

THE LIFE SCIENCES
LAW REVIEW

SEVENTH EDITION

Editor
Richard Kingham

THE LAWREVIEWS

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SEVENTH EDITION

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Editor
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Paul Howarth

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PREFACE

The seventh edition of *The Life Sciences Law Review* covers a total of 34 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged so as to describe requirements throughout the life cycle of a regulated product, from discovery to clinical trials, the marketing authorisation process and post-approval controls. Certain other legal matters of special interest to manufacturers of medical products – including administrative remedies, pricing and reimbursement, competition law, special liability regimes and commercial transactions – are also covered. Finally, there is a special chapter on international harmonisation, which is of increasing importance in many of the regulatory systems that are described in the national chapters.

The past year has seen a number of significant developments. After many years of negotiations and false starts, the United States and EU have finally begun to implement a programme of mutual recognition of inspections of drug manufacturing establishments, thus simplifying the shipment of drug products between the jurisdictions and freeing resources to carry out more inspections in third countries. In the meantime, the United States continues to debate whether to repeal the comprehensive medical care legislation enacted during the Obama administration, and is now considering measures to improve the transparency of pricing for prescription drugs. The United Kingdom is addressing changes to drug regulatory systems that must accompany the country's planned withdrawal from the EU, and drug and device manufacturers are actively planning for the effects of Brexit on their supply chains. The governments in India and China continue to consider changes in their regulatory systems for drugs and medical devices.

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

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

Richard Kingham
Covington & Burling LLP
Washington, DC
March 2019

EUROPEAN UNION

*Grant Castle and Robin Blaney*¹

I INTRODUCTION

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 European Union in this chapter can therefore often be read to encompass the entire EEA.

The European Medicines Agency (EMA) is the principal EU-level regulatory body for medicines, and its Committee for Medicinal Products for Human Use (CHMP) is responsible for the scientific evaluation of applications for EU marketing authorisations via the centralised procedure. It does so using the resources and expertise of the EU Member States. However, the European Commission is responsible for the granting of EU marketing authorisations and for defining policy in this area. It has produced detailed procedural guidance on a variety of topics, which is compiled in the Rules Governing Medicinal Products in the European Union.

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

Directive 2001/83/EC and other related EU directives are not directly effective in the EU Member States but have to be implemented into the national laws. This has resulted in national differences in the interpretation and enforcement of EU medicines legislation.

Medical devices are regulated by a series of EU directives: Active Implantable Medical Devices Directive 90/385/EEC,⁵ Medical Devices Directive 93/42/EEC⁶ and In

1 Grant Castle and Robin Blaney are partners at Covington & Burling LLP.

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.

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.

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 (IVDs). Directive 93/42/EEC applies to all other medical devices. A new Medical Devices Regulation (EU) 2017/745⁸ will replace Directive 93/42/EEC and Directive 90/385/EEC with effect from 26 May 2020, while a new In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746⁹ will replace Directive 98/79/EC with effect from 26 May 2022. 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.¹⁰ Article 2(2) of Directive 2001/83/EC formally incorporates this principle into EU law. It provides that:

In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this Directive [i.e., the medicines rules] shall apply.

EU legislation also lays down certain borderline principles. For example, Directive 93/42/EC contains specific principles for devices that are intended to administer medicines; devices and medicines that form single integral products, intended exclusively for use in the given combination and that are not reusable; and devices that incorporate, as an integral part, a substance that, if used separately, may be considered to be a medicine and that is liable to act upon the body with action ancillary to that of the device.

The European Commission also publishes various manuals on the scope of the application of EU legislation. For example, it has published a 'Manual [...] on the scope of application of the Cosmetics Regulation (EC) No 1223/2009' and a 'Manual on borderline and classification in the community regulatory framework for medical devices'. The Commission has also published concrete guidance on the borderline between medicines and medical devices in MEDDEV 2.1/3.

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 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

⁹ Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

¹⁰ C-112/89, *Upjohn Company and Upjohn NV v. Farzoo Inc and J Kortmann*.

National competent authorities, acting under the supervision of the national courts, must determine borderline issues case by case, taking into account all the characteristics of the product.

ii Non-clinical studies

Non-clinical studies to demonstrate the health or environmental safety of new chemical or biological substances must be conducted in compliance with the principles of good laboratory practice (GLP).¹¹ The principles of GLP provide a framework within which laboratory studies, both *in vitro* and *in vivo*, are planned, performed, monitored, recorded, reported and archived. Directive 2001/83/EC expressly provides that certain non-clinical (pharmaco-toxicological) studies of medicines must be carried out in conformity with GLP.

