
THE LIFE SCIENCES LAW REVIEW

FIFTH EDITION

EDITOR
RICHARD KINGHAM

LAW BUSINESS RESEARCH

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Fifth Edition

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CONTENTS

Editor's Prefacevii
	<i>Richard Kingham</i>
Chapter 1	INTERNATIONAL HARMONISATION..... 1
	<i>Richard Kingham</i>
Chapter 2	ARGENTINA 7
	<i>Emilio N Vogelius</i>
Chapter 3	AUSTRALIA 20
	<i>Anthony Muratore, Stephen Rohl and Matthew Whitaker</i>
Chapter 4	AUSTRIA..... 33
	<i>Karina Hellbert</i>
Chapter 5	BELGIUM 47
	<i>Peter Bogaert and Charlotte Ryckman</i>
Chapter 6	BRAZIL 62
	<i>Angela Fan Chi Kung and Nicole Recchi Aun</i>
Chapter 7	CHINA..... 74
	<i>Shaoyu Chen and John Balzano</i>
Chapter 8	DENMARK 109
	<i>Mikkel Vittrup and Mette Hygum Clausen</i>
Chapter 9	EUROPEAN UNION 127
	<i>Grant Castle and Robin Blaney</i>

Chapter 10	FINLAND	151
	<i>Hanna Paloheimo and Hilma-Karoliina Markkanen</i>	
Chapter 11	FRANCE	162
	<i>Sophie Pelé</i>	
Chapter 12	GERMANY.....	173
	<i>Christian Dierks</i>	
Chapter 13	GREECE.....	186
	<i>Gregory Triantafillopoulos</i>	
Chapter 14	INDIA	195
	<i>Pravin Anand and Archana Shanker</i>	
Chapter 15	IRELAND.....	205
	<i>Colin Kavanagh and Ciara Farrell</i>	
Chapter 16	ISRAEL.....	222
	<i>Dovev Apel</i>	
Chapter 17	ITALY	240
	<i>Giovanni Galimberti, Massimiliano Mostardini, Mauro Turrini and Evelina Marchesoni</i>	
Chapter 18	JAPAN	256
	<i>Takeshi S Komatani</i>	
Chapter 19	KOREA.....	278
	<i>Jung Min Jo</i>	
Chapter 20	LITHUANIA	291
	<i>Rūta Pumputienė and Ieva Balėnė</i>	
Chapter 21	MEXICO	307
	<i>José Alberto Campos-Vargas</i>	

Chapter 22	NEW ZEALAND	323
	<i>Robert Andrew Bycroft</i>	
Chapter 23	NORWAY	339
	<i>Kirti Mahajan Thomassen and Rune Nordengen</i>	
Chapter 24	PERU	350
	<i>María del Carmen Alvarado Bayo and Ricardo De Vettor Pinillos</i>	
Chapter 25	POLAND.....	361
	<i>Ewa Skrzydło-Tefelska and Jacek Myszko</i>	
Chapter 26	PORTUGAL	373
	<i>Paulo Pinheiro and Francisca Paulouro</i>	
Chapter 27	RUSSIA.....	386
	<i>Evgeny Alexandrov and Ilya Goryachev</i>	
Chapter 28	SERBIA.....	399
	<i>Bogdan Ivanišević and Slobodan Trivić</i>	
Chapter 29	SINGAPORE	411
	<i>Melanie Ho and Jacqueline Chua</i>	
Chapter 30	SPAIN.....	430
	<i>Raquel Ballesteros</i>	
Chapter 31	SWEDEN	441
	<i>Peter Forsberg and Julia Tavaststjerna</i>	
Chapter 32	SWITZERLAND	453
	<i>Markus Schott and Markus Wang</i>	
Chapter 33	TAIWAN	466
	<i>Katherine YC Juang, Jill Niu and Daisy Wang</i>	

Chapter 34	THAILAND	481
	<i>Peerapan Tingsuwan and Praween Chantanakomes</i>	
Chapter 35	TURKEY	493
	<i>Selma Ünlü and Burcu Gürel</i>	
Chapter 36	UNITED ARAB EMIRATES.....	505
	<i>Melissa Murray and Saladin Aljurf</i>	
Chapter 37	UNITED KINGDOM	514
	<i>Grant Castle and Sarah Cowlshaw</i>	
Chapter 38	UNITED STATES.....	530
	<i>Richard Kingham and Krista Hessler Carver</i>	
Appendix 1	ABOUT THE AUTHORS	569
Appendix 2	CONTRIBUTING LAW FIRMS' CONTACT DETAILS	591

EDITOR'S PREFACE

The fifth edition of *The Life Sciences Law Review* covers a total of 37 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged 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.

Now, more than ever, it is important for leaders in the pharmaceutical and medical device industries and their advisers to be knowledgeable about the laws and regulations in major jurisdictions around the world. In the past year, there have been significant developments in the regulation of drugs and medical devices, especially in the United States, where a new law – the 21st Century Cures Act – was passed at the end of 2016. There are prospects for further developments in the coming year. The new president and the Republican-controlled Congress will consider legislative measures affecting the pharmaceutical and medical device sectors, including proposed repeal of the Affordable Care Act, continuing inquiries into pricing of medical products and reauthorisation of user fee laws that fund a substantial part of the drug and device approval processes. The United Kingdom will initiate formal proceedings to begin the process of withdrawing from the European Union, with potential consequences for the medical products sectors. Other jurisdictions, including China and India, are considering reforms to their regulatory systems for medicinal products.

Each of the chapters has 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 annual publication.

Richard Kingham
Covington & Burling LLP
Washington, DC
March 2017

Chapter 1

INTERNATIONAL HARMONISATION

*Richard Kingham*¹

I INTRODUCTION

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

II ICH

i History

For many years, certain major drug regulatory agencies maintained informal arrangements for cooperation and communication, but there was no formal mechanism to agree 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 EU), the US Food and Drug Administration (FDA) and the

¹ Richard Kingham is a partner at Covington & Burling LLP.

Japanese Ministry of Health, Labour and Welfare, along with the national trade associations of the pharmaceutical industry in the EU, US and Japan.² The World Health Organization (WHO), European Free Trade Association and Canada were given observer status.³

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,⁴ as have the drug regulatory agencies and ministries of health of countries outside the EU, the US and Japan.⁵

ii Organisation and procedures

The ICH is governed by a steering committee, composed of members from the regulatory authorities and industry groups from the EU, US 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: (1) development of the scientific consensus for a guideline; (2) agreeing on the draft text of a guideline; (3) consulting with regional regulatory agencies; (4) adoption of harmonised guidelines; and (5) implementation of guidelines in the ICH regions. Although participants in the ICH process undertake to

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

3 Detailed information on the ICH and its programmes is contained on the website, www.ich.org.

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.

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.⁶ Final guidance may be supplemented by Q&As or other explanatory documents.

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 EU, the US 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

6 When the CTD was adopted, the EU 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.

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.

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 actually 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 range of topics, including study design, protection of human subjects, assurance of quality and reliability of data in clinical trials, the roles of sponsors, investigators and institutions, and many other issues. Of similar importance is the guideline on the format and content of clinical study reports,²⁷ which also serves as the model for all major developed jurisdictions. Other topics are clinical safety (including pharmacovigilance),²⁸ dose-response studies,²⁹ ethnic factors,³⁰ clinical trials generally (including statistical principles),³¹ clinical evaluation,³² clinical evaluation by therapeutic category³³ and pharmacogenomics.³⁴

The Common Technical Document

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

The CTD comprises five modules: Module 1 consists of regional administrative information, which varies by jurisdiction; Module 2 contains summaries and overview

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.

27 ICH E3.

28 ICH E1-E2F.

29 ICH E4.

30 ICH E5.

31 ICH E7-E11.

32 ICH E14.

33 ICH E12A.

34 ICH E15-E16.

35 The CTD was adopted as a multidisciplinary topic (ICH M4), as was the electronic version, or eCTD (ICH M8).

documents; Module 3 contains information on the quality of the drug product, including components, manufacturing procedures, facilities and similar matters (what the FDA calls chemistry, manufacturing and controls); Module 4 contains reports of non-clinical studies (safety); and Module 5 contains reports of clinical studies (efficacy).

MeDRA

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

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 EU, 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

36 Further details are set out in the PIC/S website, www.picscheme.org.

37 Details can be found at www.imdrf.org.

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

38 See, e.g., Council Directive 90/385/EEC on approximation of the laws of the Member States relating to active implantable medical devices; Council Directive 93/42/EEC concerning medical devices.

39 21 CFR, Part 820.

Chapter 5

BELGIUM

*Peter Bogaert and Charlotte Ryckman*¹

I INTRODUCTION

Belgium is an EU Member State and has thus implemented the EU medicines and medical devices regimes. This chapter will not repeat the substantive content of the EU chapter but instead will focus on unique features of the Belgian regime. It should be read in conjunction with the EU section. 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.² Together, these rules implement Directive 2001/83/EC³ 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 Decrees⁴ that implement the three EU Medical Devices Directives⁵ into Belgian law.

1 Peter Bogaert is a partner and Charlotte Ryckman is an associate at Covington & Burling LLP.

2 Royal Decree of 7 April 1995 on the Information and Advertising regarding Medicinal Products for Human Use, as amended; Law concerning Experiments on Human Beings of 7 May 2004, as amended.

3 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

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.

5 The Active Implantable Medical Devices Directive 90/385/EEC, the Medical Devices Directive 93/42/EEC, and the In Vitro Diagnostic Medical Devices Directive 98/79/EC.

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.

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.⁶ 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.⁷ 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 1987.⁸

6 Royal Decree of 28 October 2008 Laying Down the Composition and Operation of the Joint Commission and Implementing Article 1, Paragraph 2 of the Medicines Act.

7 Regulation (EC) No. 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods, as amended.

8 Ministerial Circular of 28 July 1987 on Article 1 of the Medicines Act.

ii Non-clinical studies

The Act on the Protection of Animal Welfare of 14 August 1986⁹ implements Directive 2010/63/EU¹⁰ into Belgian law from early 2013. The Act, combined with an implementing Royal Decree,¹¹ 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 Practices¹² (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 2004¹³ 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

9 The Law on the Protection and Welfare of Animals of 14 August 1986, as amended.

10 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

11 Royal Decree of 29 May 2013 on the Protection of Animals used for Experiments.

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.

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.

company. The liability regime sometimes raises complex questions, such as whether it extends to damage suffered by pregnant partners of trial subjects. A specific act regulates experiments on *in vitro* embryos.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/EC¹⁵ and 2005/28/EC.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 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 Belgian legislation on experiments will have to be amended in light of the new EU Regulation on clinical trials,¹⁷ which will repeal the current Directive 2001/20/EC once it becomes applicable (see the EU chapter).

Approval process: 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.

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

15 Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as amended.

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

17 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

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 prior to 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.

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 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.

In principle, unauthorised products cannot be made available in Belgium without setting up a compassionate use programme that is approved by the FAMHP. 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.

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;
- f* there are no authorised products in other countries worldwide; and
- g* 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.

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.

v Pre-market clearance

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 Medicine Act and 2006 Decree implement the EU 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.

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. 141/2000¹⁸ and Regulation (EC) No. 1901/2006¹⁹ 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. 469/2009²⁰ 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.

18 Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, as amended.

19 Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004, as amended.

20 Regulation (EC) No. 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, as amended.

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 Use²¹ and a 1993 Royal Decree on samples,²² which implement the EU advertising rules into Belgian law. These include the general requirements that advertising must not be misleading, and that it must be substantiated and accompanied by appropriate prescribing information. There is also a prohibition on pre-approval or off-label promotion of medicines, advertising of prescription-only medicines to the general public, and illegal inducements to prescribe (for further details on the latter, see Section V, *infra*). 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, *infra*.

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, which 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, *infra*.

x 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

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

22 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.

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 prior to the grant of such a licence and periodically thereafter.

Medical devices

Distributors of certain medical devices, such as sterile products that come into contact with patients, implants and dental equipment, need to notify their activities in order to obtain an accreditation from the Federal Public Service for Health and are subject to control by the FAMHP. Since 1 January 2016, distributors can only make this notification through a specific application via the FAMHP's website. The FAMHP and beMedTech also issued guidance on good distribution practices.²³ 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.

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 1971.²⁴ 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.

23 Proposal for guidelines on the best practice for the distribution of CE-marked medical devices.

24 See in particular: Royal Decree of 31 December 1930 Regulating Soporific and Narcotic Substances, and on Risk Reduction and Therapeutic Advice, as amended; Royal Decree of 22 January 1998 Regulating certain Psychotropic Substances, and on Risk Reduction and Therapeutic Advice, as amended.

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

Pricing²⁵ and reimbursement²⁶ 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.

25 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.

26 Reimbursement rules are primarily set out in the Law on the Compulsory Health Insurance of 14 July 1994, as amended; and Royal Decree establishing the Procedures, Time Frames and Conditions for the Intervention of Mandatory Health Insurance in the Cost of Pharmaceutical Specialties of 21 December 2001, as amended.

The applicable procedure for price determination depends on the type of medicine²⁷ and whether it is considered new. Price determination will either require notification to the Federal Public Service for Economic Affairs (e.g., for generics) or prior approval from the Minister for Economic Affairs (e.g., for innovative medicines). Price increases are also subject to either authorisation or notification requirements, and price decreases must be communicated. Decisions by the Minister for Economic Affairs can be challenged before the Council of State (see Section IV, *infra*). 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 Federal Health Insurance Service. 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, *infra*). 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 (known as 'Article 81 agreements'). 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.

ii Medical devices

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

²⁷ 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.

Medicinal Products. Maximum margins may also apply. Some devices can be reimbursed as such (such as implants) 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.²⁸

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 benefits to wholesalers, to healthcare professionals who can prescribe, dispense or administer medicines, and to 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 does not trigger doubts as to the scientific nature, and the support is limited to attending healthcare professionals and to the duration of the meeting. If the event takes place on several consecutive calendar days, the programme must be approved by the Minister of Health or an officially recognised body. The non-profit association Mdeon is recognised and operates the review procedure; and
- c* reasonable compensation for scientific services, in particular for clinical trials.

28 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.

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 (EFPIA) 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 of negligible value), subject to limited exceptions.

In accordance with the EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations, pharma.be has also implemented 'sunshine' rules, which require the annual disclosure of a number of transfers of value to healthcare professionals or organisations. The first reporting is required in 2016 for transfers of value during 2015. The beMedTech code of conduct imposes similar obligations on the medical device industry. A recent law, dated 18 December 2016, enshrines the sunshine rules in Belgian law. The law has yet to enter into force, as further explained in Section VIII, *infra*.

The Royal Decree of 10 November 1967 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.²⁹ 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.

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 2010.³⁰ 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 also 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.

29 Article 38 Section 2 of the Coordinated Law of 10 May 2015 on the Practice of Health-Care Professions.

30 Under the Act on Compensation for Damage caused by Health Care of 31 March 2010, as amended.

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, *supra*, Belgium has a specific no-fault liability system in relation to experiments on human beings, including clinical trials.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

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 the Competition Council on the basis of reasoned reports presented by the College of Competition Prosecutors. 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 of supplies to wholesalers who wish to engage in parallel export activities, and alleged abuse of patent or other exclusivity rights.

ii Transactional issues

The considerations and issues outlined in the EU chapter apply equally in Belgium.

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.³¹ In particular, Belgium will need to adapt its clinical trials legislation to the new Regulation (EU) No. 536/2014 on clinical trials and also to the new EU Regulations on medical devices, which are still awaiting formal adoption.

At the purely national level, many changes are currently being implemented and several initiatives, often related to expenditure, are ongoing. Some key examples are provided below.

The Law of 18 December 2016 introduced the Sunshine Act, which obliges pharmaceutical and medical devices companies to disclose details on their financial interactions with the main healthcare players. So far, this obligation existed via self-regulation (see Section V, *supra*). The disclosure obligations apply to financial interactions with healthcare professionals, healthcare organisations and patient associations. Certain interactions, such as gifts of limited value, are excluded. On a yearly basis, companies must submit their information to the FAMHP, which is responsible for publishing the information.³² It is not entirely clear when the rules will enter into force, as this is yet to be determined by Royal Decree.

31 These are discussed in the EU chapter.

32 The Sunshine Act provides that a Royal Decree could accredit a third-party organisation to carry out the publication on the FAMHP's behalf.

The Law of 18 December 2016 introduced several other changes to the Belgian pharmaceutical and medical devices regulations. Among other things, the Law incentivises the use of the electronic patient file; introduces new sanctions in relation to the clinical trial rules; modifies definitions in the medical devices legislation; changes and completes the rules on human tissue materials; and modernises some of the terminology in the hospital legislation.³³ Some of these changes have already entered into force, while others still require the adoption of a Royal Decree.

In October 2016, the Belgian Minister of Social Affairs and Health and the medtech industry signed a policy document (the Pact on Medical Technology) covering a wide range of topics, including measures to improve traceability of implantable medical devices,³⁴ provisions on data management and measures regarding medical equipment. 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). This document provides a high-level overview of the 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, *supra*). 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 the Article 81 agreements must be used more as a ‘pay-for-performance’ tool, instead of a more traditional rebate mechanism. 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 orphan drugs, with the overall purpose of alleviating the pressure of the most expensive medicines on public healthcare budgets. 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 (few) biosimilars that are currently available for the hospital sector in Belgium.

The Minister for Social Affairs also launched several initiatives to reform the healthcare landscape in Belgium. For instance, the Belgian Federal Centre for Health Care Knowledge recently published a study, commissioned by the Minister, on different collaboration and cooperation models for hospitals in Belgium. This study is expected to feed into the ongoing debate on reforming hospital financing in Belgium.

33 These are only examples of topics addressed by the law.

34 The ‘Central Registry for Traceability’, a project launched voluntarily by hospitals in 2014, serves as a basis.

Chapter 7

CHINA

*Shaoyu Chen and John Balzano*¹

I INTRODUCTION

China's drug and device legislation has developed rapidly from simple laws and regulations enacted gradually up to 2000, to a substantial body of regulation covering the major areas of research and development, pre-market approval, manufacturing and post-marketing distribution and surveillance. This is an exciting time for drug and device regulatory reform in China. A growing body of healthcare regulation, including medical ethics, pricing and reimbursement, and standards for clinical research, is also emerging to influence the drug and device industries.

In 2013, China reorganised its State Food and Drug Administration into a more powerful ministry-level agency, referred to as the China Food and Drug Administration (CFDA), and reforms in all spaces have continuously expanded since that time. In 2014, China revised the entire medical device regulatory regime. Most recently China's State Council and the CFDA have worked to implement blueprints aimed at bringing higher quality drugs and devices that meet unmet medical needs to market faster. In this respect, for medical devices, the government has implemented significant GxP reform, a priority pathway for innovative devices, and other priority pathways for key disease areas, such as oncology and devices for paediatric and geriatric indications.

The reforms for drugs have been more concentrated in 2015 and 2016. China has established a new system of registration pathways for small molecule drugs 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 world'.² China has also implemented a pilot marketing authorisation holder programme (MAH Pilot) in certain

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2 See Drug and Medical Device Registration Fee Regulations, Articles 3-4 (NDRC 2015); Drug Registration Fees Implementing Regulations, Article 3 (CFDA 2015).

cities that permits domestic research-based companies to hold the rights to the product, while contracting out manufacturing, subject to a set of obligations. The MAH programme has already begun to allow for smaller, research-based companies to undertake significant development efforts in China.

Other reforms are also aimed at improving patient access and encouraging innovation. These reforms include efforts to increase good clinical practice (GCP) compliance for both drugs and devices, new registration fees to provide greater resources for the CFDA, and other guidance documents and structural reforms within the CFDA to improve the speed of the marketing application review process.

This chapter provides an overview of the jurisdiction of the CFDA, the regulatory scheme for developing, manufacturing, and distributing drugs and medical devices. It also explores healthcare, antitrust and corporate considerations. It discusses the new reforms and the impact they are having, and it concludes with a discussion of future directions in these areas. The drug and device regulatory system will likely change and expand for many years to come.

II THE REGULATORY REGIME

i Regulatory agencies and their jurisdiction

The CFDA is the primary pharmaceutical and medical devices regulatory agency in China. This includes biologics and combination products. It enjoys power over most aspects of pre-market approval and a substantial part of post-marketing activities. Under the current arrangement, the CFDA 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 for recommending decisions for the departments to adopt and implement.

For drugs, the primary departments and centres include the Department for Drug and Cosmetic Registration and the Department for Drug and Cosmetic Safety Supervision. 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 CFDA 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 345 at the national level (not counting contract personnel), the CFDA relies on provincial food and drug administrations (PFDA) and similar food and drug regulatory authorities in the municipalities³ to carry out various activities, including accepting applications, conducting on-site checks and inspections,

3 While varying from year to year, the local food and drug agencies and affiliated organisations at PFDA and municipalities have a total approximate headcount of 80,000 (direct and affiliated).

