sciences clients in the preparation, drafting and review of numerous agreements, including clinical study agreements, pharmacovigilance agreements, CRO agreements, European authorised representative agreements, distribution agreements, and sales and promotion agreements.

**LUCA GAMBINI**

*Portolano Cavallo*

Luca assists Italian and foreign clients on corporate reorganisations and mergers and acquisitions transactions, and private equity as well as on corporate governance-related matters. Luca has gained a strong experience in mergers and acquisitions deals in the life sciences, digital and media sectors.

Luca has authored various contributions on mergers and acquisitions and corporate finance in a number of newsletters and sector-specific journals.

He was on secondment at Morrison & Foerster LLP in New York for 16 months, where he represented private equity funds and private corporate clients in complex US and cross-border M&A transactions. Luca graduated in 2006 from LUISS Guido Carli University. Prior to joining the firm, he completed an internship with a law firm in Washington, DC.

**MAURICIO GÓMEZ GUERRERO**

*CMS Woodhouse Lorente Ludlow*

Mauricio Gómez Guerrero is a partner at CMS Woodhouse Lorente Ludlow in Mexico City and leads the life sciences and healthcare practice at the firm. Before joining the firm, Mr Gómez held high-level positions as public officer both in the Federal Commission Against Sanitary Risks (COFEPRIS) and the Mexican Social Security Institute (IMSS), two of the government’s major stakeholders in the Mexican health system.

He advises clients in regulatory strategy concerning pre-market clearance for drugs and medical devices, good manufacturing practices compliance, borderline determination and classification of consumer products, regulatory enforcement administrative procedures and government affairs strategy.
Mauricio holds an LLM in global health law from Georgetown University O’Neill Institute for National and Global Health Law in Washington, DC, where he also obtained a Certificate in Food and Drug Law, a bachelor of laws from the Universidad Iberoamericana in Mexico City, a Political Analysis Diploma by the Centro de Investigación y Docencia Económica (CIDE) in Mexico City and has additional studies at Harvard Law School and Columbia University Law School.

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 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.

VAUGHN HARRISON  
Hogan Lovells (South Africa) Inc  
Vaughn Harrison is a partner at Hogan Lovells and has over 25 years’ experience in the life science sector. This includes advising clients on market entry, including licensing, and obtaining market authorisations; classification and registration of medicines, complementary medicines and medical devices; assisting with labelling and advertising of pharmaceuticals, foodstuffs and personal use products; and drafting and vetting complex commercial agreements as well as assisting multinational clients with the preparation and vetting of tenders, pitches and contracts in the healthcare and pharmaceutical industries.

He also has experience in representing clients in the healthcare, pharmaceutical, medical devices, foodstuffs and related industries in litigation, arbitration and the resolution of disputes.
Over the years he has assisted numerous multinational groups and other clients in setting up and operating businesses in South Africa and the rest of Africa.

**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 the 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 has been a lead partner in the review and drafting of the statutory framework governing Dubai Healthcare City’s healthcare professionals since 2013. She was lauded as one of the three pillars in the firm’s investigations team by *Global Investigations Review 100 2018* – 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* 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. Melanie participated in a roundtable discussion to distil the changes in the regulation of medical practices and innovation, which was featured in *Who’s Who Legal: Life Sciences 2013*. 
**JUNG MIN JO**  
*Bae, Kim & Lee LLC*  
Jung Min Jo is a partner at Bae, Kim & Lee LLC and leads the firm’s healthcare practice. For more than 15 years, Mr Jo has represented a number of domestic and foreign pharmaceutical and medical devices companies. He also works closely with the firm’s fair-trade team and data privacy experts in the healthcare practice. Recently, he successfully defended a foreign pharmaceutical company before the Korea Food and Drug Administration on the anti-kickback charges that had been aggressively brought by the agency based on the newly adopted anti-corruption laws as a part of the Korean government’s efforts to tackle industry-wide problems.

He has assisted a number of foreign pharmaceutical and medical equipment manufacturers in adopting internal compliance rules to conform to the new healthcare laws and implementing the personal information protection regulations that have become a ‘hot’ issue since the new data privacy laws came into effect in 2012. He also trained as a corporate and M&A expert, and has advised foreign healthcare companies in their inbound investments into the Korean market, including acquisitions of Korean pharmaceutical and medical device companies.

Mr Jo is currently a member of the Regulation Review Committee under the Ministry of Food and Drug Safety and serves as the auditor of the Korea Institute of Drug Safety and Risk Management. In 2012, he was selected as an External Counsel of the Year by *Asian-MENA Counsel*, a Hong Kong-based legal publication. Mr Jo received an LLB degree from Seoul National University College of Law in 1994 and an LLM degree from Columbia Law School in 2004.