All tests on animals conducted in the EEA must be carried out in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes.¹² Directive 2010/63/EU anchors the principle of the ‘three Rs’ (to replace, reduce and refine the use of animals) in EU legislation. It also lays down minimum standards for housing and care, and regulates the use of animals through an evaluation requiring an assessment of pain, suffering, distress and lasting harm.

iii Clinical trials

Medicines

Clinical trials of medicines for human use are regulated under Directive 2001/20/EC,¹³ at least until Clinical Trial Regulation (EU) No. 536/2014¹⁴ becomes applicable, which is now likely to be in 2020. Clinical trials of medicinal products in human subjects require notification to, or authorisation by, the relevant Member State’s competent authority. In addition, a clinical trial of a medicinal product requires a favourable opinion by an ethics committee. The sponsor of a clinical trial, or its legal representative, must be based in the EEA.

Clinical trials must be conducted in accordance with internationally recognised principles of good clinical practice (GCP) and must comply with the Declaration of Helsinki (1996 version). Medicines used in clinical trials must be manufactured in accordance with standards of good manufacturing practice (GMP) and released by the holder of a manufacturer’s authorisation in the EEA.

11 Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances, as amended.

12 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.

13 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.

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, as amended.

A clinical trial may be undertaken only if provision has been made for, among other things, insurance or indemnity to cover the liability of the investigator and sponsor, and the receipt of informed consent from the trial subjects.

Companies must report all suspected serious unexpected adverse reactions to the competent authorities and to ethics committees within 15 days, and seven days in the event of a fatality, and must submit an annual listing of all suspected serious adverse reactions that occurred during that period.

Although the European Commission has previously consulted on specific rules for ‘non-commercial trials’, no such rules have been adopted.

Medical devices

Clinical investigations of medical devices are governed by Directive 93/42/EEC, Directive 90/385/EEC or Directive 98/79/EC, as applicable. The rules on clinical investigations of devices apply to studies of non-CE-marked devices, and to CE-marked devices if they are not CE-marked for the purpose being investigated. The directives do not recognise the concept of the ‘sponsor’; rather, the manufacturer of the device intended for use in the clinical investigation is responsible for ensuring compliance with the relevant requirements. Compliance with certain standards, such as EN ISO 14155:2011 on clinical investigations of devices, raises a presumption that the manufacturer complies with the applicable provisions under the Directives.

The study must be conducted in accordance with the latest version of the Declaration of Helsinki, which includes requirements for the informed consent of study subjects. Prior to conducting a study in the EEA, the manufacturer, or its authorised representative based in the EEA, must seek ethics committee approval and notify the device regulators in the relevant jurisdictions. All serious adverse events must be reported immediately to the competent authorities.

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

Medical Devices Regulation (EU) 2017/745 contains detailed new clinical trial rules for medical devices, modelled on those applicable to clinical trials of medicines, which will apply from 26 May 2020. Among other things, the new rules impose obligations on the sponsor of the investigation, and contain specific requirements for compensation and insurance for injuries to study subjects. The IVD Regulation (EU) 2017/746 contains similar rules for clinical trials of IVDs, and will apply from 26 May 2022.

iv Named-patient and compassionate use procedures

Medicines

Generally speaking, no medicinal product may be placed on the market in the European Union without a marketing authorisation. However, this is subject to a number of exemptions, including the ‘named-patient’ exception.¹⁵ The named-patient exemption covers the provision of unauthorised medicines with assumed benefits in situations where alternative treatment options are either non-existent, unsatisfactory or have been exhausted.

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

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

¹⁵ Article 5(1) of Directive 2001/83/EC.

- b* formulated in accordance with the specification of a doctor and for use by his or her individual patients on his or her direct personal responsibility; and
- c* to fulfil a 'special need'. This exception must be construed narrowly, and in accordance with the overarching principle underlying Directive 2001/83/EC that 'the protection of public health must take precedence over economic considerations', and that the precautionary principle should be applied so as to err in favour of protecting public health where there is any doubt about the efficacy or safety of a product.

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

making a medicinal product [...] available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product.

To qualify for compassionate use, the medicine must be either subject to a marketing authorisation application or be undergoing clinical trials. Member States must notify the EMA whenever they make use of the compassionate use procedure outlined in the Regulation.

EU Member States interpret the named-patient and compassionate use regimes differently, and application requirements and administrative procedures vary significantly in each jurisdiction.