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 (i.e., 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 CDE's 2015 annual report indicates that it added approximately 146 reviewers in that year, indicating that the number of reviewers has grown into the hundreds, from approximately 60–70 a few years ago.⁴ The CMDE has similarly been adding reviewers but has a lower number of about 135 as of 2016.⁵ The increases in staff have been and will continue to be an important step to resolving delays.

Although the CFDA is the primary agency for pre-approval, other government agencies also play important roles in the pharmaceutical regulatory framework. For example, the National Development and Reform Commission (NDRC) plays a key role in articulating drug and device pricing policy. The State Administration for Industry and Commerce (SAIC) plays a significant role in enforcing advertising and promotion and other consumer protection laws. The National Health and Family Planning Commission (NHFP) (formerly the Ministry of Health) oversees all aspects of the medical profession and hospitals (which include CFDA-accredited clinical trial sites for drugs and devices), and it plays a role in determining the essential drugs that may be reimbursed under China's state insurance plans. The Ministry of Personnel and Human Resources also plays a role in setting the formularies for these insurance plans. For imported drugs, two additional government agencies, the Chinese Customs and the Administration of Quality Supervision, Inspection and Quarantine, are 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 CFDA administers laws, State Council regulations, rules, and guidance documents related to drugs and devices. The primary statute regulating drugs (including biologics) in China is the Drug Administration Law (DAL), which was enacted by China's national legislative body, the National People's Congress, in 1984 and then subsequently amended in 2001.⁶ Small amendments were made to the DAL in 2013 and in 2015 to support what China considered to be more pressing regulatory reforms, such as drug pricing. The State Council has enacted one general set of implementing rules for the DAL, referred to as the DAL Implementing Regulations (DALIR). The CFDA (and its predecessor agency, the SFDA) promulgated several agency rules under the DAL and DALIR to govern various activities, such as development, registration, manufacturing and marketing of drugs. These include GxPs on manufacturing, distribution, clinical development and laboratory work. The core regulation governing clinical trials and drug and biologic registration are the Provisions on Drug Registration (PDR), and the more recent reference product and MAH reforms are written into scattered State Council and CFDA documents that supersede provisions

4 Annual Report of the Center for Drug Evaluation (3 March 2016).

5 This statistic was compiled by reviewing multiple hiring announcements on CMDE's website, www.cmde.org.cn.

6 Drug Administration Law (amended February 2001), <http://eng.sfda.gov.cn/WS03/CL0766/61638.html>.

in the PDR. These reforms may be incorporated into the DAL or the PDR (or both) once they proceed past the experimental stage. The CDE also issues its own rules and guidance documents related to drug development and registration, priority pathways and supplemental applications.

China has not enacted a statute covering medical devices, but the State Council has enacted a framework regulation, the Regulations for the Supervision and Administration of Medical Devices (RSAMD). And, as with drugs, the CFDA has enacted a number of implementing rules covering registration, production and distribution.⁷ In 2014, the State Council revised the RSAMD, and the CFDA subsequently issued an entirely new set of substantially revised implementing regulations, governing device registration, manufacturing and distribution. These reforms continued well into 2016, and CFDA has not yet finalised certain rules, such as those on adverse event reporting and monitoring, recalls, and device advertising and promotion. Like the CDE, the CMDE issues its own rules and product specific guidance documents.

iii Product classification and definitions

Drugs

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.*⁸

The CFDA has significant discretion to determine whether a substance constitutes a drug or fits into another regulatory regime. As will be discussed below, the CFDA does recognise some category overlap. When products may be considered drug and device combination products, the CFDA 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. The primary pathways are either a domestically manufactured drug or an imported drug.

Before a company can market a drug in China, the DAL requires that the company submit and obtain government approval of a drug registration application, which may be divided into two parts: (1) a clinical trial application; and (2) a subsequent application for approval to market the drug.⁹ If the drug is to be manufactured in China, the company must also submit a manufacturing licence application and obtain a good manufacturing

7 RSAMD, www.cfda.gov.cn/WS01/CL0784/97814.html. 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.

8 Article 102 of the DAL.

9 Article 29 of the DAL.

practice (GMP) certification of its facilities.¹⁰ If the drug is to be manufactured abroad, the company must apply for an import drug licence.¹¹ In either event, approval requires a robust demonstration of safety and efficacy, showing that the drug's benefits outweigh its risks. After approval, a drug manufacturer is required to conduct pharmacovigilance and follow rules on advertising and promotion, as discussed in the sections below.

The DAL and PDR¹² classify a drug either as a domestic drug or as an imported drug, depending on whether the finished dosage form of the drug is manufactured inside or outside China. The PDR then classifies domestic drugs into three types: traditional Chinese medicines and natural drugs, chemical drugs and biological drugs. Within each classification, drugs are then placed into categories and subcategories. These classifications and sub-classifications determine the clinical data and other requirements necessary for registration.

In March 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 as follows:

- a* Category 1: innovative drugs. These drugs have an active ingredient that has a clear structure and is clinically valuable. The ingredient must be new to the world, not just new to China.
- b* Category 2: improved innovative drugs. These drugs have an improvement that is clinically valuable and new to the world, such as certain structural changes, dosage forms, routes of administration, strengths and indications.
- c* Category 3: generics with foreign reference products. This category is for generic drugs that use fully evaluated drugs (typically originator drugs), which are marketed abroad but not in China, as their reference products.
- d* Category 4: generics with domestic reference products. The opposite of Category 3, this category is for generics that use fully evaluated drugs that are marketed in China as their reference products.
- e* Category 5: foreign drugs. Following on from the separation between imported and domestic drugs described above, this category is either for originator drugs that are already marketed abroad (5.1) or generic drugs marketed abroad (5.2). These drugs use the import licence pathway.¹³

Biologics have not undergone a similar reform. They are under the original categorisation contained in the PDR, Appendix Three. Under the PDR, all biologics proceed along the new drug pathway, even if they might be considered biosimilars. In terms of application pathways, in Appendix III, biologics are classified as either therapeutic or preventive, then further classified into 15 subcategories under each heading.¹⁴ Classification depends on the

10 Article 8 of the DAL.

11 Article 39 of the DAL.

12 The Provisions for Drug Registration (2007), <http://eng.sfda.gov.cn/WS03/CL0768/61645.html>.

13 Notice on the Plan for New Registration Categories for Chemically Synthesized Drugs (CFDA No. 51 2016).

14 Appendix 3 of the PDR.

drug's marketing approval status in China and abroad, source material, composition and other factors. The subcategories are not mutually exclusive, which can lead to confusion and duplicative requirements.

As explained below, certain types of drugs may be subject to separate and heightened requirements and require additional special permissions. An example of this would be drugs that the CFDA classifies as 'narcotic drugs' and 'psychotropic drugs,' which are discussed in the subsections below.

Devices

The RSAMD define '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;*
- (5) pregnancy control; and*
- (6) provision of information for medical or diagnostic purposes by inspecting the samples of human bodies.¹⁵*

The RSAMD classify medical devices into three classes:

Class I medical devices means medical devices with low risks, and those for which safety and effectiveness can be ensured through routine administration; Class II medical devices means medical devices with moderate risks, which must be strictly controlled and administered to ensure their safety and effectiveness; Class III medical devices means medical devices with relatively high risks, which must be strictly controlled and administered through special measures to ensure their safety and effectiveness.¹⁶

As with drugs, the CFDA 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

15 Article 76 of the RSAMD. This is an edited version of the translation that appears on www.chinalawinfo.com.

16 Article 76 of the RSAMD.

application to the CFDA or they can treat their device as a Class III and ask the CFDA to make adjustments.¹⁷ The CFDA oversees an electronic portal that permits applications for a predetermination of device classification.

The CFDA maintains and periodically updates a classification catalogue showing its medical device classification decisions. By reference to this catalogue, along with general classification rules, the applicant can make its own determination as to classification. In 2016, the CFDA released a proposal for an amended catalogue with considerably more information, including product descriptions and intended uses.¹⁸ Soon thereafter the CFDA convened a conference of experts on the amendment, and announced that it was accelerating the revision process. It is possible, therefore, that the revision could be finalised in 2017. Because classification determines data requirements for registration, it is often important to determine the class before starting trials or filing for an exemption.

As with drugs, the RSAMD and the Administrative Measures on Medical Device Registration, classify a medical device either as a domestic device or as an imported device, depending on whether the finished device is manufactured inside or outside China. If it is an imported device, the CFDA reviews and approves a registration application for Class II and Class III devices. Class I imported devices go through a notification system, which the CFDA 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 FDA approves Class II medical device registration applications; and the CFDA reviews and approves Class III medical device registration applications.¹⁹ The Measures on the Registration of In Vitro Diagnostic Reagents, which were also amended in 2014, set out a similar classification and registration scheme for IVDs.

Combination products

The CFDA issued a notice in 2009 to govern its review of drug and device combination products.²⁰ 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 CFDA may treat as a combination product is a tissue-engineered product, which may be considered a medical device that may also have to meet certain requirements particular to the development of a biological product.²¹

Absent extenuating circumstances (e.g., substantial clinical need), the CFDA will not approve a combination product that is imported into China, if the product as a whole has not received any approval from the exporting country, or if the drug component of the product has not been approved in China or in the exporting country.

17 Article 16 of the RSAMD.

18 CFDA Notice Soliciting Comments on the Classification Catalogue for Medical Devices (CFDA 30 September 2016).

19 Article 5 of the Measures on Medical Device Registration.

20 Notice Concerning Registration of Drug and Device Combination Products (2009).

21 CFDA Notice on Tissue Engineered Medical Products and Related Application Requirements (CFDA 2007).

iv **Non-clinical studies**

Non-clinical studies for drugs must comply with the CFDA Drug Good Laboratory Practice Regulations,²² which for the most part follow similar good laboratory practice (GLP) requirements in other countries. Non-clinical studies for drugs must be conducted by institutions that have been certified by the CFDA to perform such studies to be accepted as part of a drug registration application. The CFDA also accredits laboratories that conduct pretrial testing for Class II and III devices.

v **Clinical trials**

Drugs

Before a clinical trial can be initiated in China, the sponsor must submit a clinical trial application (CTA) to the CFDA, and the CFDA must approve it and issue a clinical trial permit. Although reform in this area is ongoing, the CFDA's review of a CTA can take about one year or more; an expedited review is potentially available for drugs that fit under the new drug pathway and those that are intended to treat certain illness or patient populations (e.g., children or the elderly) that the State Council or the CFDA consider 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 CFDA is continually working to reduce this timeline for approval.²³ As discussed below, the CFDA has recently adopted a filing system for bioequivalence studies for generic drugs that is less onerous than the CTA process.

The CFDA requires that investigational drugs be manufactured at GMP facilities and comply with GMP standards. It also requires that government-certified laboratories conduct quality testing to confirm conformity with the quality standards.²⁴ The sponsor must also seek review and approval of the clinical trial by a qualified ethics committee, and if the institution has one, also by a clinical trial management committee for each clinical trial site; a process that can take more than a few weeks.

Clinical trials can be conducted only at institutions that have been inspected and certified by the CFDA for that type of clinical investigation. Clinical trials in China are also governed by pharmaceutical GCP regulations,²⁵ which largely follow similar GCP regulations in other countries. The GCP regulations and the PDR set out sponsor and investigator obligations, including for serious adverse events. The CFDA, or ethics committee, can hold or terminate a study for safety reasons.

Once a clinical trial protocol is approved by the CFDA, 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, its regulations still do not include a clear procedure for protocol amendments. This shortcoming has led to applicants having to file an entirely new CTA when making changes to their approved CTA.

22 Good Laboratory Practice Regulations (2003), www.sfda.gov.cn/WS01/CL0053/24472.html.

23 See, e.g., Proposed Opinion Regarding Implementation of Priority Evaluation and Approval for Reduction of the Drug Registration Application Backlog (CFDA 2015).

24 Articles 35 and 36 of the PDR. Also see the CFDA clinical trial flow chart: <http://eng.sfda.gov.cn/WS03/CL0769/61658.html>.

25 Pharmaceutical Good Clinical Practice Regulations (2003), www.sfda.gov.cn/WS01/CL0053/24473.html.

For investigational arms of clinical trials, in some cases the PDR specify the following minimum numbers of study subjects, and the trial must have sufficient statistical power.²⁶ The CFDA began to revise the application requirements for chemically synthesised drugs in 2016, with new data and application requirements.²⁷

	<i>Phase I</i>	<i>Phase II</i>	<i>Phase III</i>	<i>Phase IV</i>
<i>Therapeutic biologic</i>	20	100	300	Not specified
<i>Preventive vaccine</i>	20	300	500	Not specified

Because under most circumstances, China's drug regulations require approval of the drug abroad prior to submitting the CTA, many foreign manufacturers choose to apply for a multiregional clinical trial, instead of the standard local trial. Under the PDR, a multiregional clinical trial (MRCT) application does not require approval abroad, but instead only requires that the development has entered Phase II elsewhere.²⁸ Once the MRCT is complete, the applicant can apply for a waiver to the standard local trial requirement and subsequently submit its application.

In 2013, the CFDA changed its policy as to when it would accept the waiver application. This change significantly lengthened the MRCT pathway, although it still remains viable. Specifically, the CFDA revised its policy in late 2013 to require that an application to waive the local trial requirement be submitted and approved separately before the applicant may submit the final licensing application. The CFDA has been considering reform of this policy to reduce unnecessary delays. Also, China has increasingly embraced the idea of MRCTs by adopting special guidance on these types of trials in early 2015, and policies are now being proposed to encourage domestic drug manufacturers to participate in these trials.²⁹

Devices

Clinical data are used to establish safety and efficacy of medical devices that are registered for marketing in China.³⁰ In general, manufacturers must submit clinical trial data to register Class II and Class III medical devices (including *in vitro* diagnostics).³¹ No clinical trial is required for Class I devices.³²

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;

26 Appendixes 2 and 3 of the PDR.

27 New Chemical Drug Registration Category Application Material Requirements (Trial Implementation) (CFDA No. 80 May 4, 2016).

28 Article 44 of the PDR.

29 See Guidance on Drug International Multicenter Clinical Trials (For Trial Implementation) (CFDA 2015); Notice to Seek Comments on the Policies to Expedite the Reduction of Drug Registration Application Backlog (CFDA 2015).

30 Article 17 of the RSAMD.

31 Article 17 of the RSAMD.

32 Article 17 of the RSAMD.

and (3) devices that can be evaluated through pre-existing data on the same types of devices.³³ To further define these categories, the CFDA issued multiple catalogues of exempt devices,³⁴ the latest having been issued in September 2016,³⁵ 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.³⁶

Clinical trials of Class II and most Class III medical devices do not require CFDA approval. However, the CFDA 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 CFDA has accredited to conduct device trials.³⁷ The system of accreditation is still developing.³⁸ While no pre-approval from the CFDA is required (unless the device is designated as a high-risk Class III device), all medical device clinical trials must be approved by the institution's ethics committee and notified to the provincial-level government where the clinical trial sponsor is located. The CFDA issued procedures to implement this provincial notification requirement in July 2015.³⁹ In addition, under the revised RSAMD, device trials must comply with medical device GCPs. The CFDA issued new GCPs for medical device trials to support registration with the CFDA.⁴⁰ These GCPs added to the provisions on informed consent (including those on consent from children and others who lack the capacity to consent), requirements for agreements between sponsors and the site, and the coordination of multisite trials.

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.⁴¹

vi Named-patient and compassionate use procedures

China has not promulgated regulations or formally established any regularly accessible mechanism to allow named-patient or compassionate use of a drug or medical device

33 Id.

34 Notice on Issuing the Catalogue of Class II Medical Devices that are Exempted from Conducting Clinical Trials (2014), available at www.cfda.gov.cn/WS01/CL0087/105224.html; Notice on Issuing the Catalogue of Class III Medical Devices that are Exempted from Conducting Clinical Trials (2014), available at www.cfda.gov.cn/WS01/CL0087/105225.html.

35 Notice Second Batch of Medical Devices Exempt from Clinical Trials (CFDA No. 135 2016).

36 Articles 18 to 20 of the Measures on the Registration of In Vitro Diagnostic Reagents (2014).

37 Article 18 of the RSAMD.

38 Measures for the Accreditation of Medical Device Clinical Trial Institutions (draft for public comment), available at www.cfda.gov.cn/WS01/CL0779/110987.html.

39 Article 18 of the RSAMD.

40 Good Clinical Practices for Medical Device Clinical Trials (CFDA No. 25 2016).

41 Tentative Measures on the Management of Human Genetic Resources (1998).

outside clinical trials and prior to marketing authorisation. The CFDA permits limited drug compounding or medical device manufacture by hospitals for use on their own patients, sometimes without having to receive CFDA clinical trial approval or marketing authorisation.⁴² In addition, Chinese drug regulations provide for the importation of unapproved drugs to satisfy urgent clinical needs and are needed in the case of national emergencies. The urgent clinical need standard is a high one that is difficult for individual patients to meet, but may be used somewhat more commonly when the drug is necessary to treat a specific group of patients to prevent the spread of serious contagious disease.⁴³

vii Pre-market clearance

Drugs

CFDA review and approval is required for the domestic production or importation of drugs. The PDR provide five types of drug registration applications: (1) new drug; (2) generic drug; (3) imported drug; (4) supplemental applications; and (5) re-registration.⁴⁴ With the exception of (4) and (5), the type of application depends on where the finished dosage form of the drug is manufactured. If manufactured and finished outside of China, the drug is considered an imported drug, and an imported drug application must be submitted to obtain an imported drug licence.

If the drug is manufactured inside China, the drug is considered a domestic drug, and either a new drug application or a generic drug application must be submitted to obtain the drug manufacturing licence. The new MAH Pilot allows the applicant to obtain a product licence without a manufacturing licence. A new proposal for an amendment to the PDR would simplify this system and provide for different types of registration applications (e.g., clinical trial, marketing, supplement) without making a distinction between imported and domestic drugs. However, it is not clear whether that proposal, which did not have an accompanying explanation, would eliminate other distinctions between imported and domestically manufactured drugs, such as those related to regulatory exclusivity and priority review status.

Imported drug application

Under most circumstances, before submitting an application for an import licence the drug must have been approved for marketing in the country where the manufacturer has its principal place of business or where the drug is manufactured. The foreign manufacturer holding the relevant approval for the foreign regulatory health authority must be the applicant before the CFDA and, under most circumstances, will be required to present a certificate of pharmaceutical product to show marketing abroad. Under recent reform proposals, the CFDA has proposed to treat imported drugs approved abroad as falling under the category of generic drugs,⁴⁵ because of a recent policy decision (discussed below) for new drugs to be defined as new to the world, and not merely new to China.

42 Article 25 of the DAL; Article 10 of the Regulations for the Supervision and Administration of Medical Devices.

43 Article 37 of the DALIR.

44 Article 11 of the Provisions for Drug Registration (2007).

45 Notice Regarding the Solicitation of Opinions regarding the Marketing Authorization Holder System Pilot Plan and the Chemical Drug Registration Category Reform Plan (CFDA 2015).

If the drug for import is not yet approved abroad, the CFDA is given the discretion to approve it, if the application provides adequate data to establish safety and efficacy, and there is clinical need for the drug in China.

In addition, the foreign manufacturer must submit drug samples from three batches to be tested by the National Institute of Food and Drug Control (NIFDC) for conformity with product specifications and quality standards. The manufacturer must also appoint a local entity in China to act as the agent for the imported drug registration.⁴⁶ The CDE reviews the application data for safety and efficacy. Generally, if safety and efficacy are established through a trial, and the NIFDC drug sample testing results are satisfactory, the CFDA will approve the application and issue an imported drug licence.

New drug application

As noted, 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 subsection iii, *supra*. For a new drug application, the CDE assesses safety and efficacy. If established, it will order a pre-approval GMP inspection, during which drug samples will also be taken, and sent for testing by the NIFDC to check conformity with product specifications and quality standards. If the pre-approval GMP inspection and NIFDC testing are satisfactory, the CFDA will approve the application and issue a drug approval number, provided the manufacturer has already obtained a drug manufacturing facility permit.

The CFDA has now implemented the MAH Pilot for drugs manufactured in China. The MAH Pilot began in 2015 and will last until 2018, and is being implemented in 10 provinces (including Beijing and Shanghai). Under the Pilot, individuals of Chinese citizenship, research institutions and holders of drug manufacturing licences would be permitted to hold a licence for a product and have important rights and responsibilities over the final product, including the rights to sell, distribute and receive profits from the drug. However, those individuals or entities could contract out the manufacturing without holding the facility licence.⁴⁷ 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.