**KATHERINE YC 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.

**COLIN KAVANAGH**  
*Arthur Cox*  
Colin Kavanagh is a partner and head of the life sciences group at Arthur Cox. Colin advises Irish and multinational pharmaceutical, medical device, biotech, cosmetic, food, beverage and agribusiness companies in Ireland on a wide range of corporate, commercial, regulatory, intellectual property and promotional matters, both as part of their day-to-day sourcing, supply chain, manufacturing and sales activities, and in relation to their involvement in corporate transactions.

Colin is also a partner in the corporate and commercial department, with a broad-based commercial practice and a particular focus on life sciences. He advises a broad spectrum of clients on commercial, regulatory and intellectual property matters relating to the life sciences industry. Colin’s corporate and commercial practice focuses principally on commercial
arrangements between companies and corporate reorganisations across a wide range of industries.

**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 CPI (Certified Physician Investigator) accredited by ACRP (Association of Clinical Research Professionals).

He is a member of the International Association for the Protection of Intellectual Property (AIPPI) 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 Pharmaceutical Society of Japan, the Japan Pharmaceutical Association, 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.
MANDI KREBS
*Hogan Lovells (South Africa) Inc*

Mandi Krebs is a senior associate at Hogan Lovells and advises various multinational companies in the pharmaceutical and medical device industries on legal and regulatory matters, including marketing authorisations, licensing, product labelling, advertising and marketing activities as well as pricing and reimbursement matters in South Africa.

In addition, Mandi advises multinational pharmaceutical companies regarding market entry into various jurisdictions across Africa.

Mandi has valuable experience in advising clients on matters related to interactions with healthcare professionals and patients, reimbursement models, and challenging competitor's claims.

Mandi is very experienced in liaising with enforcement authorities and regulatory bodies in South Africa and across Africa.

BRIDGET McGRATH
*Arthur Cox*

Bridget McGrath is an associate in the litigation and dispute resolution group at Arthur Cox and advises Irish and multinational pharmaceutical, medical device and biotech clients on healthcare, life sciences, product liability and regulatory and compliance matters.

ABRIANNE MARAIS
*Hogan Lovells (South Africa) Inc*

Abrianne Marais is an associate at Hogan Lovells and has experience in advising companies in the pharmaceutical and medical device industries on legal and regulatory matters. In addition, he has general experience including the drafting of commercial agreements, undertaking due diligence investigations and conducting regulatory and legal compliance audits.

ENZO MARASÀ
*Portolano Cavallo*

Enzo’s focus is on antitrust, as well as regulatory and unfair commercial practices.

During his 15-year career, Enzo has assisted national and multinational companies on issues of competition and EU law: merger control, anticompetitive agreements, abuses of a dominant position, challenging decisions of antitrust authorities, private antitrust litigation, restrictive regulatory measures on free movement in the single market, distribution or cooperation agreements between competitors, technology transfers, implementation of antitrust compliance programmes, etc.

He has particular experience in the following sectors: telecommunications and the internet, electronic payment services, e-commerce, fashion and luxury, and pharmaceutical and biomedical. Enzo represents clients before the Italian Competition Authority, the European Commission and the courts of the European Union.

Enzo was awarded a law degree in 2003 and a postgraduate diploma in 2004 on national and EU competition law, both by Università degli Studi di Milano Statale.

He has authored numerous articles and publications in national newspapers and legal journals in the field of competition law.
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.

VICTORIA MONTERO
*Leâ Abogados*

Victoria Montero joined Leâ 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
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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.

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Rune Nordengen has 18 years of experience as a business lawyer working mainly with intellectual property (IP), life sciences, IT and technology law, and legal business
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A significant part of Rune’s work relates to international clients. He has worked in many areas of chemistry and pharmacy. He is an experienced litigator in complicated patent and technology cases, and is very experienced in trademark matters. Rune also has broad experience in developing and executing strategies in anti-counterfeiting.

He advises on compliance with medical law and advertising regulations for a broad range of products and mediums, including packaging, labelling and distribution. Rune is very experienced in advising on misleading and unfair commercial practices. His practice also includes advice on compliance with codes of conduct. The practice includes bringing complaints and defending cases before regulators, appeals of regulator decisions and court processes.

Rune also has extensive experience within public procurement in the health sector.

He has litigation experience from district courts, courts of appeal and the Supreme Court, especially within the areas of patent, trademark, marketing and contract law.

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Roman Norek is a junior associate at the Bird & Bird office in Prague, focusing mainly on general commercial law, intellectual property and data protection. He graduated from the Faculty of Law at the Masaryk University in Brno and completed part of his studies at the University of Antwerp in Belgium. During his studies, Roman also focused on European Union law and private international law. His experience in the area of life sciences covers pharmaceutical regulatory matters in particular.

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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.

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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...
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Sophie Pelé is a national partner at Dechert LLP. She focuses her practice on life science regulatory matters and is experienced in competition, litigation and public law matters in a wide variety of regulated industries. Her ‘strong regulatory expertise’ was noted in *The Legal 500 EMEA* 2015. Ms Pelé has substantial experience in clinical trial agreements, manufacturing or promotion agreements, marketing authorisations, pricing and reimbursement with governmental authorities, distribution schemes, import–export and parallel trade, public procurement in hospitals, compliance and interaction with healthcare professionals, advertising, and substitution of generic and biosimilar products.