Medical devices

A medical device must comply with the applicable essential requirements and bear a CE mark before it can be placed on the market in the EEA. There is no EU-wide 'named-patient' or 'compassionate use' exemption for medical devices, although a number of Member States operate similar schemes under national laws for medical devices. However, the EU medical devices directives permit the supply of 'custom-made devices' without a CE marking, provided they meet applicable requirements under the directives. A 'custom-made device' is 'any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his or her responsibility, specific design characteristics and is intended for the sole use of a particular patient'. The definition excludes mass-produced devices that need to be adapted to meet the specific requirements of the medical practitioner or any other professional user.

The manufacturer of a custom-made device must draw up a statement containing certain information, including:

- a* the manufacturer's name and address;
- b* a statement that the device is intended for exclusive use by a particular patient, 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, 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 European Union and, by extension, the EEA.

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

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

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

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

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

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

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

Medical devices

There is no pre-market government review of medical devices in the European Union unless the device also contains a medicine or a blood derivative. However, all medical devices placed on the market in the EEA must meet the relevant essential requirements set out in Directive 93/42/EEC, Directive 90/385/EEC or Directive 98/79/EC, as applicable, taking account of the intended purpose of the device.

More detailed requirements and technical specifications are set out in voluntary harmonised European standards. Compliance with harmonised standards is not mandatory, provided that the manufacturer demonstrates compliance with the essential requirements. However, compliance with applicable standards raises a presumption of conformity with the essential requirements.

Manufacturers must demonstrate that their devices comply with the relevant essential requirements through a conformity assessment procedure. The method for assessing conformity varies depending on the type and class of the product, but normally involves a combination of self-assessment by the manufacturer and a third-party assessment by a notified body, an independent and neutral entity appointed by a country to conduct the conformity assessment. As a general rule, clinical evidence is required to demonstrate that the device functions as intended and that it is safe. The clinical evidence may comprise studies on the device itself and, where appropriate, relevant data on equivalent devices from the peer-reviewed literature. Devices that conform to the essential requirements must bear a CE mark and can then be commercially distributed throughout the EEA.

For IVDs, custom-made devices and Class I devices, where the manufacturer self-declares conformity with the essential requirements, the manufacturer, or its authorised representative in the EEA, must register with the competent authority in the country in which it is established prior to placing any such product on the market.

The general principles for CE marking will remain the same under the new Medical Devices Regulation (EU) 2017/745 and the new IVD Regulation (EU) 2017/746, although there will be additional regulatory authority involvement in the conformity assessment of certain Class III and Class IIb devices, as well as devices incorporating medicinal substances or tissues and cells of human or animal origin.

vi Regulatory incentives

Medicines

A supplementary patent certificate, extending the term of a patent with respect to a particular medicinal product, will be granted if, in the EU Member State in which the application is submitted and at the date of the application:

- a* the product is protected by a basic patent in force;
- b* a valid marketing authorisation has been granted for the product;
- c* the product has not already been the subject of a certificate; and
- d* the marketing authorisation in question is the first marketing authorisation for that product.

The certificate takes effect at the end of the patent term for a period equal to that between the filing date of the basic patent and the date of first marketing authorisation for the product, reduced by five years, provided that the duration of the certificate cannot exceed five years.

Regulatory data exclusivity in Europe is independent of a product's patent position. New chemical entities approved on the basis of a complete, free-standing data package are entitled to eight years' regulatory data exclusivity from the date on which the product is first approved in the EEA. During that period, generic applicants cannot file applications referring to the innovator's safety and efficacy data. At the end of that eight-year period, generic applicants may file and the authorities may review applications. However, the innovator is granted a further two years of 'market exclusivity' before any generic product may launch. This period of market exclusivity can be extended by a further year if a new therapeutic indication that provides a significant clinical benefit is approved during the first eight years of data exclusivity. For applications prior to 20 November 2005 for centralised approvals, authorisation holders were entitled to 10 years' data exclusivity protection. For applications for national approvals prior to 30 October 2005, authorisation holders are entitled to 10 years' exclusivity in Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Sweden and the United Kingdom, but six years in every other EEA jurisdiction.

Regulation (EC) No. 141/2000 contains additional data exclusivity provisions for 'orphan medicinal products'.¹⁶ These are products intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EEA; or that without incentives is unlikely to generate sufficient return to justify the necessary investment. An orphan designation can be granted only if there is no satisfactory method of diagnosis, prevention or treatment of the condition authorised in the EEA, or if the product will be of significant benefit.

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

If a medicine is approved as a designated orphan medicine, the product will benefit from 10 years' market exclusivity during which regulators cannot accept applications for similar medicinal products for the same indication, unless they offer a significant clinical benefit (i.e., in terms of safety or efficacy). Similar medicinal products are those with the same or similar active moieties.