Generic drug application

With the exception of originator 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 or an *in vitro* study, if the drug qualifies for an exemption. In other cases, the applicant may have to conduct an efficacy study. In most cases, the reference product will be an originator product, but the CFDA will also permit an 'internationally recognised' generic product to serve as a reference product.⁴⁸

Generics on the market that are on the Essential Drug List (2012 version) for reimbursement in healthcare institutions and in solid oral forms must demonstrate equivalence

46 Articles 84 to 95 of the PDR.

47 Id. Notice for Issuing the Plan for the MAH Pilot (State Council General Office No. 41 2016).

48 Opinion on Developing Therapeutic and Quality Equivalence Evaluation for Generic Drugs (State Council General Office No. 8 2016).

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.⁴⁹

The CFDA has been developing and implementing a new set of guidelines for demonstrating bioequivalence. Under this new system, bioequivalence studies may begin after the applicant has notified the CFDA through an electronic platform.⁵⁰ The CDE review of a generic drug application proceeds in parallel with manufacturing site inspection and collection of drug samples by the provincial FDA, as well as drug quality testing by the NIFDC. If results are satisfactory, the CFDA will approve the application and issue a drug approval number to the applicant, which should have already obtained a drug manufacturing facility permit, unless it is part of the MAH Pilot.⁵¹

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 PDR require that all biologics go through the application pathway for new drugs, and do not provide for a separate biosimilar category.⁵² But 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.⁵³

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. The new guidance also includes some provisions on labelling and pharmacovigilance.⁵⁴ The way that this guidance is intended to interact with existing law and regulation governing the approval process for all biologics is still not entirely clear.

Approval timelines

In 2015, the CFDA began examining what had become a huge application backlog for both drugs and devices. The Agency has tens of thousands of applications pending, with thousands more being filed each year. The State Council and the CFDA have committed to significantly reducing this backlog by 2018. The CDE's last annual report, released on 3 March 2016, indicated that the drug backlog had been reduced from approximately

49 Notice on Several Matters Related to the State Council General Office's Option on Demonstrating Therapeutic and Quality Equivalence of Generic Drugs (CFDA No. 106 26 May 2016).

50 Provisions on Chemical Drug Bioequivalence Study Notifications (CFDA 2016).

51 Chapter 5 of the PDR.

52 Article 12 of the PDR.

53 Appendix 3 of the PDR.

54 Draft Guidance on the Research and Development and Technical Evaluation of Similar Biotherapeutic Products, available at www.cde.org.cn/zdyz.do?method=largePage&id=212.

22,000 to 17,000 applications, which is a reduction of around 22 per cent.⁵⁵ The CFDA has also committed to increasing the speed of the reviews and criteria for review and approval by adding review personnel and creating review guidelines.

With these new reforms still in progress, 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 PDR 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 also sometimes repeated, although the CDE is required to avoid repeated requests. Reviewers may meet with the applicant upon request but may not do so unless the drug is new to the world or has an improvement that is new to the world.

Priority review is available for certain drugs that treat serious or life-threatening conditions, including new drugs for treatment of HIV, cancer or orphan diseases, and new drugs that treat unmet medical needs. The CFDA has recently introduced new priority categories, including drugs that treat diseases prevalent among children and the elderly, that are on national scientific research plans, foreign innovative drugs that transfer manufacturing to China, and drugs that are being developed simultaneously in the US and Europe.⁵⁶ Priority status facilitates applications by permitting 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. Past practice indicates that priority status can improve timelines reducing them down to nine months, and even six in some rare instances.

Re-registration application

The registration for an imported or domestic drug is valid for five years. Six months prior to expiry of the registration, the applicant must submit a re-registration application to the CFDA if it is an imported drug or to the PFDA if it is a domestic drug. Re-registration applications generally do not require new clinical data, though data from the required Phase IV study may be a condition of renewal. The CFDA or PFDA 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.⁵⁷ On 29 December 2016, the CFDA released a proposal to transfer the decision-making power

55 Annual Report of the CDE (3 March 2016).

56 Notice on Several Questions of Policy Related to Drug Registration Evaluation and Approval (CFDA 2015).

57 Chapter 9 of the PDR.

over re-registration applications for imported drugs to the CDE. If adopted, it is assumed that this approach would reduce the delays encountered when the CDE transfers the application to the CFDA to make a final decision following the CDE's technical review.⁵⁸

Supplemental drug application

Certain post-approval changes to a drug, whether imported or domestic, require CFDA approval of a supplemental drug application. The applicant must be the company that holds the existing marketing or manufacturing authorisation. While major post-approval changes require the CFDA or PFDA review and approval, some minor changes can be notified to the agency and implemented without review and approval.⁵⁹ The proposal described above related 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 CFDA 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 PFDA. Class III medical devices, as well as Class II and III imported medical devices, must be approved at CFDA 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.

The statutory time frame for agency decisions on the different types of devices depends on the class of the device and type of technical review required. For Class I devices, either the municipal FDA or the CFDA (if an imported device) will make an immediate determination of the completeness of materials and, if complete, accept the notification.⁶⁰ 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 (e.g., 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

58 Decision on Adjusting the Procedures Related to Part of the Examination and Approval of Certain Administrative Matters.

59 Chapter 8 of the PDR.

60 Notice on Several Matters Related to Class I Medical Device Notification (2014), available at www.cfda.gov.cn/WS01/CL0087/100816.html.

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 CFDA has 20 days to make a decision.

In reality, applicants may experience significant delays waiting for certain stages of this process to begin, although the CFDA is applying similar measures to those described above for drugs to combat these delays for devices and the existing device application backlog.⁶¹ The CFDA 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 the elderly and other devices that serve urgent clinical needs.⁶² Those accepted to these pathways get priority access to CMDE reviewers to regarding the design of their application.

After approval, a medical device registration certificate is issued by the appropriate level of FDA, and the certificate is valid for five years. Six months prior to the expiration 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 that the licence expires, then 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.⁶³

viii Regulatory incentives

Chinese regulation is designed in some respects to encourage innovation and development and manufacturing of products in China for which there is particular clinical need and value through expedited pre-market approval pathways. In contrast, post-approval regulatory incentives are very weak and their implementation is incomplete. China has established a system of patent protection for drugs and devices. There is some limited regulatory data protection for a new chemical entity, although these data protection are difficult to enforce in practice, and China has a kind of *de facto* market exclusivity implemented through a new-drug monitoring period (described below) for a drug that has not been manufactured in China or is locally manufactured in China.

61 Articles 33 to 36 of the Measures on the Registration of Medical Devices.

62 Procedures on Priority Review and Approval for Medical Devices (CFDA No. 168 2016).

63 Articles 49 to 53 of the Measures on the Registration of Medical Devices.

Drugs

Patent protection

China gives 20 years of patent protection. It does not give patent term extension to compensate for CFDA's drug registration review and approval time. An applicant is required to provide information on patent status in China as part of its drug registration application. If there are relevant third-party patents in force, the applicant must make a declaration of non-infringement, which the CFDA will publish.⁶⁴ In practice, however, the CFDA has not implemented these provisions rigorously, and there is no true patent linkage system in China. Non-infringement declarations do not automatically trigger the requirement that the applicant notify the patent owner, nor can an originator manufacturer apply to stay the CFDA's approval decision if they discover an infringing application. If the drug is covered by third-party patent rights and the applicant is not able to file a non-infringement declaration, the applicant can file the application two years prior to the patent expiration, and the CFDA can review the application and, if approvable, grant the approval upon expiry of the patent.⁶⁵ In a recent proposal to amend the PDR, the CFDA proposed to further reduce this protection, asking applicants to make the determination on their own and offering no regulatory pathway to stop approval of the generic. Under this amendment, applicants would resort to the Patent Law to resolve any disputes.

Data protection

Pursuant to its obligation under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and other related bilateral commitments, China offers six-year regulatory data protection to new chemical entities. This protection is formally provided in Article 20 of the PDR and Article 35 of the DALIR. Within six years of approval, the CFDA is not allowed to approve another application (usually a generic drug application) that includes or refers to the innovator's data unless the innovator has authorised such use, or the innovator data have been publicly disclosed.

In practice, this provision is difficult to implement because the term 'new chemical entity' is not defined, and the CFDA has not issued procedures surrounding various aspects of this protection. As such, companies have not experienced a true benefit from this protection. Innovator companies have continued to express concerns about the operation of the data protection provisions, including whether the CFDA approves generic drug applications prior to the expiration of the data protection period. The CFDA has promised to include a definition of a new chemical entity in amendments to drug legislation or regulations. However, in its final plan for restructuring the chemical drug registration categories, the CFDA did not include a definition for a new chemical entity for purposes of regulatory data protection. In its 2016 proposal to revise the PDR, the CFDA removed provisions on regulatory data protection altogether, making the future of such protection uncertain.

Marketing exclusivity

China does not have true regulatory marketing exclusivity. Article 66 of the PDR provides that the CFDA has the discretion to 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

64 Article 17 of the Provisions on Drug Registration.

65 Articles 18 to 19 of the PDR.

period is not available for imported drugs and, under 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 CFDA 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 CFDA can approve another domestic or imported drug application. The monitoring period does not provide complete exclusivity, however, because if the CFDA has approved the CTAs of other applicants for the same drug, those applications may proceed to registration.

Devices

The regulations for the registration of medical devices do not require patent certification or contain provisions on data or market exclusivity. The revised RSAMD expressly state that any patent disputes will be handled under the relevant laws (i.e., the Patent Law).⁶⁶ There are procedures for expedited review and approval of medical devices where 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 CFDA during development and registration.⁶⁷

The CFDA has also created an expedited pathway for review of applications for ‘innovative devices’. To qualify as an innovative device:

- a* the patent for the technology must be held in China;
- b* the primary work on the product’s design and use mechanisms must have been the first of its kind in China;
- c* its safety or functionality must be a fundamental improvement over comparable technology;
- d* it must be leading technology internationally; and
- e* the device must have clear clinical value.

In addition, well-controlled preliminary research must be completed and there must be a basic product model. The data must be complete and traceable.⁶⁸ 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 CFDA regarding its application and the ability to hold a licence without a manufacturing facility. As noted above, the CFDA has recently released procedures on additional priority pathways, which are based on more on clinical needs and not other IP-related criteria.

66 Article 48 of the RSAMD.

67 Articles 4 to 5 of the Procedures for Emergency Review and Approval of Medical Devices (2009).

68 Article 2 of Procedures on the Examination of Innovative Medical Devices (Trial Implementation) (2014), available at www.sda.gov.cn/WS01/CL1237/96654.html.

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.⁶⁹ In 2011, the CFDA 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 FDAs at national, provincial and municipal levels to set up adverse event collection systems, and imposes 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.⁷⁰

For medical devices, the CFDA promulgated the Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation (Interim), and issued Guidance on the Monitoring of Medical Device Adverse Event (Interim) to impose detailed adverse event reporting obligations on device manufacturers, distributors and user facilities. The system and requirements are similar but not identical to those for drugs.

In late 2015 and then again in late 2016, China released a revised version of the Measures on the Administration of Medical Device Adverse Event Monitoring and Re-evaluation for public comment. That draft introduced a more concrete role for technical monitoring institutions; modifications to the timelines for manufacturers, distributors and healthcare institutions to report on and evaluate adverse events both on an individual and periodic basis; a clearer definition of a serious adverse event; and more concrete requirements and guidelines for targeted monitoring of certain devices and device re-evaluation.⁷¹

The CFDA has the authority to order mandatory recalls of drugs and medical devices because of serious adverse reactions or other safety issues.⁷² 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' (i.e., an unreasonable risk of bodily harm under normal conditions of use) with the device. A defect obligates the manufacturer to recall the device. The manufacturer must also classify the recall into one of three classes, the first class

69 See, e.g., Articles 41 to 44; 67 to 68; and 121 of the PDR, and Article 169 for drugs, and Article 48 of the RSAMD (requires manufacturer to establish device AE reporting system, and tracking system on Class III devices).

70 The Measures on the Administration of Adverse Drug Reaction Reporting and Monitoring (2011), Chapters 2 to 6.

71 Notice Soliciting Comments on the Revised Draft of Administrative Measures on Monitoring Medical Device Adverse Events and Re-Evaluation (CFDA/NHFPC 2015); Notice Soliciting Comments on the Revised Draft of Administrative Measures on Monitoring Medical Device Adverse Events and Re-Evaluation (State Council OLA 2016).

72 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.

being the highest risk and the third being the lowest. If a manufacturer does not conduct a recall voluntarily, then the CFDA may order one. The manufacturer must report on the progress of the recall and its final results.

Transfer of licences

Transfer of licences is more difficult to achieve in China than in, for example, the United States. Part of the reason is that CFDA regulations give extremely limited guidance on this issue and regulatory changes have created further uncertainty. Another reason is because of the connection between the product permission and the manufacturing facility permissions.

Although the marketing authorisation holder system described above may ultimately change this, for domestically manufactured drugs, the licences are issued to the specific manufacturer, for the specific manufacturing site and for the manufacturing of the particular drug. In other words, the Chinese system is a combination of manufacturing authorisation and marketing authorisation. As a result, any transfer will typically trigger a review and approval process, where the qualifications of the transferee will be carefully examined. The supplemental application will be denied if the transferee does not meet the relevant requirements, such as having qualified personnel necessary to comply with applicable GMP requirements. There are two licences involved: the drug manufacturing facility licence, which is issued to the manufacturing site and requires renewal every five years, and the drug manufacturing licence and the corresponding drug registration certificate and approval number, which require renewal every five years. The second licence can only be issued to an entity that has the first licence.

For drugs, transfer of licences in China would probably need to involve the transfer of the ownership of the manufacturing facility, and this is usually done via an equity acquisition of the holder of the two licences. In fact, the CFDA regulations have specifically prohibited any 'purchase and sale, rental, or other loan of the licences', and engaging in those activities could trigger revocation of the relevant licence.

Regarding devices, these issues are somewhat different. The CFDA 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 would likely 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, depending on the details of the deal. These procedures are not laid out in the regulations but are an internal procedure that the CFDA and its provincial counterparts follow.⁷³

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.⁷⁴

73 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. 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.

74 Article 18 of the Medical Device Manufacturing Regulations (CFDA 2014).

Note that for imported drugs and medical devices, there is no manufacturing licence. Accordingly, it is easier to transfer the imported drug or device licence as long as the transferee meets the requirements of a new applicant or licence holder for the China imported drug or device licence (e.g., it must be a manufacturer that holds the foreign marketing authorisation that provided the basis for the CFDA to grant the China licence).

Suspension or revocation of approvals

The CFDA can suspend or terminate a clinical trial, or suspend or revoke a marketing authorisation if there are serious product safety issues, or if the manufacturer fails to comply with associated regulatory requirements. In comparison with many other regulatory schemes, the CFDA has many more grounds to suspend or revoke an approval. First, the marketing authorisation needs to be renewed periodically every five years for drugs and devices. Every year, the CFDA decides not to renew many products, based on various grounds set out under the law. The PDR, for example, provides in Article 126 that:

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 disease or for public health emergencies are not met.⁷⁵

Second, there are multiple 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:

- a* if there is production or sale of counterfeit or substandard drugs;⁷⁶
- b* if there is non-compliance with customs rules for imported drugs;⁷⁷ or
- c* where the labels do not meet applicable requirements.⁷⁸

75 Article 55 of the RSAMD.

76 Articles 74 and 75 of the DAL.

77 Article 81 of the DAL.

78 Article 86 of the DAL.

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

- a* new developments in science and technology raise questions about the safety and effectiveness of the device;
- b* adverse event reporting raises questions about the safety and effectiveness; and
- c* any other circumstances that the CFDA determines warrant a re-evaluation.⁷⁹

The revised RSAMD provide that obtaining a licence via fraudulent or corrupt means is grounds for revocation of the licence.⁸⁰ 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.

x Manufacturing controls

Drug and Class II and III device manufacturing facilities located in China must hold a manufacturing licence, and be certified as compliant with drug or device Good Manufacturing Practices. Class I device facilities submit a notification to local food and drug regulatory authorities.

For drugs, any proposed establishment of a facility must be approved by government agencies responsible for economic planning, and by the PFDA 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. Product sample testing by government labs is required as a part of the review and approval of clinical trial and marketing authorisation processing, and pre-approval inspections are required, all designed to ensure GMP compliance.

All device enterprises must comply with quality management rules (i.e., GMP and other medical device standards). 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.⁸¹ If any manufacturer is found to be non-compliant with rules, and does not correct the violation, it can be fined or shut down.⁸²

Contract manufacturers must be similarly GMP-compliant, and hold the requisite manufacturing licence. Under some circumstances, in which the CFDA has determined that the products present heightened risk, such as in the case of implantable devices, biologics, psychotropic drugs or narcotic drugs, the agency will not permit contract manufacturing.⁸³

79 Article 51 of the RSAMD.

80 Article 64 of the RSAMD.

81 Article 10 of the Measures for the Supervision and Administration of Medical Device Manufacturing.

82 Article 67 of the RSAMD; Article 67 of the Measures on the Supervision and Administration of Medical Devices.

83 Article 12 of the Regulations on Drug Contract Manufacturing (2014).

xi Advertising and promotion

*Drugs**Advertising*

The CFDA 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, the legislature has made it more prominent that the definition of advertisement will include websites, mass emails, and postings on microblogs and other social media sites.⁸⁴ Article 3 of the Detailed Rules on Implementation of Administration of Advertisements – which was issued in 2004 but remains effective – also contains a generally phrased list of the 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 prior to CFDA approval is prohibited, although some strictly limited scientific exchange may be permissible.

The drug-specific advertisement requirements and prohibitions are provided in a number of Chinese laws and regulations, including the Measures for Review of Drug Advertisement (Advertisement Measures) and the Standards for Drug Advertisement Review and Release (Advertisement Standards), both of which were promulgated jointly by the CFDA and the SAIC in 2007. The SAIC began revising the Drug Advertisement Standards in 2015, but the draft that it issued did not propose to make substantial changes to the basic features of the system.⁸⁵ The CFDA issued a proposal to revise its procedures for approving drug, device and health food advertisements in late 2016, but it has not yet finalised that rule. As the Advertising Law sets many of the limits on substantive content, the CFDA’s rule was primarily procedural.

The provincial FDA 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 CFDA-approved medical journals (currently, the CFDA has approved about 557 such journals). 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 CFDA has posted on its website all advertisements that have been approved and those against which there has been enforcement.

84 Draft for Comment of the Interim Measures on Supervision of Internet Advertising (2015). To date, these measures do not appear to have been finalised. Under the Advertisement Law of China (2015), which applies to all advertising, including drug or device advertising, the term advertisement is defined in Article 2 as ‘any commercial advertisement, which a commodity or service provider bears the costs for, through certain media or forms, directly or indirectly introducing their commodities being sold or services being provided’.

85 Drug Advertisement Examination Standards Draft for Comment (SAIC 2105).

The penalties for unapproved changes to an approved advertisement include 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. Such heavier penalties include the provincial FDA 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.

Promotion

The term ‘promotion’ is not defined under Chinese law. Any activity related to a drug is promotional, if the intent is promotional, as that 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. As noted above, scientific information exchange, including exchange of off-label information, can be viewed as non-promotional 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.

China prohibits advertising or promotion 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 CFDA, must not expand or maliciously conceal, and must not contain any theories, viewpoints, or similar contents that are outside the drug instructions.

The Regulations on Administration of Drug Product Instructions and Labels require that: ‘drug instructions and labels shall be approved by the CFDA, the labels must be based on the drug instructions, and the contents of the labels shall not exceed the scope of product instructions, and shall not contain wording or symbols that imply therapeutic effectiveness, misleading use, or inappropriate promotion’. The Drug Administration Law of China also prohibits off-label promotion through other means, such as labelling materials, including the spoken words and written or video materials used by sale representatives in promotional discussions with physicians.

Devices

Device advertisements also currently require pre-approval. Regulation of advertising and promotion of medical devices are somewhat similar to those 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.⁸⁶

86 Draft Standards on the Examination of Medical Device Advertisements (SAIC 2015).

xii Distributors and wholesalers

China requires a licence for a company to engage in the retail or wholesale distribution of drugs that are manufactured by other companies. No such distribution licence is required for a drug manufacturer to distribute the drugs that it manufactures for itself, provided it has obtained a CFDA drug registration and approval number. Similar to licensing of drug manufacturing facilities, the distributor must meet: the economic planning requirements (for a retail distributor or pharmacy, e.g., factors include the number of residents for the area to be served, the public transportation available to the residents and actual local demand); and the ability to meet quality requirements, as evidenced by the passing of a good supply practice (GSP) inspection and receipt of a GSP certificate. Distribution of drugs via the internet is also restricted and requires the CFDA's permission.