Ms Pelé regularly represents multinational companies before authorities in French administrative jurisdictions.

Prior to joining Dechert, Ms Pelé served as a senior associate in the competition and regulatory department of another international law firm. Her previous experience also includes working at another leading law firm in life sciences in Paris.

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Stephen Rohl is an associate who practises in intellectual property law, focusing on patent litigation. Stephen has represented a range of clients from the pharmaceutical, biotechnology and medical devices industries in infringement and revocation litigation in the Federal Court and the High Court of Australia, as well as in disputes in the Australian Patent Office. His experience includes matters involving patents relating to small molecules, antibodies and CRISPR gene-editing technology, as well as the first occasion on which the High Court was called to rule on the patentability of methods of treatment of human beings and isolated nucleic acids. In addition to his law degree, Stephen holds a bachelor of science degree (honours) in applied chemistry.

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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 (APAA), Association Internationale pour la Protection de la Propriété Intellectuelle (AIPPI) and the Fédération Internationale des Conseils en Propriété Industrielle (FICPI). 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 IPAB, 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 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.


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Surabhi Singhi is a corporate lawyer based in the UAE. She has been practising in the UAE for around five 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 United Arab Emirates 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,
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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.

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Elisa Stefanini has a wide regulatory and compliance experience with a particular focus on the life sciences sector.

She has also gained significant experience in matters of protection of personal data in the context of clinical trials, with particular regard to the processing of genetic data, including through biobanks.

From 2006 to 2010, she was Contract Professor in Public and Constitutional Law at the Luigi Bocconi University.

After being awarded a *cum laude* law degree by the Luigi Bocconi University in 2004, Elisa earned a postgraduate diploma at the Academy of European Law, European University Institute in Fiesole, in 2006, and completed her PhD in constitutional law at Milan University in 2008. During her doctoral studies, Elisa conducted research at King’s College London. She is the author of several publications in the field of biotechnology and scientific research, and of numerous articles published in some of the field’s most prestigious journals. Elisa is on the register of experts of the National Agency for Regional Health Services (AGENAS).

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Rosa Virginia Superlano joined Leğa 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
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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.

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Odd Swarting is a partner at Calissendorff Swarting. 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.

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Kirti Mahajan Thomassen is a head of the competition and procurement practice at Bull & Co Advokatfirma AS. She is recognised by Who’s Who Legal as an expert in life sciences regulatory law and has nearly 20 years of practical experience. Her competence and experience encompasses the entire spectrum of regulatory legal framework for the healthcare sector. She advises clients within the following topics: permissions, authorisations, approvals, registrations, etc.; CE marking; import and export of pharmaceuticals; pricing and reimbursement; distribution and market access; pharmacies, including internet pharmacies; marketing; interaction with healthcare professionals (HCPs); mutual recognition of professional qualifications for HCPs; administrative sanctions against HCPs; product liability for pharmaceuticals and medical devices; regulatory due diligence; and ancillary advice in M&A processes.

Furthermore, Kirti has extensive and practical experience with procurement procedures in the healthcare sector and offers valuable understanding of practical and legal challenges that regularly emerge in these processes. She assists suppliers with quality control of bids before submission and in safeguarding their interests during the entire procurement process, including complaints and court processes.

She is also a seasoned adviser in relation to competition law in the life sciences sector. She has previously advised leading pharmaceutical manufacturers in relation to, inter alia, the scope for reducing orders without abusing a dominant position, and merger control in transactions involving competing products.
PEERAPAN TUNGSUWAN

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Peerapan Tungsuwan is a corporate and M&A partner in the Bangkok office who specialises in highly regulated industries, including the healthcare industry. She is currently chair of the AEC healthcare harmonisation subcommittee of Baker McKenzie’s Asia-Pacific healthcare industry group, of which she was head from 2007 to 2013. Within the Bangkok office, she heads the healthcare industry and natural resources groups, and co-leads the mergers and acquisitions practice group and Japan advisory group. Ms Tungsuwan is exceptionally fluent in legal matters relating to healthcare, consumer protection and natural resources. Her client list includes a Japanese-based Fortune 500 company, multinational manufacturers, pharmaceutical companies, and oil and gas companies. Ms Tungsuwan assists clients on complex mergers and acquisitions, joint ventures, corporate structures and restructuring, as well as in negotiating commercial contracts and complying with Thai regulatory requirements. She also works closely with industry associations; for example, advising the Pharmaceutical Research and Manufacturers Association on various industry issues, including its code of conduct revisions and advising it on relevant transparency issues.

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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 The Life Sciences Law Review in 2016.

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).

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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
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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.

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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 practise in a large, renowned Zurich business law firm. In 2015, Walder Wyss elected Andreas Wildi as their partner.
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