Regulation (EC) No. 1901/2006 also provides specific incentives for the development of products with paediatric indications.¹⁷ 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

¹⁷ 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.

prevent or minimise the risks associated with the product, and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation. Such risk-minimisation measures or post-authorisation obligations may include additional safety monitoring, more frequent submission of PSURs or the conduct of additional clinical trials or post-authorisation safety studies.

A new marketing authorisation is valid for five years. Upon renewal, the authorisation will become valid indefinitely, unless the competent authority concludes that safety grounds merit a further five-year fixed term.

Variation applications must be submitted to the competent authorities to make any amendments to marketing authorisations, the summary of product characteristics or package leaflet for the product, or the underlying dossiers.¹⁸ Variations are classified as Type IA, which should be implemented and then notified to the competent authorities, Type IB, which should be notified to the competent authorities in advance and may be implemented if the authorities have not objected within 30 days, and Type II, which require prior approval from the competent authority.

Transfers of marketing authorisation require the prior approval of the competent authority. The procedure and timing varies depending on the marketing authorisation approval procedure and the country, but in all cases an application will need to be submitted to the competent authority, with documentation provided by both the transferor and the transferee. There will usually be an agreed transition period of three to six months before the transfer is completed. Generally speaking, the competent authorities discourage transfer applications while renewal or variation procedures for the marketing authorisation are in train.

The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or lacks therapeutic efficacy, that the risk-benefit balance is not favourable or that its qualitative and quantitative composition is not as declared. Marketing authorisations may also be suspended, revoked or varied if incorrect information was submitted in the marketing authorisation application, the marketing authorisation has not been updated appropriately, or conditions of the marketing authorisation, such as commitments to perform post-authorisation safety studies, have not been satisfied.

Once a product has been launched in a jurisdiction, there is an obligation on marketing authorisation holders and their distributors to meet demand in that jurisdiction. EU law includes sunset clauses for marketed medicines. These provide that a marketing authorisation shall cease to be valid if the product is not placed on the market within three years of the marketing authorisation being granted, or if a previously marketed product is no longer actually present on the market for a period of three consecutive years. For centrally approved products, the sunset provisions would not be triggered provided the product was marketed in at least one EEA jurisdiction.

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

Medical devices

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

A device manufacturer must maintain a copy of the technical documentation underpinning its CE marking and make this available for inspection by national device regulators on request. The dossier should be kept up to date. If the applicable conformity assessment procedure has involved a notified body, any significant changes to the dossier or the manufacturer's quality system should be submitted to the notified body for approval and may require an update or reissue of any certificates of conformity issued by the notified body.

Notified body certificates of conformity are valid for a fixed duration. Throughout the term of the certificate, the manufacturer will be subject to periodic surveillance audits to verify continued compliance with the applicable requirements. In particular, there will be a new audit by the notified body before it will renew any certificate.

There is no set process for transferring ownership of notified body certificates of conformity. The transferor and transferee should contact the relevant notified body and agree on the process. If the transferee will be operating the same manufacturing process at the same facility, a new or updated certificate of conformity can be issued in a matter of days. If, however, the transferee will be manufacturing the device at a different facility, the notified body may need to conduct a new conformity assessment prior to issuing a certificate of conformity in the name of the transferee.

viii Manufacturing controls

Medicines

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

Medicinal products must be manufactured in accordance with the principles of GMP, set out in Directive 2003/94/EC¹⁹ 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.

19 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.

The procedure for transfers of manufacturing authorisations is a matter of national law, but the EU rules require manufacturers to notify the competent authority of any changes to the particulars in the manufacturing authorisation application, including in particular any change in the identity of the qualified person.

Active substances intended for use in the manufacture of medicinal products must have been manufactured in accordance with GMP. Importers, manufacturers and distributors of active substances must register with the competent authority in the EU Member State in which they are established and may be subject to an inspection. The registration application must identify the active substances and the premises concerned. The applicant must update the registration annually, and must notify the competent authority immediately of any changes that may have an impact on the quality or safety of the active substances.

Medical devices

There are no EU rules requiring approval of manufacturing facilities for medical devices. However, the conformity assessment procedures may involve a notified body assessment of the manufacturer's quality system. The manufacturer can demonstrate conformity with the requirements for the quality system by complying with the applicable harmonised standards, including ISO 13485:2012 on Standards for Quality Management System on Medical Devices. Any changes to the assessed quality system must be submitted to the notified body for approval.

ix Advertising and promotion

Medicines

Medicines advertising is defined broadly to include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products. It includes visits by sales representatives, the supply of samples, provision of gifts and hospitality, and sponsorship of meetings. Certain activities are specifically exempted from the medicines advertising rules, including responses to specific questions about a medicinal product and the dissemination of factual, informative announcements and reference material. These are only exempted if they are non-promotional in nature.