A similar system of device distribution licences also exists for Class III medical devices, unless the manufacturer is distributing its own devices from its facility. Distributors of Class II devices no longer need a licence, but those distributors must submit a notification to their local municipal governments. 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.⁸⁷ The CFDA also finalised GSPs for devices in December of 2014, which became effective as of their release date.⁸⁸

xiii Prescription status

The CFDA classifies drugs as prescription drugs or over-the-counter (OTC) drugs, and requires the CFDA's review and pre-approval for both. For the purposes of distribution and sale, the CFDA 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 places, such as convenience or grocery stores if approved by provincial governments. The National Health and Family Planning Commission regulates prescribing behaviour for physicians, including a requirement that physicians use the non-proprietary names of drugs. The CFDA has not set up prescription or non-prescription classifications for medical devices.

xiv Imports and exports

Imported drugs or medical devices for marketing in China must be pre-approved by the CFDA and fully comply with the applicable regulations by the CFDA and the Chinese customs before they can be imported into China for distribution and sale. Additional requirements, such as special import or export permits, are required for narcotic or psychotropic substances.⁸⁹

87 Articles 29 to 31 of the RSAMD.

88 Article 66 of Medical Device Good Supply Practices, available at www.cfda.gov.cn/WS01/CL0087/110920.html.

89 Article 45 of the DAL.

Drugs that are imported for processing and re-export do not require CFDA pre-approval. Only provincial FDA notification is required for such products provided they will not be sold or used in China.⁹⁰ Additional testing at the border may be required.⁹¹

The CFDA generally does not impose the same requirements for export of drugs or devices and relies instead on the regulatory oversight of the country where the drug will be exported. 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 drug⁹² and two types of device,⁹³ which the CFDA has placed into the catalogue of drugs and devices subject to full CFDA supervision.⁹⁴ In addition, special export permits are required for the export of some narcotics or psychotropic substances. In most cases, drug and device manufacturers must also submit a filing to their local government prior to export.⁹⁵ Certificates of free sale for foreign import authorities may be available from provincial governments, provided that the China manufacturer meets the relevant requirements.

xv **Controlled substances**

China exercises heightened control over narcotics and psychotropics. The State Council promulgated the Rules on the Administration of Narcotics and Psychotropics in 2005, and the CFDA, the Ministry of Public Security, and the Ministry of Health recently jointly issued the revised Catalogue of Narcotics (2013) and the revised Catalogue of Psychotropics (2013). Special heightened control is exercised by multiple government agencies over the growing of plants where narcotics or psychotropics are extracted, and the clinical trial, manufacturing, transportation and distribution of narcotics and psychotropics. For example, government agencies set the total amount of narcotics and psychotropics needed annually, while the CFDA then sets the annual production plan based on the current supply and stockpile, and the CFDA and the department of agriculture together set the annual growing plan. Special permits are given only to limited entities to study, produce and distribute narcotics and psychotropics.

xvi **Enforcement**

Enforcement against violations of drug or medical device requirements is undertaken by the FDAs at national, provincial and lower local levels, with cooperation from other government agencies such as the SAIC, NHFPC, and the public security bureau (China's police force)

90 Regulations on the Administration of Drug Processing for Export (2003).

91 Administrative Measures for the Inspection and Supervision of Imported Medical Devices (2007).

92 Gentamicin, atorvastatin, sildenafil, oseltamivir, cefoperazone, glycerine, heparin, artemisinin and traditional Chinese medicine in finished dosage form and indicated for erectile enhancement.

93 Glucose-testing strips and condoms.

94 Notice on Implementing Catalogue Administration on certain drugs and devices for export (2008), available at www.sfda.gov.cn/WS01/CL0245/33456.html.

95 Article 3 of the Administrative Regulations on Filings for Contract Manufactured Drugs for Foreign Enterprises (2005); Article 70 Administrative Measures on the Manufacturing of Medical Devices (2014).

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 the for-cause inspections. The CFDA 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 GxPs (GLP, GCP, GMP, GSP), 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, *supra*) on post-approval controls in many more situations than in the US. Other penalties include administrative fines, seizures of product, disgorgement of profits and blacklisting of companies and individuals. Monetary penalties tend to be lower than in the US. 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.⁹⁶

Recently, the CFDA has been requiring manufacturers, distributors and clinical trial sponsors to conduct self-evaluations into GxP compliance and report on the results to the CFDA. For example, in mid-2016, all holders of device distribution licences were required to take stock of compliance with device distribution regulations and GSP over a two-year period and report back to the CFDA on any non-compliances and plans for remediation. Failure to comply risked the holder's distribution licence.⁹⁷ The CFDA has required similar self-evaluation for drug clinical trials and certain device manufacturers.

III PRICING AND REIMBURSEMENT

China has recently begun to reform its system for drug pricing. Specifically, it has abolished the 'maximum retail price' for drugs, and is now implementing a plan to permit those prices to be set more by the market and by reimbursement standards negotiated more openly by stakeholders. Specifically, for drugs that are reimbursed on China's state insurance plans (discussed below) the price will be determined by reimbursement rates. For patented drugs produced exclusively by one manufacturer, the price will be set through transparent negotiations between the manufacturer, government and healthcare industry representatives. Prices will still be set or guided by the government for certain types of drugs, such as narcotic drugs and psychotropic drugs. For all other drugs, however, the prices may be freely set by the manufacturers, provided that they accurately reflect costs.⁹⁸

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), with a total of 2,151 drugs in its most recent version, which the government is considering revising in 2017. The covered drugs for the rural plan may vary by province.

96 Article 141 of the Criminal Code of the People's Republic of China.

97 Notice on Regulating Distribution Activities in Medical Device Circulation (CFDA 112 7 June 2016).

98 Circular Concerning Opinions on Advancing the Drug Pricing Reform (National Development and Reform Commission 2015).

The NRDL is categorised into A and B 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 the provincial level. Pricing 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. The pricing and coverage decisions are taken primarily by the NDRC and its local counterparts (the pricing bureau), as well as the Ministry of Human Resources and Social Security. Drug manufacturers and distributors are required to report various production costs and sales information to the government agencies, and based on such information, the government agencies decide on the prices by applying complex formulae.

By contrast, the commercial insurance sector is very small, but the government is trying to expand it.⁹⁹ For example, in the past three years the government has been trying to promote critical disease insurance for individuals that 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.¹⁰⁰

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 CFDA focus on challenging concrete CFDA 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. Statistics from China's Office of Legislative Affairs show that in 2013, the CFDA was involved in a total of 150 administrative reconsideration cases, and only one administrative lawsuit was brought against the agency.¹⁰¹

99 Several Opinions on Accelerating the Development of the Modern Insurance Service Industry (State Council 2014).

100 Opinions on the Full Implementation of the Critical Disease Insurance Program for Urban and Rural Residents (State Council 2015).

101 2013 National Administrative Reconsideration and Administrative Litigation Statistics and Data Table, available at www.chinalaw.gov.cn/article/jggz/fztjxx/201403/20140300395412.shtml.

i Administrative reconsideration

When an applicant is not satisfied with a government agency's decision, the applicant may file an administrative reconsideration request for review by either the government agency itself or its supervising ministry or department within 60 days.¹⁰² To file an administrative reconsideration request challenging a CFDA decision, the applicant must have legal standing to do so. The complaint must name the respondent and the specific decision the applicant is challenging.¹⁰³ Permissible grounds for reconsideration are:

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

A special division in the CFDA, the Administrative Reconsideration Office (ARO), is responsible for handling administrative reconsideration requests to challenge decisions made by the CFDA 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 CFDA and ranks higher than the ARO, will hear the case.

The ARO or ARC will examine the request and decide within five days if it meets the requirements for reconsideration.¹⁰⁴ 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 of the ARO and ARC are legally effective upon the signature of the head of the CFDA.¹⁰⁵ The applicant can appeal the decision of the ARO or ARC 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 within 15 days after the time limit for reconsideration expires.¹⁰⁶ 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:

- a* the major evidence was inadequate;
- b* the administrative agency erroneously applied the law or regulations;

102 Administrative Reconsideration Law (1999).

103 Administrative Reconsideration Measures of the CFDA (2013).

104 Article 17 of the Administrative Reconsideration Law; see also Article 48 of the Regulations on the Implementation of the Administrative Reconsideration Law (2007).

105 Article 20 of the Administrative Reconsideration Measures of the CFDA.

106 Article 38 of the Administrative Litigation Law (2014).

- c* the administrative act violated legal procedures;
- d* the administrative act exceeded authority; or
- e* administrative power was abused.¹⁰⁷

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 SAIC 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 NHFPC 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 include:

- a* no linkage between healthcare provider incomes and profits from drug sales or medical services;
- b* no rebates for prescribing medicine or referrals for services or drugs;
- c* no overcharging of patients;
- d* no accepting illegal donations;
- e* no illegal advertisements or promotion of drugs, devices, food or other products by medical institutions or healthcare providers;
- f* no collation of statistics for commercial purposes or personal gain by healthcare providers;
- g* no private buying or selling of drugs, devices or other equipment by healthcare providers;
- h* no acceptance of kickbacks or commissions from healthcare companies or engagement in entertainment activities provided by those companies; and
- i* no solicitation or acceptance of financial benefits from patients.¹⁰⁸

In late 2013, nine agencies, including the NHFPC and CFDA, issued a joint opinion (a blueprint of sorts) intended to create higher standards for ethical conduct by physicians and

107 Article 54 of the Administrative Litigation Law; see also Article 6 of the Provisions of the Supreme People's Court on Several Issues Concerning the Hearing of Administrative Cases of International Trade (2002). Similar interpretations can be found in Provisions of the Supreme People's Court on Several Issues Concerning the Application of Laws in the Hearing of Anti-Dumping Administrative Cases (2002) and Provisions of the Supreme People's Court on Several Issues Concerning the Application of Laws in the Hearing of Countervailing Administrative Cases (2002).

108 Notice on Improving the Medical Health-Care Workstyle and Establishing the Nine Prohibitions.

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 NHFPC 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.¹⁰⁹

In order to further control improper incentives given by the drug industry to Chinese hospitals, in 2015, the NHFPC 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.¹¹⁰ Anti-corruption investigations and physician kickbacks continue to be significant issues in China.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

Compensation can rely on provisions specifically on drugs and devices in the Tort 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. Compensation is available when the product is defective or not made according to 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 TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

China's Anti-Monopoly Law (AML) took effect on 1 August 2008 and enforcement has become increasingly prominent in the healthcare industry in the past four years. Three enforcement agencies are responsible for enforcing the law: the Anti-Monopoly Bureau of the Ministry of Commerce (Mofcom), the Anti-Monopoly and Anti-Unfair Competition Enforcement Bureau of the SAIC and the Price Supervision and Anti-Monopoly Bureau of the NDRC.

Mofcom reviews 'concentration' – defined as a merger, an acquisition of assets or equity that confers control over another company, or an acquisition of a decisive influence over another company through contract or other means. The NDRC and SAIC handle price-related and non-price-related violations, respectively, in connection with monopoly agreements and abuse of dominance.

109 Administrative Measures on the Development of Clinical Research Projects at Medical Health Institutions (NHFPC 2014).

110 Administrative Measures on Accepting Donations for Public Welfare by Healthcare Entities (for Trial Implementation) (NHFPC 2015).

All three agencies have bought enforcement actions against companies in the life sciences sector. Mofcom imposed conditions on two transactions involving life sciences companies: *Pfizer/Wyeth* (2009) and *Novartis/Alcon* (2010). In the *Pfizer/Wyeth* case, Mofcom conditioned its clearance on Pfizer's commitment to spin off, under the supervision of a trustee, its swine mycoplasma pneumonia business, including tangible assets and intellectual property rights necessary to compete. Novartis, rather than facing a structural remedy like Pfizer, was barred from selling its Infectoflam product or similar ophthalmological anti-infective products in China and required to terminate within 12 months a distribution agreement it had with Hydron (the largest contact lens distributor in China) regarding Novartis's contact lens-care products, as a condition for the approval of its acquisition of Alcon. Hydron had been appointed as the sole distributor for Novartis in China since 2008 and Mofcom was concerned that, post-transaction, the distribution agreement could lead to coordination in prices, quantity and sales regions between Novartis and Hydron.

Since 2013, the NDRC has stepped up its enforcement of the AML, particularly in the area of pricing of pharmaceutical drugs and medical devices. The agency conducted surveys on the pricing and marketing practices of over 100 pharmaceutical and medical device firms in 2016, and has formally initiated investigations against a number of multinational and domestic firms in the sector. In some respects, these pricing investigations were overshadowed by commercial bribery cases in the healthcare sector.¹¹¹

In 2013, a Shanghai High Court ruled in favour of a plaintiff in the first successful private suit under the AML for vertical price-fixing. The case, which involved Johnson & Johnson's device business for surgical sutures in China, related to a distribution contract setting minimum resale prices, also known as resale price maintenance (RPM). The court found that the plaintiff had carried its burden of showing that the defendant's conduct created a vertical restraint that had an anticompetitive effect. The court analysed: (1) whether there was sufficient competition between manufacturers in the market; (2) whether the defendant exercised market dominance; (3) the defendant's motives in entering into the distribution agreement; and (4) whether the anticompetitive effects of the conduct outweighed any negative effects on fair competition. The court awarded approximately US\$85,000 in lost profits as a result of its finding of these violations.¹¹²

In 2016, the NDRC is continuing to pursue pharmaceutical and medical device firms for vertical anticompetitive agreements (e.g., RPM). In December 2016, the NDRC fined Medtronic (Shanghai) Management Ltd, the China subsidiary of Medtronic, US\$17.3 million for engaging in RPM and other vertical restraints.¹¹³ The NDRC stated in its decision that Medtronic deployed a multilayer distribution system in China and, through distribution agreements, email notifications and oral discussions, Medtronic restricted the resale prices of its distributors at all levels, despite the fact that these distributors are independent market players

111 Benjamin Shobert and Damjam P. DeNoble, 'Understanding China's Antimonopoly Investigations', *China Business Review*, 30 March 2014, available at www.chinabusinessreview.com/understanding-chinas-antimonopoly-investigations/.

112 Chunfai Lui & Stephenson Harwood, 'A Landmark Court Ruling in China: Resale Price Maintenance As Examined in the Johnson & Johnson Case', *CPI Antitrust Chronicle*, available at www.competitionpolicyinternational.com/file/view/7010.

113 See 'The NDRC's Administrative Penalty Decision [2016] No. 8,' available at www.ndrc.gov.cn/fzgggz/jgjdylfd/fjgld/201612/t20161209_829717.html.

rather than Medtronic's affiliated entities. It also restricted the bidding prices of its distributors and prohibited them from selling to customers outside of the allocated geographic markets or from selling competitors' products. According to the NDRC, such vertical restraints, including RPM, harmed both intra-brand and inter-brand competition in the relevant markets. The NDRC thus considered that such conduct violated Article 14(1) and (2) of the AML and does not qualify for exemptions set forth under Article 15. The monetary penalty accounts for 4 per cent of Medtronic's sales of the relevant products in 2015.

In addition to RPM investigations, the agency also investigated horizontal anticompetitive agreements (i.e., cartels under Article 13 of the AML) in 2016. In January 2016 and July 2016, the NDRC fined eight Chinese companies approximately US\$1 million for two cartels involving API and tablets of allopurinol, a medication used to decrease high blood uric acid levels,¹¹⁴ and estazolam, a basic drug treating insomnia,¹¹⁵ respectively. According to the NDRC, the companies engaged in price-fixing and allocating geographic markets for the sales of their products, and were considered as violating Article 13 of the AML.

The SAIC, the agency focusing on non-price related AML violations, also actively pursued enforcement in 2016. In December 2016, a local branch of the SAIC fined a domestic API supplier for refusal to deal (i.e., refusal to supply downstream manufacturers of a drug treating clavus with the necessary API that it has been supplying continuously for the past few years).¹¹⁶ The company, Chongqing Southwest No. 2 Pharmaceutical Plant, is said to be the only remaining China-based manufacturer of phenol APIs, an essential raw material for the production of salicylic acid and phenol plasters. In 2014, the company appointed an exclusive agent and stopped supplying other drug manufacturers with the API for 23 months. Chongqing AIC thus considered that the company abused its dominant position by refusing to deal with its customers without justification. The company's illegal gains in the amount of approximately US\$70,000 was confiscated and a punitive penalty of approximately US\$2,500 was imposed.

The pharmaceutical/medical devices sector in China is becoming increasingly sophisticated, not only because it is a highly regulated industry, but also because the government is working hard to curb rising medical costs, reduce the burden on the health insurance system and eliminate corruption. Against that background, the sector has become one of the top enforcement priorities of the government agencies. As the sales to hospitals involve a public procurement and bid process, legal compliance is further complicated by the intersection with bid rigging and anti-bribery rules, and the role of the SAIC and other agencies. It appears to be a growing trend that companies seek antitrust, anti-corruption and unfair competition advice in order to better adapt to China's evolving regulatory environment as all three antitrust law enforcement agencies in China continue to step up their efforts in the sector in 2017.

114 See 'The NDRC's Administrative Penalty Decision [2016] No. 1-4,' available at http://jjs.ndrc.gov.cn/fjgld/201602/t20160202_774107.html.

115 See 'The NDRC's Administrative Penalty Decision [2016] No. 5-7,' available at http://jjs.ndrc.gov.cn/fjgld/201607/t20160727_812579.html.

116 See 'The Chongqing Municipal AIC's Administrative Penalty Decision [2016] No. 15,' available at www.saic.gov.cn/zwgk/gggs/jzzf/cfd/201612/t20161213_173318.html.

ii Transactional issues

Government approval is a key issue to bear in mind for any M&A or joint venture deals in China. Depending on the nature of the target company and the deal structure, different types of approvals may be required. For example, an acquisition of an onshore Chinese target company will require approvals from a number of government agencies including the Ministry of Commerce (or their local counterparts) and the NDRC. In addition, if structured as an asset acquisition of a Chinese pharmaceutical business, additional approval from the CFDA is required for the relevant operating permits to be reissued (such as the drug manufacturing licence or the drug distribution licence, as the case may be).

Joint ventures are commonly used for Western life sciences companies seeking to enter the Chinese market. Approval by the Ministry of Commerce or one of its local counterparts is required for setting up joint ventures. In addition, if the joint venture wishes to engage in business activities requiring special licences, such licences must be obtained before the relevant activities may be included in the joint venture's business scope. By way of background, a corporate entity in China is only permitted to conduct business activities listed in its business scope on its business licence issued by the government authority. This is particularly relevant for companies in the life sciences space because many activities in this space require specific licences, such as a drug manufacture licence or drug distribution licence. In recent years, the Chinese government has limited the issuance of new drug distribution licences by significantly raising the threshold requirements, making them very difficult to obtain.

Apart from mergers and acquisitions and joint ventures, complex life sciences transactions commonly seen in the US and Europe, such as licensing and collaboration arrangements, have been rare in China. This is owing to the fact that China's life sciences industry has traditionally been dominated by generic players and there are few innovative assets in China. This is now beginning to change; fostered by government policies encouraging innovations in biotech, increasing numbers of innovative biotech companies have sprung up in China. At the same time, more Chinese generic companies seek to grow into the innovative side of the business by partnering with Western companies. As a result, the number of licensing and collaboration deals has increased markedly in the past few years.

VIII CURRENT DEVELOPMENTS

China has been revising its framework statutes for drugs, devices, food and cosmetics for the past three years. Following the revision of the RSAMD, the revision of the implementing regulations related to devices continued throughout 2016 with new regulations or proposals on classification, device naming and inspections, as well as proposed regulation in areas such as advertising and adverse events. The CFDA will most likely finalise its substantial revision to the device classification catalogue in 2017, and work to streamline review and approval processes to reduce the application backlog and wait times for devices that fill critical needs.

In the drug space, the CFDA will likely continue to reduce application wait times and streamline approval processes. It will also continue to refine and develop the projects on reference products for generic small molecule drugs and the MAH Pilot.

The larger questions are the timing of revisions to the DAL and PDR. As discussed herein, the CFDA released a substantial amendment to the PDR in July 2016 that included a more uniform approach to clinical applications and marketing applications. It remains unclear as to whether the CFDA will finalise the PDR revision prior to the revision of the DAL and, if so, when. It is unlikely that the DAL will be finalised in 2017, although it is

possible that a draft could emerge. The CFDA may also want to let its pilot projects play out before finalising the DAL and PDR. For example, the MAH Pilot does not end until 2018, and its results, while promising thus far, will still be emerging at that time.

On the issue of enforcement, GxPs will likely remain an important area for both drugs and devices. As noted in Section II.xv, *supra*, the CFDA has conducted several investigations into GxP compliance, and it is possible that it will focus on additional areas. The CFDA is likely to continue to promote enforcement of its new medical device GCPs and it may finalise its new drug GCPs in 2017.

It is expected that China will to reform its drug and device pricing and reimbursement system. The reforms of the pricing system that began two years ago are supposed to involve a more open and transparent mechanism, involving more stakeholders, for determining reimbursement rates. These rules are still taking shape.

Chapter 9

EUROPEAN UNION

*Grant Castle and Robin Blaney*¹

I INTRODUCTION

In the European Union, medicines for human use are regulated primarily by Directive 2001/83/EC² and Regulation (EC) No. 726/2004.³ The legislation lays down the requirements and procedures for marketing authorisation, as well as harmonised provisions for manufacturing, distribution, pharmacovigilance and advertising of medicines. By virtue of the European Economic Area Agreement, European Economic Area (EEA)⁴ Member States (Iceland, Liechtenstein and Norway) have implemented the EU's pharmaceutical regime and references to the EU 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 grant 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.

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2 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

3 Regulation (EC) No. 726/2004 of the European Parliament and of the Council 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.

4 The EEA comprises the 28 EU Member States plus Iceland, Liechtenstein and Norway.

National competent authorities regulate medicines approved by national procedures, the decentralised procedure and the mutual recognition procedure, and are also largely responsible for the 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 the EU medicines legislation.

Medical devices are regulated by a series of EU directives: the Active Implantable Medical Devices Directive 90/385/EEC,⁵ the Medical Devices Directive 93/42/EEC⁶ and the In Vitro Diagnostic Medical Devices Directive 98/79/EC.⁷ As the names imply, Directive 90/385/EEC applies to active implantable medical devices and Directive 98/79/EC applies to *in vitro* diagnostic devices. Directive 93/42/EEC applies to all other medical devices. There is no central EU agency with responsibility for the regulation of medical devices, although the European Commission has produced various guidance documents. The competent authority in each Member State therefore has complete responsibility for the regulation of medical devices within its territory.

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.⁸ 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

5 Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, as amended.

6 Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, as amended.

7 Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices, as amended.

8 C-112/89, *Upjohn Company and Upjohn NV v. Farzoo Inc and J Kortmann*.

application of the cosmetics Directive 76/768/EEC' 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.

National competent authorities, acting under the supervision of the national courts, must determine borderline issues on a case-by-case basis, 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).⁹ The principles of GLP provide a framework within which laboratory studies, both *in vitro* and *in vivo*, are planned, performed, monitored, recorded, reported and archived. Directive 2001/83/EC expressly provides that certain non-clinical (pharmaco-toxicological) studies of medicines must be carried out in conformity with GLP.

All tests on animals conducted in the EEA must be carried out in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes.¹⁰ 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,¹¹ at least until Clinical Trial Regulation (EU) No. 536/2014¹² becomes applicable, most likely in late 2018. 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

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- 9 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.
- 10 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.
- 11 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as amended.
- 12 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

(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.

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 immediately reported 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.

iv Named-patient and compassionate use procedures

Medicines

Generally speaking, no medicinal product may be placed on the market in the EU without a marketing authorisation. However, this is subject to a number of exemptions, including the 'named-patient' exception.¹³ The named-patient exemption covers the provision of unauthorised medicines with assumed benefits in situations where alternative treatment options are either non-existent, unsatisfactory or have been exhausted.

The named-patient exemption applies only where the supply of a medicine is:

- a* in response to a *bona fide* unsolicited order;
- b* formulated in accordance with the specification of a doctor and for use by his or her individual patients on his or her direct personal responsibility; and

13 Article 5(1) of Directive 2001/83/EC.

- c* to fulfil a 'special need'. This exception must be construed narrowly, and in accordance with the overarching principle underlying Directive 2001/83/EC that 'the protection of public health must take precedence over economic considerations', and that the precautionary principle should be applied so as to err in favour of protecting public health where there is any doubt about the efficacy or safety of a product.

Article 83 of Regulation (EC) No. 726/2004 also specifies that Member States may make certain medicines available for 'compassionate use'. The Regulation defines 'compassionate use' to cover:

making a medicinal product [...] available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who 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 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:

- a* the manufacturer's name and address;
- b* a statement that the device is intended for exclusive use by a particular patient, together with the name of the patient;
- c* the name of the medical practitioner or other authorised person who made out the prescription for the product;
- d* the specific characteristics of the product as indicated by the prescription; and
- e* a statement that the device conforms to the essential requirements and, where applicable, indicating which essential requirements have not been fully met, together with the grounds.

v Pre-market clearance

Medicines

Manufacturers of medicines must obtain a marketing authorisation before they can place their products on the EEA market. For certain products, including, in general terms, biotechnology products, advanced therapy medicinal products, orphan drugs and new active substances for the treatment of AIDS, cancer, neurodegenerative disorder, diabetes, autoimmune diseases, other immune dysfunctions and viral diseases, the marketing authorisation application must be submitted to the EMA for review through the centralised procedure. The CHMP also has the discretion to permit other products to use the centralised procedure if it considers them sufficiently innovative. Using the resources of selected national medicines agencies, the CHMP considers the application and gives an opinion on the approvability of the product. However, the marketing authorisation itself is granted by the European Commission and this is valid throughout the EU and, by extension, the EEA.

For all other products, the competent authorities of the Member States are responsible for granting marketing authorisations for products that are sold in their markets. Applicants who intend to market such products in more than one Member State may seek marketing authorisations under the mutual recognition procedure or the decentralised procedure. If the product has already been authorised in one Member State, the mutual recognition procedure facilitates mutual recognition of the existing authorisation in another Member State. The decentralised procedure, on the other hand, may be used in cases where the product has not received a marketing authorisation in any Member State. Under this procedure, the applicant submits an identical dossier to each relevant Member State, and one, known as the reference Member State, takes the lead in reviewing the application.

The applicant for a marketing authorisation under any of these procedures must be established in the EEA. It must submit sufficient data to demonstrate the quality, safety and effectiveness of the product. The format for the marketing authorisation application form and the underlying dossier is consistent for all medicinal products. Dossiers must follow the International Conference on Harmonisation common technical dossier format, in which quality and manufacturing, preclinical and clinical trial sections are accompanied by associated summary reports.

There is scope for applicants to omit some or all of the preclinical and clinical trial data if the product falls within the definition of a generic of a reference product for which regulatory data exclusivity protection has expired. The marketing authorisation underpinning the reference medicinal product must be based on a complete dossier; a generic application referring to a generic dossier is not possible. Generic applicants may need to submit additional preclinical or clinical data if their product does not fall within the definition of a generic (i.e., where there are differences in active substances, therapeutic indications, strength, pharmaceutical form or route of administration, in relation to the reference medicinal product, or where bioequivalence cannot be demonstrated through standard bioavailability studies). In these cases, bridging data is required to demonstrate that the differences do not affect the product's relative safety and effectiveness inappropriately.

Preclinical and clinical data can be omitted and replaced with references to scientific literature if the product has been in well-established medicinal use in the EU for at least 10 years. An existing marketing authorisation holder may also give consent for a subsequent applicant to reference the pharmaceutical, preclinical and clinical data on file for the original product.

Specific rules govern biological medicinal products and acknowledge that complex substances, or mixtures of substances, of biological origin are sensitive to changes in source materials and manufacturing processes. The rules therefore focus less on the characterisation of substances themselves from a chemical perspective and more on control of the manufacturing and quality control processes to produce substances or mixtures of comparable quality, safety and effectiveness. This is reflected in special rules for the approval of biological medicinal products that are similar to a reference product. Once the reference product's data exclusivity period has expired, the applicant may file an application equivalent to a generic application but will generally need to submit a body of data demonstrating comparable quality, safety and efficacy.

There is a simplified registration process for traditional herbal medicinal products. A herbal product is only 'traditional' if the applicant can produce bibliographical or expert evidence that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, 15 of which must have been within the EU.

There is also a simplified procedure in the EU for homeopathic medicines. Although the safety and quality of such products has to be demonstrated, the products are not permitted to make medicinal claims. The scheme is restricted to homeopathic products for oral and external use and does not allow indications (the descriptions of diseases or conditions for which the medicine is intended to be used).

Medical devices

There is no pre-market government review of medical devices in the EU unless the device also contains a medicine or a blood derivative. However, all medical devices placed on the market in the EEA 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 marking 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.

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'.¹⁴ An orphan medicinal product is a product 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.

14 Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

Regulation (EC) No. 1901/2006 also provides specific incentives for the development of products with paediatric indications.¹⁵ If a product is approved on the basis of a dossier that includes paediatric clinical trial data generated in accordance with an approved paediatric investigation plan, the applicant will benefit from one of two periods of exclusivity: (1) if the product is an orphan medicine, it will benefit from an additional two years of orphan drug exclusivity (i.e., a total of 12 years' orphan exclusivity); or (2) if the product is not an orphan medicine and is eligible for patent term extension (referred to as a supplementary protection certificate), the patent term will be extended by six months.

Medical devices

The EU medical devices rules do not provide for any form of regulatory exclusivity. These innovations are almost exclusively protected through patent rights and protection of confidential know-how.

vii Post-approval controls

Medicines

The marketing authorisation holder for a medicine is ultimately responsible for any product placed on the market under its approval, and must also fulfil several obligations by virtue of its status. While the associated legal responsibility and liability cannot be delegated, the marketing authorisation holder can delegate the performance of related tasks to third parties, provided that this delegation is appropriately documented.

The marketing authorisation holder must establish and maintain a pharmacovigilance system and must have permanently and continuously at its disposal within the EEA a qualified person for pharmacovigilance, who is responsible for oversight of the pharmacovigilance system, documented in a pharmacovigilance system master file. Key requirements include expedited reporting of suspected serious adverse reactions within 15 days, reporting of suspected non-serious adverse reactions within 90 days and submission of periodic safety update reports (PSURs). The marketing authorisation holder must comply with good pharmacovigilance practice guidelines adopted by the EMA.

The marketing authorisation holder must have a 'scientific service' responsible for disseminating scientific and medical information on its medicinal products, predominantly to healthcare professionals, but also to regulators and patients.

Since July 2012, all new marketing authorisation applications must include a risk management plan (RMP) describing the risk management system that the marketing authorisation holder will put in place. Previously, an RMP was only required 'where appropriate', such as for biological products or products containing a new active substance. The RMP must identify or characterise the safety profile of the product, document measures to prevent or minimise the risks associated with the product, and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation. Such

15 Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004.

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.¹⁶ 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 are ongoing for the marketing authorisation.

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 grant of the marketing authorisation, or if a previously marketed product is no longer actually present on the market for a period of three consecutive years. For centrally approved products, the sunset provisions would not be triggered provided the product was marketed in at least one EEA jurisdiction.

Medical devices

Device manufacturers are required to put in place and maintain a systematic procedure for review of post-market experience, including reporting of incidents to competent authorities when required, and to implement any necessary corrective actions.

16 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.

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.

viii Manufacturing controls

Medicines

Manufacturers of both marketed or investigational medicinal products must have a manufacturing authorisation from the competent authority in the EU Member State in which they are established. The manufacturing authorisation will be limited to the premises and the medicinal products specified in the manufacturer's application. Importers of medicinal products from outside the EEA may also require a manufacturing authorisation.

Medicinal products must be manufactured in accordance with the principles of GMP, set out in Directive 2003/94/EC¹⁷ and the European Commission's guidelines in Volume 4 of the Rules governing medicinal products in the European Union.

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

17 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

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 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 in the EU 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,¹⁸ a code of practice on

18 EFPIA Code of Practice on the promotion of prescription-only medicines to, and interactions with, healthcare professionals.

interactions with patient organisations¹⁹ and a code of practice on the disclosure of transfers of value.²⁰ 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 such devices cannot be marketed or put into service until they have been made to comply with the relevant rules.

x **Distributors and wholesalers**

Medicines

Any company engaged in wholesale distribution of medicinal products in the EU must have an authorisation to engage in the activity, and the licence must state the premises for which it is valid. Manufacturing authorisations include the right to engage in wholesale distribution. Wholesale distribution is defined as all activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public.

Traditionally, most Member States have taken the view that wholesale distribution only takes place where the products are handled physically; mere paper transactions have not been regarded as wholesaling. In some Member States, however, the authorities interpret the terms ‘procuring’ and ‘supplying’ to cover the act of buying and selling medicines (i.e., the transfer of legal title), even if the company never physically handles the product. This interpretation is becoming more prevalent, following references in Directive 2011/62/EU to ‘wholesale distributors, whether or not they physically handle the medicinal products’.²¹

Wholesalers may only obtain their supplies from authorised manufacturers or wholesalers, and may only supply medicinal products to other wholesalers or to persons entitled to supply medicinal products to the general public. The holder of a wholesale dealer licence is subject to various record-keeping obligations, to demonstrate that product is only supplied to those entitled to receive it and to allow for an effective recall of product if necessary. The licence holder must also have at its continuous disposal the services of an

19 EFPIA Code of Practice on relationships between the pharmaceutical industry and patient organisations.

20 EFPIA Code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations.

21 Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

appropriately qualified responsible person, who is responsible for ensuring that a quality management system is implemented and that the company complies with the principles of good distribution practice (GDP).

Directive 2011/62/EU introduced the concept of brokering, defined as all activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.

Brokers must have a permanent address and contact details in the EU, so as to ensure accurate identification, location, communication and supervision of their activities by competent authorities. They must register with the competent authorities in which they have their permanent address. Brokers must comply with the principles of GDP and are subject to the same record-keeping obligations that apply to wholesale distributors.

Medical devices

There are 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 no EU-harmonised rules that govern the import or export of medical devices.

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 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.²² 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 is ongoing, 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

22 Commission Regulation (EC) No. 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No. 726/2004 of the European Parliament and of the Council, as amended.

healthcare insurance systems.²³ 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/EEC²⁴ 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. Directive 89/105/EEC does not harmonise national pricing and reimbursement measures in the EU, nor does it identify substantive criteria on which Member States must base their pricing and reimbursement decisions. This is in line with the limited competence of the EU in the field of management of healthcare resources and the principle of minimum interference in the organisation by Member States of their domestic social security policies, as confirmed by European case law. For example, in *ABPI v. MHRA*²⁵ the CJEU confirmed that public bodies forming part of a national public health service are not precluded from implementing prescribing incentive schemes, which 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 Commission and EMA concerning medicinal products. Article 263 of the Treaty on

23 Article 168(7) of the TFEU and European case law, for example, *Roussel Laboratoria BV and others v. État néerlandais* (Case 181/82) [1983] ECR 3849, *Duphar BV and others v. The Netherlands State* (Case 238/82) [1984] ECR 523, and *Commission of the European Communities v. Kingdom of Belgium* (Case C-249/88) [1991] ECR I-1275.

24 Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.

25 *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*).

the Functioning of the European Union (TFEU) permits direct challenges to the legality of EU acts and allows the EU courts²⁶ 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 of the 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 Treaty on the Functioning of the European Union 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., the 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 of the TFEU.

Article 267 of the 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 such action may challenge the validity of the decision on which the action is based via the national courts.²⁷ Under Article 267(3) of the 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* doctrine²⁸ 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 subsection i, *supra*, apply to challenges of decisions or acts of EU institutions, bodies or agencies that concern medical devices, such as an unfavourable decision of 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.

26 The EU courts are known as the Court of Justice of the European Union (CJEU) and comprise three courts: the Court of Justice; the General Court; and the Civil Service Tribunal.

27 *TWD Textilwerke Deggendorf GmbH v. Germany* (Case C-188/92) [1994] ECR I-833.

28 *Firma Foto-Frost v. Hauptzollamt Lübeck-Ost* (Case 314/85) [1987] ECR 4199.

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,²⁹ 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 medicines 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 the EU level by the EFPIA Code on the promotion of prescription-only medicines to, and interactions with, healthcare professionals (the EFPIA HCP Code), which provides additional guidance to companies on problematic compliance areas, including gifts, sponsoring of healthcare professionals and hospitality.³⁰

ii Medical devices

There is no EU harmonised legislation that governs the interaction of medical device companies with prescribers and payers. MedTech Europe, the European medical device

29 See Section II.ix, *supra*.

30 EFPIA HCP Code, updated June 2014.

trade association, however, has published guidelines³¹ and a question and answer document³² on interactions with healthcare professionals (together, the Eucomed Code) that provides detailed guidance on this issue.

The Eucomed Code is intended to assist medical device companies comply with general anti-bribery and corruption law concepts by setting minimum standards that companies and their representatives should adhere to when interacting with healthcare or other government officials. However, the Eucomed 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 Eucomed Code provides specific guidance on some key compliance areas, including gifts, sponsoring healthcare professionals to attend scientific meetings and the level of subsidy, entertainment and hospitality associated with such events. The provisions of the Eucomed Code are enforced through a self-regulatory regime operated mainly at the national level. Where no dispute resolution mechanism exists under a national applicable code, the Eucomed Compliance Panel may rule on the dispute. Eucomed 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 Eucomed 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 EU against whom they can bring a claim. The term includes any manufacturer of finished products, raw materials or parts within the EU; importers of products from outside the EU; and any person who places their name or mark on a product (which would include a product’s marketing authorisation holder). It also includes any intermediate suppliers of products, which could include distributors, retailers,

31 Eucomed Guidelines on Interactions with Health-care Professionals, Code of Business Practice, September 2008.

32 Q&A on the Eucomed Guidelines on Interactions with Health-care Professionals, updated June 2015.

33 Directive 2001/20/EC; see Section II.iii, *supra*, on clinical trials.

34 Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products.

healthcare professionals and their employers. However, intermediate suppliers are only liable under the Directive if they fail to identify any other producer further up the supply chain within a reasonable period.

Separately, Directive 2001/83/EC provides that in the event of a public health emergency (e.g., an influenza pandemic) companies should not have civil or administrative liability in respect of the supply or use of unapproved medicinal products or use of approved medicines outside their authorised indications, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. The effect of this provision is that, in circumstances where a national competent authority recommends or requires the use of a medicinal product pre-approval or off-label in response to an emergency threat, the company has statutory immunity from liability in negligence or contract for the consequences of that use. Strict liability under Directive 85/374/EEC, however, will remain as a cause of action for persons injured by the product.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 of (totalling €146 million).³⁸ Lundbeck and the generic companies have appealed the General Court's judgment to the European Court of Justice. The General Court's judgment in *Servier* is expected soon.

Pay-for-delay agreements have also attracted regulatory scrutiny from the national competition authorities (NCAs). The UK'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),

35 Article 5(4) of Directive 2001/83/EC.

36 Commission Decision of 19 June 2013 in Case COMP/AT.39226 – *Lundbeck*.

37 Commission Decision of 9 July 2014 in Case COMP/AT.39612 – *Perindopril (Servier)*.

38 Case T-472/13 *Lundbeck v. Commission* [2016].

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 UK.³⁹ The decision has been appealed to the UK Competition Appeal Tribunal.

NCA's 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).⁴⁰ 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 UK.⁴¹ At least two other investigations relating to excessive and unfair prices charged are ongoing in the UK. 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 NCA's. 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 NCA's have since pursued sector inquiries (e.g., the Italian Competition Authority announced on 25 May 2016 the results of its sector inquiry into 'Markets for vaccines of human use' and the Danish Competition Council published its analysis on competition between pharmaceutical wholesale suppliers in October 2016).

ii Transactional issues

EU competition law prohibits agreements that have as their object or effect the prevention, restriction or distortion of competition within the EU. The European Commission has issued a series of block exemptions, which grant an automatic exemption to certain categories of agreement, provided that the market shares for the products covered by the agreement are below the specified threshold; and the agreement does not contain any 'hard-core' restrictions, such as resale price maintenance or prohibitions on unrelated research and development. Two block exemptions are particularly relevant to in-licensing and collaboration agreements in the pharmaceutical and medical device sectors: the R&D Block Exemption,⁴² which provides for a market share threshold of 25 per cent in the case of agreements involving competitors, and the Technology Transfer Block Exemption,⁴³ 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

39 Case CE/9531-11, Paroxetine investigation: anticompetitive agreements and conduct.

40 Case A480, Antitrust's investigation on the price increase for Aspen's anticancer drugs.

41 CE/9742-13, Phenytoin sodium capsules: suspected unfair pricing.

42 Commission Regulation (EU) No. 1217/2010 of 14 December 2010 on the application of Article 101(3) of the TFEU to certain categories of research and development agreements.

43 Commission Regulation (EU) No. 316/2014 of 21 March 2014 on the application of Article 101(3) of the TFEU to categories of technology transfer agreements.

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.

VIII CURRENT DEVELOPMENTS

The EU is in the process of revising the regulatory framework for medical devices. Under the Commission's proposals,⁴⁴ the three EU Directives governing medical devices (Directive 90/385/EEC Directive 93/42/EEC and Directive 98/79/EC) will be replaced by two regulations: one on medical devices and one on *in vitro* diagnostic medical devices. Importantly, unlike directives that must be implemented into national laws, the regulations will be directly applicable in all EU Member States. The proposed 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. We expect that the final text of the regulations will be published in early 2017 and that they will take effect in 2019, subject to transitional arrangements.

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 EU. 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 October 2018 once the new EU

44 Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009, COM(2012) 542 final, and Proposal for a Regulation of the European Parliament and of the Council on *in vitro* diagnostic medical devices, COM(2012) 541 final.

45 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

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.

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. 1049/2001.⁴⁶ 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 data submitted in support of marketing authorisation applications public 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.

46 Regulation (EC) No. 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents.

Chapter 37

UNITED KINGDOM

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I INTRODUCTION²

Medicines for human use are regulated primarily by the Human Medicines Regulations 2012³ (the Medicines Regulations). The Medicines Regulations implement Directive 2001/83/EC⁴ and most other EU medicines laws into UK law. The Medicines Regulations also consolidated most UK medicines legislation – including the majority of the Medicines Act 1968 – into one statutory instrument to provide a comprehensive regime for the authorisation, manufacture, import, distribution, advertising, sale and supply of medicinal products for human use. However, the Medicines Act 1968 continues to regulate some aspects, such as pharmacies and the dispensing of medicines.

Medical devices are regulated by the Medical Device Regulations,⁵ which implement the three EU Medical Devices Directives⁶ into UK law.

The Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the Department of Health, is the United Kingdom's national competent and

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2 This chapter summarises the UK regimes governing medicines and medical devices. Since the United Kingdom is an EU Member State and has implemented the EU medicines and medical devices regimes, this chapter will not repeat much of the substantive content of the EU chapter. This chapter will focus on unique features of the UK regimes and should be read in conjunction with the EU section.

3 The Human Medicines Regulations 2012 (SI 2012/1916).

4 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

5 The Medical Devices Regulations 2002 (SI 2002/618), as amended.

6 The Active Implantable Medical Devices Directive 90/385/EEC, the Medical Devices Directive 93/42/EEC, and the In Vitro Diagnostic Medical Devices Directive 98/79/EC.

enforcement authority for the regulation of both medicinal products and medical devices. However, the ‘licensing authority’ is responsible for the grant, 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 on a case-by-case basis 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 1986⁷ implemented Directive 2010/63/EU⁸ 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 1999⁹ transpose Directive 2004/10/EC¹⁰ into UK law. They require 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

Medicines

Clinical trials of medicines for human use are regulated under the Medicines for Human Use (Clinical Trials) Regulations 2004¹¹ (the Clinical Trial Regulations), which implement Clinical Trials Directives 2001/20/EC¹² and 2005/28/EC¹³ 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 and investigational medicinal product dossier (IMPD) 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

7 Animals (Scientific Procedures) Act 1986 (Chapter 14), as amended.

8 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

9 The Good Laboratory Practice Regulations 1999 (SI 199/3106), as amended.

10 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.

11 Medicines for Human Use (Clinical Trials) Regulations 2004, as amended (SI 2004/1031).

12 Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as amended.

13 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.

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.

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. 536/2014,¹⁴ the United Kingdom is currently working towards the establishment of a system for the grant 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 also is 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 from the 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 and must also register details of the IVD for performance evaluation with the MHRA.

14 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

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.

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. In order for medicines to qualify for the EAMS, they must meet the following criteria:

- a* the product is needed to treat a life-threatening or seriously debilitating condition, and there is a high unmet need;
- b* the medicinal product is likely to offer significant advantages over methods currently used in the UK;
- c* the potential benefits of the medicinal product outweigh the adverse effects; and
- d* the applicant is able to supply the product and to manufacture it to a consistent quality standard of GMP.

Medical devices

The Medical Devices Regulations permit the supply of custom-made medical devices that meet the essential requirements but have not been CE-marked, and also devices that do not meet the essential requirements, provided that the MHRA authorises their use.

The use of an individual non-complying medical device, for a single named patient, is permitted only in exceptional circumstances; for example, where no alternative CE-marked devices are available or where it has been demonstrated that the morbidity or mortality of patients is significantly reduced with the use of the device in question as compared to those using alternative available treatment. The MHRA requires that an application be made for each patient, which includes information from the manufacturer and relevant clinician.

v **Pre-market clearance**

Medicines

Regulation 46 of the Medicines Regulations implements Article 6(1) of Directive 2001/83/EC, which requires that a medicinal product has a marketing authorisation prior to being placed on the market. It is an offence for any person to sell or supply, or offer to sell or supply, an unauthorised medicinal product or a medicinal product otherwise than in accordance with the terms of a marketing authorisation.

The MHRA is the UK national competent authority for review of marketing authorisation applications under the national, mutual recognition and decentralised procedures, although the relevant ministers acting through the licensing authority grant the authorisations.

Medical devices

The EU chapter summarises the conformity assessment and CE-marking procedures for medical devices. Since there is little regulatory pre-market review and approval of medical devices (with the exception of European Medicines Agency review of devices incorporating medicinal products and blood products), the MHRA has no involvement in the process leading up to CE marking.

However, the Medical Device Regulations require that manufacturers and authorised representatives based in the United Kingdom that are placing Class I or custom-made devices on the market to register details of themselves and the medical devices with the MHRA. Manufacturers or authorised representatives for IVDs must register themselves and their IVDs via the EU database, Eudamed.

vi **Regulatory incentives**

Medicines

The Medicine Regulations implement the EU periods of eight years' regulatory data exclusivity (during which generic applicants cannot file) followed by two years' market exclusivity (during which regulators may review generic applications, but generic manufacturers cannot launch) under Directive 2001/83/EC for products for which qualifying national applications were submitted after 30 October 2005. For complete free-standing applications submitted on or before that date, UK marketing authorisation holders would benefit from 10 years of data exclusivity protection, during which generic applicants cannot file. These regulatory exclusivity periods begin when the product is first approved anywhere in the EEA, not necessarily in the United Kingdom.

The additional data exclusivity provisions for 'orphan medicinal products' and for products with paediatric indications developed in accordance with an approved paediatric investigation plan under Regulation (EC) No. 141/2000¹⁵ and Regulation (EC) No. 1901/2006,¹⁶ respectively, apply directly.

15 Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

16 Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004.

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. 469/2009.¹⁷

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 1977.¹⁸ 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.

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 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 pre-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.

17 Regulation (EC) No. 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products.

18 Patents Act 1977 (Chapter 37), as amended.

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.

x **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, 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 dealer's 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 that 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.

xi **Classification of products**

Medicines

The Medicines Regulations presuppose that new medicinal products are generally restricted to use under medical supervision and made available only on prescription. There is also scope for imposing additional restrictions, such as requiring that certain products are prescribed only by specialists, or in hospitals. Non-prescription status is appropriate only for products with an appropriate level of safety and where self-diagnosis and treatment is appropriate without a healthcare professional's intervention or supervision.

There are two classes of non-prescription or over-the-counter drugs in the United Kingdom. Consumers must obtain pharmacy supply products bearing the designation 'P' from pharmacies, where they are dispensed under the supervision of a registered pharmacist. General sale list products may be sold through general retail channels, such as supermarkets, convenience stores, petrol stations and the like. These products bear the designation 'GSL'.

Medical devices

There are no UK rules governing the classification of medical devices that restrict their sale to the public.

xii Imports and exports

The United Kingdom's regulations governing the import and export of medicinal products reflect those at the 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 1971¹⁹ and subordinate legislation including the Misuse of Drugs Regulations 2001²⁰ 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 drugs; for example, registered pharmacists.

xiv Enforcement

Medicines

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 such 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 has recently been removed.

When the PMCPA Panel rules there is a breach of the ABPI Code under the self-regulatory scheme, the company concerned must give an undertaking not to repeat the offending advertisement or activity. The company, whether a member of the ABPI or not, must also pay an administrative charge of £3,500 per matter (or £4,500 per matter for non-members) where it accepts the Panel's decision that it breached the Code. The charge increases to £12,000 per matter (or £13,000 per matter for non-members) where the company appeals the Panel's decision and is unsuccessful. At the conclusion of a case, the PMCPA will also publish a detailed case report in its Code of Practice review and on its website.

19 Misuse of Drugs Act 1971 (Chapter 38), as amended.

20 Misuse of Drugs Regulations 2001 (SI 2001/3998), as amended.

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 1987.²¹ 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 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 a 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. Companies that do not participate in the PPRS must participate in a statutory scheme whereby the Department of Health imposes price reductions. In addition, the National Institute for Health and Care Excellence (NICE) assesses medicinal products to determine if 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 Health²² 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 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

21 Consumer Protection Act 1987 (Chapter 43), as amended.

22 Pursuant to the powers conferred upon the Department of Health by Section 262 of the National Health Service Act 2006 (Chapter 41).

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 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 is currently contemplating whether to move to a more flexible 'value based' approach to health technology assessment.

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

In the United Kingdom, 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',²³ 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'.²⁴

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.²⁵

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 also interactions between pharmaceutical companies and healthcare professionals. The legal position in the United Kingdom concerning communications or activities of pharmaceutical companies involving prescribers and payers is therefore the same as in the EU, 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 usage in the industry before 1 January 1993.

The Blue Guide and the ABPI Code clarify or establish additional requirements governing interactions with payers and prescribers. For example, the ABPI Code also governs the offer of inducements to administrative staff and prohibits promotional aids, except for inexpensive items for patient support. The ABPI Code also contains guidelines governing certain interactions between companies and NHS entities.

ii Medical devices

There are no specific UK rules that govern the interaction between medical devices companies and healthcare professionals.

The ABHI Code includes guidelines and a question-and-answer document on the minimum standards device companies should comply with when interacting with healthcare

23 Section 31(3) of the Senior Courts Act 1981 (Chapter 54).

24 Civil Procedure Rules 1998 (SI 1998/3132) Part 54.5(1).

25 *Council of the Civil Service Unions v. Minister for the Civil Service* [1985] A.C. 374. List of grounds for review cited is not exhaustive and may be added to in the future.

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.

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) 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.²⁶ 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.

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 EU 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

²⁶ Section 2 of the VDPA 1979 (Chapter 17), as amended.

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 two other investigations relating to excessive and unfair prices are ongoing in the UK. 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 UK. The decision has been appealed to the UK Competition Appeal Tribunal.

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 the price-fixing of opiate drugs. The OFT found that Napp abused a position of dominance approaching monopoly in the UK market for the supply of morphine tablets by charging excessively low, predatory or exclusionary prices in the hospital segment of the market, and excessively high prices in the community segment of the market. The OFT ordered Napp to cut the price of its morphine products to the community and reduce the difference between community and hospital prices.

ii Transactional issues

The considerations and issues outlined in the EU chapter apply equally in the United Kingdom.

VIII CURRENT DEVELOPMENTS

In June 2016, the UK voted to leave the EU. This decision may have significant implications for the pharmaceutical and medical devices industries in the UK, and for international companies operating in the UK. Its impact will very much depend on the form a post-Brexit UK will take, the relationship that the UK chooses to have with the EU, and indeed the relationship that the EU is willing to accept. The UK Prime Minister's public statements suggest that the UK will issue a formal notice, in accordance with Article 50 of the Treaty on the Functioning of the European Union, to leave the EU in March 2017. This will trigger a two-year period (or longer if all of the other EU Member States agree) for the UK to negotiate the arrangements for its withdrawal, taking into account the framework of its future relationship with the EU. Assuming that Article 50 is triggered by March 2017, this puts the UK on course for Brexit by the second quarter of 2019.

At the time of writing, the UK government had indicated that it intends to introduce draft legislation in the form of the 'Great Repeal Bill' that will enshrine into UK law all EU law, including pharmaceutical and medical device legislation, on the day of Brexit. The UK will thus have an 'unprecedented...common regulatory framework with the EU Single Market' on day one of Brexit. Thereafter, the government will review those laws derived from

EU law and seek to either amend, repeal or maintain said laws. The effects this will have on the pharmaceutical and medical devices legislation remains to be seen, but the government has indicated that it is planning for a 'hard' Brexit. That means the UK will not join either the EEA or European Free Trade Agreement and the extent to which the UK continues to participate in the EU regulatory schemes will need to be defined in bilateral trade agreements.

At the purely national level, there is a growing realisation that NICE technology appraisal methodologies struggle to deal with products for smaller patient populations and those used towards the end of a patient's life (e.g., in the oncology space). Possible replacements include a value-based pricing scheme, or one that seeks to reward innovation.

There are also signs that the MHRA is adopting a more aggressive enforcement stance, particularly where non-compliance causes, or has the potential to cause, a public health concern.

Chapter 38

UNITED STATES

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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 \$33 billion for 2017, 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 \$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 certain 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 manufacturing facilities and 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

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2 The FDA budget request for fiscal year 2017 states that \$2.3 billion of the total budget of \$5.1 billion will come from user fees. An executive order issued by the President in January 2017 imposed a temporary hiring freeze for most government agencies. It is unclear how this will affect the FDA.

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 by a Deputy Commissioner, manages the agency’s inspectional and enforcement programmes, staffed by several thousand employees who are located in regional, district and field offices around the United States and in several foreign countries.³

The main statute administered by the FDA is the Federal Food, Drug and Cosmetic Act (FDCA), originally enacted in 1938, which governs foods (including dietary supplements), drugs, devices, cosmetics, veterinary drugs, radiation-emitting products and tobacco.⁴ The statute prohibits ‘adulteration’ and ‘misbranding’ of regulated products and imposes numerous other requirements for specific types of products (e.g., pre-market approval or clearance procedures for certain drugs and medical devices). The FDA also administers portions of the Public Health Service Act (PHSA), including requirements for licensure of biological products, as well as numerous other regulatory statutes.⁵

The Drug Enforcement Administration (DEA), an agency within the Department of Justice, administers the Controlled Substances Act and other statutes relating to narcotics, psychotropics and other drugs with potential for abuse. Manufacturers of controlled substances are licensed and inspected by the DEA and may be required to obtain permits for specific activities (e.g., import and export licences and manufacturing and import quotas for certain products).

United States attorneys, located in every state, can bring cases to enforce the FDCA and other regulatory statutes governing drugs and devices. Federal prosecutors may act on referrals from FDA or on their own initiative.

The Federal Trade Commission (FTC) regulates the advertising of non-prescription drugs and medical devices (other than restricted devices) and also 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 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.

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.

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.⁶ The same product may, however, be covered by two or more definitions and thus be subject to multiple regulatory requirements. Many of the classifications depend on the 'intended use' of an article, which is ordinarily determined by statements made in advertising, labelling or other materials issued by the seller. Thus, a fluoride toothpaste for which anti-cavity claims are made is regulated as a drug because it is intended to prevent tooth decay and a cosmetic because it is intended to clean the 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'.⁷ 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 such actions against dietary supplements for which therapeutic claims were made, on the basis that those products were unapproved new drugs. Such 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, and it has taken several enforcement actions in recent years.

6 Under the FDCA, the term 'drug' includes articles recognised in official pharmacopoeias; articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; and articles (other than food) intended to affect the structure or any function of the body (21 USC, Section 321(g)). The term 'device' is defined in substantially similar terms, but applies to articles that do not achieve their primary intended purposes 'though chemical action within or on the body...' and which are not 'dependent upon being metabolised for the achievement of [their] primary intended purposes' (21 USC, Section 321(h)). Under the PHSA, the term 'biologic' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesised polypeptide) or analogous product or arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment or cure of a disease or condition in humans (42 USC, Section 262(i)(1)).

7 21 CFR, Part 3.

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.⁸ 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 governing 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 institutional review boards, or IRBs.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.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 must be carried out under an investigational new drug application (IND).¹¹ The application contains information on 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 on the investigators who will carry out the trial. The FDA accepts INDs in the common technical document (CTD) 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

8 21 CFR, Part 58.

9 21 CFR, Parts 50, 56.

10 21 CFR, Part 54.

11 See generally, 21 CFR, Part 312.

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 take 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, record-keeping, and reporting. Studies conducted in accordance with ICH GCP guidance will normally be acceptable to the FDA. There is no requirement for sponsors to maintain insurance or compensate subjects for injuries in 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 that may be drug-related and 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 they 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.¹²

Devices

Sponsors of device clinical trials 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).¹³ 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.¹⁴ In August 2014, the FDA issued guidance on

12 See 21 CFR, Section 312.120.

13 21 CFR Section 812.3(m).

14 Pub. L. No. 112-144, Section 601, 126 Stat. 193 (2012) (creating Section 520(g)(4)(C) of the FDCA).

its considerations for decision-making regarding IDEs and its plan to provide sponsors with feedback on study limitations that could preclude clearance or approval even though they would not preclude study initiation.¹⁵

'Abbreviated' IDE requirements apply to investigations of non-significant risk devices (i.e., those that do not meet the regulatory definition of SR). The sponsor must obtain IRB approval and informed consent and comply with record keeping and reporting requirements, but need not submit or obtain FDA approval of an IDE before commencing the study. Further, some device investigations are exempt from the IDE and abbreviated IDE requirements, including investigations of certain non-invasive diagnostic devices.

Device sponsors may obtain informal advice from the FDA on study design and other issues through a 'pre-submission' process (formerly the 'pre-IDE' process). In February 2014, the FDA issued a final guidance on the pre-submission programme.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.¹⁷ In 2012, Congress codified the FDA's approach in Section 569B of the FDCA. In February 2013, the FDA proposed to amend its regulations to permit supportive use of foreign data that are collected in accordance with GCP and subject to validation.¹⁸ The amended regulation would apply to data in other device submissions, not just PMAs. The FDA also has issued draft 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.¹⁹

iv Named-patient and compassionate use procedures

There are several procedures under which drugs or devices can be made available to treat patients even though they have not been cleared for commercial distribution.

Drugs

The FDA has established rules for 'expanded access' to investigational drug products that are intended to treat serious or life-threatening diseases. These include provisions for emergency INDs that permit physicians to treat individual patients following relatively simple applications to the FDA and treatment INDs, which provide for larger-scale use of investigational products. In certain cases, the FDA can authorise sponsors to charge for

15 FDA, Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff: FDA Decisions for Investigational Device Exemption Clinical Investigations (August 2014).

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 (February 2014).

17 21 CFR, Section 814.15(b).

18 78 Fed Reg 12664 (25 February 2013).

19 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States (April 2015).

investigational drug products under treatment INDs; prices are limited to recovery of 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,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.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 president in November 2013, establishes two regulated entities: traditional compounders, which prepare products at the request of physicians for specific patients, and ‘outsourcing facilities’, which prepare compounded products in larger quantities. Traditional compounders will be regulated primarily by state boards of pharmacy, while outsourcing facilities will be regulated by the FDA. If they register with the agency, submit to inspections and comply with other requirements, their products will not be subject to requirements for pre-market approval. The new provisions apply only to drugs and do not contain any exemption from requirements for pre-market approval of biologics.²²

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 that a pandemic is imminent, and authorisations remain valid only while the declaration is in effect.

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 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 also are available for devices.

20 21 USC, Section 353a.

21 *Thompson v. Western States Medical Center*, 535 US 357 (2002).

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.

‘Custom devices’ are exempt from the requirements for an approved PMA and compliance with performance standards under Section 520(b) of the FDCA.²³ Traditionally, the FDA interpreted this exemption narrowly. 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 recently issued final guidance implementing the amended custom device provision.²⁴

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.²⁵ 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. The FDA provided this notice on 31 July 2014, indicating its intent to publish two draft guidances describing a proposed regulatory framework for LDTs, and providing anticipated details of those draft guidances.²⁶ Thereafter, on 3 October 2014, the FDA formally announced the publication of the draft guidances in the Federal Register and opened a 120-day comment period ending on 2 February 2015.²⁷ Congress also began considering several different potential legislative approaches to address LDTs. The FDA stated that it intended to publish final guidance on the issue in 2016;²⁸ however, in November 2016, following the presidential election, the FDA announced that it would not move forward with efforts to finalise the draft guidances. Congress is expected to continue to consider potential legislation addressing LDTs.

The FDA also 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)²⁹

23 21 USC, Section 360j(b).

24 FDA, Guidance for Industry and Food and Drug Administration Staff: Custom Device Exemption (September 2014).

25 75 Fed. Reg. 34463 (17 June 2010).

26 Sally Howard, Deputy Commissioner for Policy, Planning, and Legislation, Notification to Congress (31 July 2014), www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.

27 79 Fed. Reg. 59776 (3 October 2014); 79 Fed. Reg. 59779 (3 October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) (October 2014).

28 CDRH Fiscal Year 2016 (FY 2016) Proposed Guidance Development and Focused Retrospective Review of Final Guidance, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm467223.htm.

29 21 CFR, Section 809.10(c)(2).

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 RUO and IUO.³⁰

v **Pre-market clearance**

Drugs other than biologics

‘New drugs’, which are defined to mean 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.³¹ 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.³² 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 rulemaking procedures are under way.³³ Newer OTC drug products and virtually all prescription drug products are marketed under approved NDAs or ANDAs.³⁴

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

30 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).

31 21 CFR, Parts 330-361.

32 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.

33 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.

34 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.

demonstrating the safety and effectiveness of the product and proposed labelling.³⁵ Although the FDA has not amended its regulations to require use of the common technical document (CTD), in practice the agency expects submissions to be made in that format, and the FDA is in the process of requiring that all submissions be made electronically (in the eCTD format). 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.³⁶

Legislation originally enacted in 1992 and known as the Prescription Drug User Fee Act (PDUFA),³⁷ requires sponsors of originator products to pay fees upon the submission and filing of NDAs and supplemental NDAs (proposing changes in approved NDAs), as well as annual fees for manufacturing establishments and products that are subject to the user fee requirement. The fees are adjusted each year according to a formula set out in the law.³⁸ As part of the process leading to enactment of each version of the PDUFA, the FDA has made commitments to Congress in the form of performance goals for the NDA review process, including (among many other things) requirements to hold prompt meetings with applicants prior to and during the NDA review process, timelines for the completion of reviews and procedures for appeals of negative decisions. Under current PDUFA commitments, the FDA aims to review non-priority applications within 12 months of submission and priority applications within eight months.³⁹ In practice, the actual time from submission to approval of most NDAs is more than a year. 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

35 An NDA may rely on information contained in another NDA, an IND or a drug master file, subject to a right of reference from the submitter of that information. FDA regulations provide for submission of DMFs for active substances, inactive ingredients and drug packaging materials, as well as other types of information by prior agreement with the agency (21 CFR, Section 314.420).

36 Regulations governing the content and review of NDAs are set out in 21 CFR, Part 314.

37 The PDUFA sunsets every five years unless re-enacted by Congress. The most recent enactment, passed in July 2012 as part of the FDA Safety and Innovation Act (FDASIA), is commonly referred to as 'PDUFA V'.

38 For fiscal year 2017, the fees are as follows: for an application containing clinical data, \$2,038,100; for an application that does not contain clinical data, \$1,019,050; for an establishment, \$512,000; and for a product, \$97,750.

39 Priority designation is granted if FDA determines that a drug would represent a significant improvement in the treatment, diagnosis or prevention of a disease as compared with existing therapies. There are provisions under which the sponsor of an NDA for a rare paediatric disease 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.

of a review ‘cycle’, the FDA either issues an approval or a ‘complete response’ informing the applicant why approval was not granted and identifying additional information required for approval.⁴⁰

To approve an NDA, the FDA must determine that the product will be safe and effective for the conditions of use recommended in its labelling, that the manufacturing process and facilities are adequate and in compliance with requirements for current 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. Legislation enacted in 2012 requires the FDA to establish a ‘structured risk-benefit assessment framework’ for the new drug approval process.⁴¹

As interpreted by the FDA, the Drug Price Competition and Patent Term Restoration Act of 1984 (often called the Hatch-Waxman Act) establishes two pathways for less-than-full applications that refer to prior approvals: ANDAs, submitted under Section 505(j) of the FDCA,⁴² which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2),⁴³ which rely on the finding of safety and effectiveness for a reference product but contain clinical data or other information in support of a change (e.g., a new indication or dosage form, a new combination of active substances or a different salt or ester of an active moiety). The starting point for such submissions is an FDA publication known as the Orange Book, which lists all products subject to approved NDAs with information on relevant patents and regulatory exclusivity periods (described in more detail below).⁴⁴

A generic product for which an ANDA is submitted must ordinarily be the same as the reference product in terms of active ingredients, dosage form, route of administration and strength; contain safe and suitable inactive ingredients; bear the same labelling as the reference product except for changes owing to differences in the manufacturer (e.g., differences in inactive ingredients or in the composition of the product); and 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

40 If the sponsor elects to resubmit the NDA with additional studies or other information to correct the deficiencies identified in the complete response, the FDA is ordinarily obligated to act on the resubmission within two or six months, depending on the complexity of the submission. In lieu of resubmitting the NDA, the sponsor may invoke its right to a formal evidentiary hearing, which will eventually lead to a decision by the Commissioner of Food and Drugs that can be appealed to a federal court of appeals. Sponsors rarely invoke this right, however, because the process is time-consuming and seldom leads to a change in the outcome.

41 NDAs must contain data on paediatric use, unless the FDA grants a waiver or deferral of the requirement or the application is exempt (orphan drugs).

42 21 USC, Section 355(j).

43 21 USC, Section 355(b)(2).

44 The official name of the publication is Approved Drug Products with Therapeutic Equivalence Determinations.

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 Generic Drug User Fee Act, the FDA will aim to clear the backlog of pending applications by the end of 2017 and set a 10-month target for review of new applications. Part of the new revenue will fund increased FDA manufacturing inspection programmes in the United States and abroad.⁴⁵

Biologics

Biological products are subject to a separate statutory approval system under Section 351 of the PHSA. Sponsors of originator products submit biologic license applications (BLAs) that contain essentially the same information as NDAs, in the CTD 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 assure that they continue to comply with these standards. The statute does not expressly require 'substantial evidence' of effectiveness (i.e., reports of adequate and well-controlled clinical investigations), and the FDA to an extent, therefore, has more discretion in determining whether efficacy has been demonstrated. In practice, however, the agency has ordinarily demanded the same evidence of efficacy for biologics as it expects for ordinary drugs.

In 2010, Congress enacted legislation⁴⁶ establishing an approval process for follow-on versions of biological products, or 'biosimilars'. Such a product must be 'highly similar' to a reference product 'notwithstanding minor differences in clinically inactive components'; have no clinically meaningful differences from a reference product in safety, purity or potency; be labelled for a condition of use for which the reference product is approved; have the same route of administration, dosage form and strength as the reference product; and be manufactured in facilities designed to assure 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.⁴⁷

45 Application fees for 2017 are \$70,480 for new ANDAs; \$35,240 for supplements requiring prior approval; \$51,140 for DMFs; \$44,234 for domestic facilities that manufacturer active substances; \$59,234 for foreign facilities that manufacture active substances; \$258,646 for domestic facilities that manufacture finished products; and \$273,647 for foreign facilities that manufacture finished products.

46 The Biologics Price Competition and Innovation Act (BPCIA), Pub. L. No. 111-148, Title VII, Subtitle A, 124 Stat. 119, 804–821 (2010).

47 A small number of biological products, including recombinant insulin and somatropin, were originally approved under the FDCA rather than the PHSA and were therefore eligible for submission of follow-on applications under Sections 505(b)(2) and 505(j) before the BPCIA was enacted. The FDA approved an application under Section 505(b)(2) for a follow-on

User fees for biosimilar applications are currently the same as those for originator products. To provide immediate funding for the review programme, however, portions of that fee must be prepaid. A portion of the application fee is due when a sponsor seeks development advice from the FDA, and thereafter, another 10 per cent is due annually as a biosimilar development fee. The initial and annual fees are 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 and many important issues remain undecided – for instance, how the FDA will interpret the statutory standard for interchangeability.

Expedited programmes

The FDCA and FDA regulations establish special procedures for the approval of drugs and biologics for serious or life-threatening diseases that provide meaningful benefits over existing therapies. For instance, pursuant to accelerated approval, effectiveness may be demonstrated on the basis of surrogate or intermediate clinical endpoints, with a commitment to carry out post-marketing studies to confirm the validity of those endpoints as predictors of clinical outcomes. The FDA may impose special restrictions on such drugs (e.g., pre-submission of promotional materials or restrictions on distribution). If post-marketing studies fail to confirm clinical benefit, approval may be withdrawn through an expedited procedure.

Medical devices

The pre-market clearance requirements for a device depend on the device's class, which in turn depends on the level of risk that the device presents. Class I devices present the least risk, and they generally are exempt from pre-market review. Class II devices present moderate risk, and most require clearance of a pre-market notification under Section 510(k) of the FDCA prior to marketing. Class III devices – the highest-risk category – typically require approval of a PMA before marketing. A special classification rule applies to 'post-amendments' devices (i.e., those that were not in commercial distribution before 28 May 1976, when Congress enacted the Medical Device Amendments to the FDCA). These devices are automatically in Class III. If, however, the manufacturer obtains clearance of a pre-market notification or the agency grants a *de novo* petition (discussed below), the FDA will place the device in Class I or II and allow the manufacturer to distribute the device.

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,

version of recombinant somatropin in 2006, based on a substantial package of non-clinical and clinical data. In 2015, the FDA approved an application under Section 505(b)(2) for a follow-on insulin. In 2020, the proteins regulated under the FDCA will transfer to the PHSA. Id. Section 7002(e).

proposed labelling, a device description, and the submitter's rationale for concluding the device is substantially equivalent to the predicate device. In some cases, it may need to contain clinical data. The submitter also must pay a small 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. In August 2015, the FDA issued a final guidance describing its refuse to accept policy for 510(k) notifications, and the situations in which the agency will refuse to accept 510(k)s as incomplete.⁴⁸ The submitter may not market the device until the FDA has 'cleared' the 510(k) notification, even if the FDA misses the applicable deadline.

If the FDA determines that it cannot clear the device, it will issue a 'not substantially equivalent' determination, indicating that the device is Class III and cannot be marketed without a PMA. The submitter then has 30 days to request *de novo* classification of the device, if desired. This procedure is intended to permit clearance of low or moderate-risk devices that have no predicate device. In addition, under amendments made in the FDASIA, a manufacturer also may submit a *de novo* request in lieu of submitting a 510(k). The statute calls for the FDA to rule on a *de novo* request within 120 days, although no performance goals apply to review of *de novo* requests. In August 2014, FDA issued a draft guidance on the submission and review of *de novo* requests.⁴⁹

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, 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 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.⁵⁰ 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 the device represents a breakthrough technology or the device offers the potential to, compared to existing alternatives, reduce or eliminate the need for hospitalisation, improve patient quality of life, facilitate patients' ability to manage their

48 FDA, Refuse to Accept Policy for 510(k)s: Guidance for Industry and Food and Drug Administration Staff (August 2015).

49 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (August 2014).

50 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).

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 also may reclassify devices under a procedure that was streamlined in the FDASIA. Prior to the FDASIA, the FDA use notice-and-comment rulemaking to reclassify devices, and this proved burdensome. As amended by the FDASIA, the statute permits 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'.⁵¹ Although this language suggests the three activities must occur in chronological order, in a proposed rule to amend the governing regulations to conform to the FDASIA, among other things, the agency stated: 'The panel meeting must occur before the final order is published, and may occur either before or after the proposed order is published.'⁵²

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 the 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).⁵³

The Hatch-Waxman Act establishes several incentives for development of originator 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

51 FDASIA, Section 608 (amending FDCA, Section 513(e)).

52 79 Fed. Reg. 16252, 16254 (25 March 2014).

53 See 21 USC, Sections 360n-360ff; 21 CFR, Part 316. The FDA also demands a showing of clinical superiority when an applicant seeks an orphan designation for a drug containing the same active ingredient for the same indication as one previously granted orphan status. In *Depomed, Inc. v. Department of Health and Human Services*, Case No. 1:12-cv-01592 (D.D.C. 2014), a federal court rejected this policy as inconsistent with the language of the statute, but the FDA subsequently issued a notice reaffirming its position and stating that the decision in the Depomed case was limited to its facts. 79 Fed. Reg. 76,888 (23 December 2014).

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.⁵⁴

Second, the statute provides for periods of data exclusivity (i.e., protection against approval of ANDAs and Section 505(b)(2) applications) for originator 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) 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 filed until the 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 can be submitted during the three-year period but approvals cannot be made effective until the period expires.⁵⁵

Third, the statute contains complex provisions linking the approval of follow-on products to patents for reference drugs. Sponsors of originator products are required to submit patent information for their products, including expiry dates, which the FDA includes in the Orange Book. Sponsors of follow-on products are required to make one of four patent certifications:

- a* that no patents are listed for the reference product;
- b* that all listed patents have expired;
- c* that patents are listed and have not expired, but the applicant wishes that approval of its product be made effective upon expiry; or
- d* that the listed patents are 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 originator 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.⁵⁶

Finally, the Hatch-Waxman Act provides for a 180-day period of generic marketing exclusivity for the first ANDA applicant that files a successful Paragraph IV certification (e.g., if the patent for the reference product is held to be invalid, unenforceable or not infringed, or in certain other circumstances, including situations in which the generic applicant launches

54 35 USC, Section 156.

55 21 USC, Section 355(j).

56 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.

‘at risk’ when patent litigation extends beyond the period of the administrative stay on approval of an ANDA). 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 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.⁵⁷

Most recently, 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-, five- and three-year exclusivity under the Hatch-Waxman Act and seven-year orphan drug exclusivity.⁵⁸

Biologics

Under the BPCIA, applications for biosimilar products may not be filed until four years, and may not be approved until 12 years, after the approval 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. 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 July 2015, the Federal Circuit held that these procedures are optional, but also concluded that a provision of the BPCIA requiring the biosimilar applicant to give the reference product sponsor 180 days’ notice of its planned commercial launch is triggered on the day the FDA licenses the biosimilar.⁵⁹

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*. Patent term extension is also available for PMA-approved devices.

57 21 USC, Section 355a.

58 21 USC, Section 355f.

59 *Amgen v. Sandoz*, 794 F.3d 1347 (Fed. Cir. 2015). An appeal is pending in the US Supreme Court.

The humanitarian device exemption (HDE), rather than regulatory exclusivity, is available for sponsors of devices for rare disease or conditions. It exempts the device from compliance with the effectiveness requirements of Section 515, 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) it will not be available to these patients without the exemption, and no comparable device (other than another humanitarian use device (HUD)) is available for them; and (3) it will not expose patients to an ‘unreasonable or significant risk of illness or injury’, and the probable benefit from using the HUD outweighs its risks. IRB approval is required before use of HUDs. Sponsors may charge a commercial, rather than cost-recovery, price for an HUD intended for use in a paediatric population or subpopulation, or a disease or condition that is very rare or non-existent in children, if certain conditions are met. For example, the number of devices distributed annually cannot exceed the ‘annual distribution number’ (i.e., the number of devices reasonably needed to treat, diagnose, or cure 8,000 people in the United States).

vii Post-approval controls

Drugs

FDA regulations establish requirements for the reporting of adverse events associated with approved drugs and biologics, including expedited (15-day) reports of serious, unexpected events as well as periodic adverse drug experience reports (PADERs). In lieu of PADERs, the FDA will grant waivers to permit submission of periodic safety update reports (PSURs) in the CIOMS 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.⁶⁰ Manufacturers of approved drugs and biologics are also required to notify the FDA of discontinuance or interruption 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’.⁶¹

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 safety 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. Such requirements are imposed on many vaccines and certain other products regulated by the CBER.

60 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).

61 21 USC, Section 356c.

FDA regulations establish detailed rules for changes in products that are subject to approved NDAs or BLAs.⁶² 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, or PAS). Less significant changes can be made after submission of a changes-being-effected supplement; in some cases, the applicant is required to wait 30 days before implementing a change, but certain changes can be made immediately upon submission.⁶³ 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.); the guidance for biologics is less detailed.

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, depending on the circumstances, may require 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.⁶⁴ 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 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.

62 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).

63 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 a causal relationship to the drug (21 CFR, Section 314.70). 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)).

64 This power has been exercised only once, in relation to the oral hypoglycaemic drug phenformin in 1977. See *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977), appeal denied as moot, CCH Food Drug Cosm. L. Rpts. Paragraph 38,241 (D.C. Cir. 1979).

Devices

The FDCA's 'general controls' apply to all devices, including Class I devices exempt from pre-market review. The general controls include prohibitions on adulteration and misbranding, as well as requirements for 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 generally must file reports if it becomes aware of information that reasonably suggests that its marketed device: may have caused or contributed to a death or serious injury; or malfunctioned, and recurrence of this malfunction in the device (or any similar device marketed by the manufacturer) would be likely to cause or contribute to a death or serious injury.⁶⁵ 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 serious injuries only to the manufacturer. Manufacturers must usually 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 the public health.⁶⁶ Importers must complete their reports within 30 days, and for user facilities, the deadline is 10 days.⁶⁷ 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.⁶⁸ Also, in December 2016, the FDA issued a final guidance describing when and how the agency will provide public notice of emerging postmarket safety signals for devices.⁶⁹

The FDA also requires manufacturers and importers to report certain device corrections and removals 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 to some other location for remediation or destruction.⁷⁰ 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'.⁷¹ In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.⁷²

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.⁷³ 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

65 21 CFR, Section 803.50(a).

66 21 CFR, Section 803.40.

67 21 CFR, Section 803.10.

68 FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device Reporting for Manufacturers (November 2016).

69 FDA, Guidance for Industry and Food and Drug Administration Staff: Public Notification of Emerging Postmarket Medical Device Signals (December 2016).

70 21 CFR, Section 806.2(d) and (i).

71 21 CFR, Section 806.10(a).

72 FDA, Distinguishing Medical Device Recalls from Medical Device Enhancements: Guidance for Industry and Food and Drug Administration Staff (October 2014).

73 FDCA, Sections 519(e), 522.

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.⁷⁴

Different frameworks apply to post-approval changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.⁷⁵ Major changes (i.e., those affecting safety or effectiveness) require approval of a PMA supplement. Certain other changes, including some labelling changes and some manufacturing changes, may be implemented with prior notice to the FDA. Other changes may be reported in periodic reports that are required as a condition of device approval. A different approach applies to 510(k)-cleared devices. Some modifications to these devices may be made without submitting a new 510(k), provided that the manufacturer documents the changes in a ‘letter to file’. Others require a new pre-market notification (not a supplement). 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.⁷⁶ In August 2016, the FDA issued two draft guidances describing how manufacturers should determine whether a new 510(k) should be submitted for change to an existing device.⁷⁷ These draft guidances, when final, will replace the agency’s existing final guidance on the topic, which was issued in 1997.⁷⁸

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.⁷⁹

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.⁸⁰ The FDA also may temporarily suspend approval of a PMA and IDE 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 a 510(k) notification, although there is no specific statutory or regulatory basis for this position. In 2011, a device manufacturer challenged the FDA’s claimed authority in court. The district court found that the FDA has inherent authority to rescind a 510(k) clearance in ‘rare situation[s]’, if the agency acts within

74 78 Fed. Reg. 58,786 (24 September 2013).

75 See 21 CFR, Section 814.39.

76 21 CFR, Section 807.81(a)(3).

77 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (August 2016); FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Software Change to an Existing Device (August 2016).

78 FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (January 1997).

79 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Transfer of a Premarket Notification (510(k)) Clearance – Questions and Answers (December 2014).

80 21 USC, Sections 360e(e), 360j(g)(5), 360j(m)(5).

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.⁸¹ 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.⁸²

viii Manufacturing controls

Drugs

Facilities that manufacture drugs or biologics for distribution in the United States, including foreign facilities, must be registered with the FDA, but the procedure is ministerial and there is no requirement for a manufacturing authorisation. NDAs and BLAs contain detailed information on manufacturing facilities, which are normally inspected by the FDA before marketing authorisations are granted. All facilities that manufacture drugs or biologics (including ‘old’ drugs, such as monograph OTCs, for which prior approval is not required) must comply with regulations governing current GMP,⁸³ which are supplemented by detailed guidances. Transfer of ownership of drug manufacturing facilities does not normally require prior approval from the FDA, but changes must be made in establishment registrations, and other changes resulting from a transfer of ownership may require supplemental applications for products made in an establishment.

Devices

The FDA also requires establishment registration for device facilities through a ministerial procedure. Devices must be manufactured in accordance with the FDA’s QSR, which includes provisions governing design control and validation, and GMP.⁸⁴ PMAs must contain a detailed description of methods, facilities, and controls used in manufacturing the device.⁸⁵ The FDA may also conduct 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.⁸⁶ For 510(k)-cleared devices, the manufacturer must assess whether a facility change requires a new 510(k) (i.e., whether the change could significantly affect the device’s safety or effectiveness).

ix Advertising and promotion

Drugs

The FDA regulates advertising and promotional labelling for prescription drugs. Detailed rules govern the content of advertisements, including requirements for fair balance, adequate substantiation of claims, consistency with the approved prescribing information, inclusion of a ‘brief summary’ of the prescribing information and prominent disclosure of

81 *Ivy Sports Medicine v. Sebelius et al.*, 938 F. Supp.2d 47, 58, 59, 61 (D.D.C. 2013).

82 *Ivy Sports Medicine, LLC v. Burwell*, 767 F.3d 81, 87 (D.C. Cir. 2014).

83 21 CFR, Parts 210, 211.

84 21 CFR, Part 820.

85 21 CFR, Section 814.20(b)(4)(v).

86 21 CFR, Section 814.39(a)(3).

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.⁸⁷

Promotional labelling (e.g., brochures and similar materials used by sales representatives) is subject to similar requirements, except that the full prescribing information (in lieu of the brief summary) must accompany all such labelling (except for reminder labelling).

Direct-to-consumer (DTC) advertising of prescription drugs is permitted in the United States. Print advertisements must fully comply with the general rules on prescription drug advertising, using language that is understandable to the ordinary person. Broadcast advertisements, including television advertisements, must maintain fair balance, provide important safety information and incorporate mechanisms by which listeners or viewers can obtain complete information (e.g., websites, print advertisements or other measures). Although FDA pre-clearance of DTC advertisements is not ordinarily required, companies often submit television advertisements for FDA review prior to use.

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.⁸⁸

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), and 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.⁸⁹ Decisions by the US Supreme

87 See 21 CFR, Part 202.

88 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).

89 See *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

Court in 2011,⁹⁰ an influential federal court of appeals in 2012,⁹¹ and most recently, a federal district court in 2015,⁹² suggest the need for the FDA to consider further changes to its existing rules, but as yet the FDA has not done so.⁹³

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 Federal Trade Commission regulates the advertising of non-prescription drugs under general 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 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.⁹⁴ Similarly, the principles for FDA's regulation of device promotion and restricted device advertising are generally consistent with those for regulation of drug promotional labelling and advertising.⁹⁵ 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

90 *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.

91 *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.

92 *Amarin Pharma, Inc. v. FDA*, No. 15-3588, 2015 WL 4720039 (S.D.N.Y. 7 August 2015).

93 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). The docket for written submissions remains open until April 2017. 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.

94 Michael S Labson, 'Regulation of Advertising, Promotion, and Distribution of Drugs, Medical Devices, and Biologics', Section 6.1.3, in *Fundamentals of Life Sciences Law*.

95 *Id.*

differences include the lack of a 'substantial evidence' standard for substantiation and the lack of an express requirement for 'fair balance' in the regulations.⁹⁶ Device promotion remains subject to the statutory prohibitions on false and misleading representations, however.⁹⁷

x 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 licensing of pharmaceutical distributors and distribution facilities, and the FDA has issued guidelines for the states.⁹⁸

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.⁹⁹ 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.

xi 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.¹⁰⁰ For prescription drugs, elements to ensure safe use, established as part of FDA-imposed REMS, can limit use of a product to certain medical specialties or settings (e.g., hospitals).

Devices, like drugs, may be limited to prescription status. The FDA may also classify a device as restricted and limit access and distribution of the device this way, if 'there cannot otherwise be reasonable assurance of its safety and effectiveness'.¹⁰¹ 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.

96 Id.

97 21 USC, Sections 502(a) and (q).

98 21 CFR, Part 205.

99 21 CFR, Part 203.

100 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.

101 21 USC, Section 360j(e).

xii Imports and exports

The FDCA includes a limited exemption under which certain drugs and biologics 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.¹⁰² 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.¹⁰³

xiii Controlled substances

Narcotics, psychotropics and other drugs that are liable to abuse are regulated under the Controlled Substances Act,¹⁰⁴ which is administered by the Drug Enforcement Administration 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, 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

102 21 USC, Section 381(e).

103 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 US 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.

104 21 USC, Section 801 et seq.

recommendation to the DEA for the appropriate scheduling of the product, although the actual rulemaking to include a new substance in a schedule under the statute is conducted by the DEA.¹⁰⁵

xiv 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 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*).¹⁰⁶ Felony penalties may be imposed upon proof that a violation was committed with intent to defraud or mislead, or upon a second conviction for a strict liability offence.¹⁰⁷ 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 voluntary 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.

Recent 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

105 The FDA has required applicants to agree not to market new drugs containing controlled substances until the DEA issues a final scheduling regulation. In recent years, the DEA process has often not been completed until months after FDA approval, thus delaying access to the new drug and effectively depriving the applicant of the value of a portion of any period of market exclusivity. This led one manufacturer to sue the FDA, demanding a proportionate extension of its market exclusivity period, but the court ruled in the FDA's favour. *Eisai, Inc. v. FDA*, Case No. 1:14-cv-01346-RCL, 2015 WL 5728882, at *12 (D.D.C. 30 September 2015). On 25 November 2015, however, Congress enacted legislation providing that approval of the NDA will not take effect until the DEA issues an interim final rule scheduling the drug. The legislation also imposes a 90-day deadline for the DEA's scheduling action running from the later of: (1) the date when the DEA receives the FDA's scheduling recommendation; or (2) the date when the DEA receives notification that the FDA has approved the drug. Pub. Law No. 114-89 (2015).

106 *United States v. Park*, 421 US 658 (1975); *United States v. Dotterweich*, 320 US 277 (1943).

107 The FDCA imposes penalties of \$1,000 and imprisonment for one year per violation for misdemeanours and \$10,000 or imprisonment for three years for felonies. General federal criminal legislation provides for significantly greater fines than those imposed under the FDCA.

rules on safety reporting and clinical investigations.¹⁰⁸ 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.

III PRICING AND REIMBURSEMENT

Reimbursement for prescription drugs in the United States is provided through a mixed system of private and public coverage. More than 60 per cent of all patients have private insurance, often provided through their employer, which covers prescription drugs,¹⁰⁹ 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 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 dependents, 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 specialty 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.¹¹⁰

Public programmes also use mechanisms to control costs similar to those used by private plans. Medicare Part D, which covers outpatient prescriptions, imposes significant beneficiary cost sharing in a coverage gap known as the 'donut hole' (although recent legislation will close the donut hole by 2020). Drug manufacturers whose 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.

108 It is estimated that total judgments in such cases over the past decade have exceeded \$20 billion. The largest settlement to date related to GlaxoSmithKline, which agreed to pay a total of \$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.

109 United States Census Bureau, *Health Insurance Coverage in the United States: 2014* (2015), www.census.gov/content/dam/Census/library/publications/2015/demo/p60-253.pdf.

110 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.

Access to coverage is likely to expand as a result of the health insurance mandate set forth in the Affordable Care Act (ACA) enacted in 2010, which is intended to provide health coverage for those individuals (by some estimates, as least 30 million) who are not covered by other programmes. Although the ACA is not fully effective until 2018, provisions already in effect establish minimum requirements for health insurance programmes, require most individuals to purchase insurance and subsidise premiums for low-income individuals. In particular, prescription drug coverage is 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.¹¹¹

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.¹¹² The majority of disputes are, however, resolved through less formal mechanisms. The FDA regulations establish a general right to informal review of any decision within the agency hierarchy.¹¹³ Certain FDA commitments made under the PDUFA (e.g., to decide appeals of clinical holds of INDs and complete responses to NDA and BLA submissions) include dispute resolution procedures with deadlines for completion. Statutory provisions authorising the FDA to require REMS, post-approval safety studies and safety labelling changes afford sponsors a right to an informal dispute resolution procedure.¹¹⁴ 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.¹¹⁵ 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”’.¹¹⁶

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

111 The incoming Administration and Republican leaders in Congress have announced plans to repeal the Affordable Care Act, but it remains unclear when or how this will be accomplished. In the meantime, there is continued focus on prices charged for innovative medicines in the US, and there is a possibility that measures will be introduced in response to that issue.

112 21 USC, Section 355(d), (e).

113 21 CFR, Section 10.75. If a request for review is denied, the requestor may appeal to the agency’s Chief Mediator and Ombudsman. 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.

114 21 USC, Sections 355(o), 355-1.

115 FDCA Section 517A(b).

116 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).

(APA).¹¹⁷ 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.¹¹⁸

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.¹¹⁹ 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.¹²⁰

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.¹²¹

117 5 USC, Section 501 et seq.

118 5 USC, Section 706. Subject to somewhat complex rules enunciated by the Supreme Court and the US Court of Appeals for the District of Columbia Circuit, the federal courts often defer to FDA's interpretation of the statutes and regulations it administers, and in practice they also tend to give great weight to the agency's findings on matters of science and medicine within its special areas of expertise.

119 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's filing under Section 505(q)(1)(F) of the FDCA. Pre-enforcement review is available as to final regulations issued by the FDA. *Abbott Laboratories v. Gardner*, 387 US 136 (1967).

120 See, e.g., *Biotics Research Corp v. Heckler*, 710 F.2d 1375 (9th Cir. 1985); but see *Den-Mat Corp v. United States*, CCH Food Drug Cosm. L. Rpts. Paragraph 38,272 (D. Md. 1992).

121 See, e.g., *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982) (competitor alleging unlawful use by FDA of confidential information in its NDA); *Pharmaceutical Manufacturers Association v. FDA*, 484 F. Supp. 1179 (D. Del. 1980), aff'd per curiam 634 F.2d 106 (3d Cir. 1980) (trade association and physician organisations challenging patient labelling requirements for oestrogen drug products).

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.¹²² Instead, these are subject to provisions of law enforced by the Department of Justice and the OIG of the Department of Health and Human Services. The federal Anti-Kickback Statute¹²³ 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 *qui tam* lawsuits on behalf of the federal government under the False Claims Act.¹²⁴ 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.

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.¹²⁵ In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers,¹²⁶ and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals.¹²⁷

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 to the Department of Health and Human Services for disclosure on a public website.¹²⁸ The federal requirement pre-empts some, but not all, such 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

122 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).

123 42 USC, Section 1320a-7b.

124 31 USC, Sections 3729-3733.

125 42 CFR, Section 1001.952.

126 68 Fed. Reg. 23731 (5 May 2003).

127 PhRMA Code on Interactions with Healthcare Professionals – www.phrma.org-guidelines/code-interactions-healthcare-professionals.

128 www.cms.gov/openpayments.

Vaccine Injury Act of 1986.¹²⁹ 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 \$250,000); a \$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.

Section 304 of the Homeland Security Act of 2002¹³⁰ 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 2005¹³¹ 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.¹³²

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.¹³³ 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

129 42 USC, Section 300aa-10 et seq.

130 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.

131 42 USC, Section 247d-6d.

132 In December 2014, a PREP Act declaration was issued for designated vaccines under development for Ebola virus disease.

133 The number of lawsuits between pioneer and generic drug companies increased significantly after the enactment of the Hatch-Waxman Act. FTC, *Generic Drug Entry Prior to Patent Expiration: An FTC Study (July 2002)* (FTC Generic Drug Entry Report), available at www.ftc.gov/os/2002/07/genericdrugstudy.pdf.

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 a payment or other 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 the expiration 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 with 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 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.¹³⁴

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.¹³⁵ 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.¹³⁶

134 A 2010 analysis by the FTC asserts that reverse payment settlements cost consumers \$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.*

135 *FTC v. Watson Pharms. Inc.*, 677 F.3d 1298 (11th Cir. 2012); *In re Ciprofloxacin Hydrochloride Antitrust Litig.*, 544 F.3d 1323 (Fed. Cir. 2008), cert. denied, 557 US 920 (2009); *In re Tamoxifen Citrate Antitrust Litig.*, 466 F.3d 187 (2d Cir. 2006), cert. denied, 551 US 1144 (2007); *Valley Drug Co v. Geneva Pharms Inc.*, 344 F.3d 1294 (11th Cir. 2003), cert. denied, 543 US 939 (2004); *Schering-Plough Corp v. FTC*, 402 F.3d 1056 (11th Cir. 2005), cert. denied, 548 US 919 (2006).

136 See, e.g., *In re Tamoxifen Citrate Antitrust Litig.*, 466 F. 3d at 213.

The Third Circuit rejected the ‘scope of the patent’ standard in a significant 2012 decision, *In re K-Dur Antitrust Litigation*.¹³⁷ 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.¹³⁸ 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’.¹³⁹ 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*.¹⁴⁰ 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 procompetitive benefits. The application of the *Actavis* ruling to particular cases is extremely fact-intensive. Significant uncertainty remains as the lower courts begin to 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 whether the reverse payment required by the *Actavis* decision must be a cash payment or whether other forms of consideration flowing from the innovative company to the generic can subject the settlement to antitrust scrutiny.¹⁴¹

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 necessary to protect public health.¹⁴² In view of these provisions, courts may be reluctant to hear antitrust claims based on the allegation that citizen petitions delayed market entry of generics.¹⁴³

137 See *In re K-Dur Antitrust Litig*, 686 F. 3d 197 (3d Cir. 2012).

138 *Id.* at 219.

139 *In re K-Dur Antitrust Litig*, 686 F.3d 197, 214 (3d Cir. 2012).

140 *Federal Trade Commission v. Actavis Inc*, 570 US __, 133 S.Ct. 2223 (2013).

141 See *In re Loestrin 24 FE Antitrust Litig*, No. 13-md-2472 (D.R.I. Sept. 4, 2014) (dismissing antitrust challenge where no cash payment was made).

142 21 USC, Section 355(q).

143 See *Apotex Inc v. Acorda Therapeutics Inc*, No. 11 Civ. 8803 (LTS) (S.D.N.Y. 7 February 2013).

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 IP and regulatory regimes also differ from those in Europe in ways that must be expressly addressed in agreements for the United States. For example, joint patent owners have an equal and undivided interest in the joint patent, and in the absence of contract language to the contrary each may exploit it freely without accounting to the other. Also, the royalty term under a patent licence typically may not extend beyond the life of the licensed patents. In addition, patent and regulatory regimes for drug products are linked, which requires special provisions dealing with patent listings, patent term restoration and the enforcement of patents against generic competitors. Similarly, the recently enacted, and evolving, biosimilar regime in the United States may require drafting attention depending on the interests of the parties.

Product liability is also 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 December 2016, President Obama signed the 21st Century Cures Act, which amends the FDCA and PHSA, among other laws, with the aim of accelerating the discovery, development and delivery of new medicines, and medical technologies.¹⁴⁴ The 21st Century Cures Act includes a number of provisions related to the discovery, development and delivery of drugs devices. Significant features of the legislation include provisions:

- a* reauthorising the priority review voucher programme for certain drugs intended to treat rare paediatric diseases;
- b* creating a new priority review voucher programme for drug applications determined to be material threat medical countermeasure applications;

144 Public Law No. 114-255.

- c* requiring the FDA to create a programme to evaluate the potential use of ‘real world evidence’ to help support approval of new indications for approved drugs and satisfy post-approval study requirements;
- d* providing a new ‘limited population’ approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections;
- e* creating a process for the FDA to designate a drug as a ‘regenerative advanced therapy’, which is eligible for the same actions to expedite the development and review of a marketing application as breakthrough-designated drugs, and may be eligible for priority review and accelerated approval (with certain modifications for drugs with the new designation);
- f* broadening the safe harbour created by Section 114 of the Food and Drug Administration Modernization Act for communication of healthcare economic information by drug sponsors to payer audiences;
- g* significantly revising the FDCA provisions on combination product regulation with the aim of streamlining review of combination product applications;
- h* establishing of a statutory ‘breakthrough’ designation and review pathway for medical devices;
- i* carving out of the FDA’s jurisdiction certain health software, including certain clinical decision support functions that make patient-specific recommendations to providers; and
- j* expanding the size of the patient population that may be served by a ‘Humanitarian Use Device’.

Additional changes to the laws regarding the regulation of drugs (including, in particular, non-prescription drugs), biosimilars and their reference products, or devices are also possible in connection with the reauthorisation of the corresponding user fee statutes, the Prescription Drug User Fee Act, the Biosimilars User Fee Act and the Medical Device User Fee Act, all three of which must be renewed in 2017.

Cybersecurity for medical devices is an area of increasing concern and activity for the FDA, as devices become increasingly networked and digital health technologies continue to develop. In October 2014, the FDA issued a final guidance describing cybersecurity issues that manufacturers should consider in the design and development of devices and in preparing premarket submissions.¹⁴⁵ And the agency issued a final guidance document addressing the post-market management of cybersecurity in medical devices in December 2016.¹⁴⁶ The FDA also issued its first safety communication related to cybersecurity vulnerabilities with a particular device, encouraging healthcare facilities to discontinue use of the device.¹⁴⁷ Both the guidance and the safety communication suggest that the FDA is treating cybersecurity vulnerabilities in a similar matter to more traditional product risks. The FDA, in

145 FDA, Guidance for Industry and Food and Drug Administration Staff: Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (October 2014).

146 FDA, Guidance for Industry and Food and Drug Administration Staff: Postmarket Management of Cybersecurity in Medical Devices (December 2016).

147 FDA, Cybersecurity Vulnerabilities of Hospira Symbig Infusion System: FDA Communication (31 July 2015), www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm456815.htm.

collaboration with HHS and the Department of Homeland Security, held public workshops in October 2014 and January 2016 to discuss models for evaluating cybersecurity status and unresolved challenges hampering process in advancing medical device cybersecurity.¹⁴⁸ Finally, as part of omnibus spending legislation, Congress passed the Cybersecurity Act of 2015, which requires HHS to establish a healthcare industry cybersecurity task force and to establish voluntary consensus guidelines that support adoption and implementation efforts to improve safeguards that address cybersecurity threats.¹⁴⁹

The regulation of diagnostic tests, including LDTs, next-generation sequencing (NGS)-based tests, and companion diagnostics, continues to evolve in light of rapid technological advancements and increasing focus on precision medicine. In 2014, the FDA issued draft guidances describing a proposed regulatory framework for LDTs.¹⁵⁰ Although the agency recently 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. 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.¹⁵¹ The agency also issued two draft guidance documents in July 2016 that address the use of public genetic variant databases to support a demonstration of clinical validity for NGS-based tests and the use of standards in the agency's oversight of NGS-based tests used for diagnosing germline diseases.¹⁵² The FDA has stated that it intends to finalise both guidances in 2017.¹⁵³ Finally, also in July 2016, the FDA issued a draft guidance document providing recommendations on the co-development of a companion diagnostic with a therapeutic product.¹⁵⁴

148 79 Fed Reg 56814 (23 September 2014); 80 Fed Reg 76022 (7 December 2015).

149 Consolidated Appropriations Act, 2016, H.R. 2029, Div. N.

150 FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) (October 2014).

151 79 Fed Reg 78092 (29 December 2014); 80 Fed Reg 54290 (9 September 2015); 80 Fed Reg 54292 (9 September 2015); 81 Fed Reg 1426 (12 January 2016); 81 Fed Reg 1955 (14 January 2016); 81 Fed Reg 56656 (22 August 2016).

152 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 (July 2016); FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used For Diagnosing Germline Diseases (July 2016).

153 CDRH Fiscal Year 2017 (FY 2017) Proposed Guidance Development and Focused Retrospective Review of Final Guidance, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm529396.htm.

154 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).

Changes to the agency's regulation of electronic health technologies and software-based devices are also possible. The 21st Century Cures Act included a provision removing certain types of software functions from the statutory definition of a device. Many of the software functions that are the subject of this provision were subject to the agency's enforcement discretion and were not required to comply with the regulatory requirements for devices pursuant to final guidance documents addressing general wellness products and mobile medical apps.¹⁵⁵ But the new provision expands those software functions that will not be regulated as devices to include certain software that supports clinical decision-making by healthcare professionals. The scope and impact of the new legislative provision remain to be seen.

There is the potential for further court challenges to the FDA's regulations governing 'off-label' promotion of approved prescription drugs and devices, based on the argument that they prohibit truthful claims in violation of the First Amendment to the US Constitution. Even if these are successful, it is unlikely that enforcement actions by the FDA or the Department of Justice will abate significantly, since it will remain possible to pursue cases relating to fraudulent and misleading claims.

155 FDA, Guidance for Industry, Food and Drug Administration Staff: Mobile Medical Applications (February 2015); FDA, Guidance for Industry, Food and Drug Administration Staff: General Wellness: Policy for Low Risk Devices (July 2016).

Appendix 1

ABOUT THE AUTHORS

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Richard Kingham is a senior counsel in the firm of Covington & Burling LLP, where he serves as co-head of the life sciences industry group and the industry, regulatory and legislative practice 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 he 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).

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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.

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