All medicines advertising must be consistent with the product's approved summary of product characteristics, factual, accurate, balanced and not misleading. Advertising of medicines pre-approval or off-label is prohibited. Advertisements to healthcare professionals must also be presented in a certain format, for example, indicating the brand and generic name of the relevant product with suitable prominence, and must contain certain minimum information about the product. Direct-to-consumer advertising of prescription medicines is prohibited, and there are strict rules governing the content of direct-to-consumer advertising of non-prescription medicines.

No gifts or other benefits may be given to healthcare professionals unless they are inexpensive and relevant to the practice of medicine. Any hospitality provided in conjunction with an event must be limited to the main purpose of the event and given only to healthcare professionals. There are also specific rules on the provision of samples to healthcare professionals.

Medicines advertising enforcement is largely on the basis of self-regulation. The European Federation of Pharmaceutical Industry Associations (EFPIA) has adopted a code

of practice on interactions with healthcare professionals,²⁰ a code of practice on interactions with patient organisations²¹ and a code of practice on the disclosure of transfers of value.²² Most national pharmaceutical industry associations have adopted their own codes of conduct based on the EFPIA codes.

Medical devices

Unlike the medicines rules, there are no harmonised European level rules governing the advertising and promotion of medical devices, resulting in Member States adopting somewhat divergent approaches to the regulation of medical device advertising. However, the general advertising rules requiring that advertisements are substantiated, factual, balanced and not misleading apply to medical device advertising.

Medical devices and IVDs may be displayed at trade shows and exhibitions before they are CE-marked and placed on the market, provided that they are not used for their intended medical or diagnostic purpose and that a sign makes clear that the devices cannot be marketed or put into service until they have been made to comply with the relevant rules.

x Distributors and wholesalers

Medicines

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

Traditionally, most Member States have taken the view that wholesale distribution only takes place where the products are handled physically; mere paper transactions have not been regarded as wholesaling. In some Member States, however, the authorities interpret the terms 'procuring' and 'supplying' to cover the act of buying and selling medicines (i.e., the transfer of legal title), even if the company never physically handles the product. This interpretation is becoming more prevalent, following references in Directive 2011/62/EU to 'wholesale distributors, whether or not they physically handle the medicinal products'.²³

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

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

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

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

23 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.

holder must also have at its continuous disposal the services of an appropriately qualified person, who is responsible for ensuring that a quality management system is implemented and that the company complies with the principles of good distribution practice (GDP).

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

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

Medical devices

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

xi Classification of products

Medicines

Competent authorities must classify medicines as prescription-only or non-prescription but are entitled to further subdivide this classification. For example, competent authorities can, if they wish, classify prescription-only medicines as being subject to 'special medical prescription' (e.g., controlled substances under the UN Conventions and other substances with a risk of abuse or dependency) or 'restricted prescription' (e.g., products that can only be used in a certain setting or by certain specialists). Some Member States also subdivide the classification of non-prescription medicines to allow for products that can only be supplied under the supervision of a pharmacist, over-the-counter products and products for general retail sale.

Medicinal products must be classified as prescription-only if they:

- a* are likely to present a danger either directly or indirectly if utilised without medical supervision;
- b* are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health;
- c* contain substances or preparations, the activity or adverse reactions of which require further investigation; or
- d* are normally prescribed by a doctor to be administered parenterally.

The applicant for a marketing authorisation has to identify in the initial application a proposed classification of the product. However, the classification is ultimately decided by the competent authorities when they grant the marketing authorisation.

The marketing authorisation holder can apply to have the product reclassified in light of new information (such as significant post-marketing experience with the product). If the change of classification has been authorised on the basis of significant preclinical tests or clinical trials, the competent authorities may not refer to the results of those tests for one year when examining reclassification applications by other marketing authorisation holders.

Medical devices

Medical devices are classified as Class I, IIa, IIb or III, but this is for the purposes of determining the appropriate conformity assessment procedure. Other than the differentiation between active implantable medical devices, *in vitro* diagnostic devices and other medical devices, there are no EU-harmonised rules that govern the classification of medical devices for the purposes of prescription or sale. Manufacturers often choose to classify devices as being for professional use only.

xii Imports and exports

Medicines

An entity importing medicinal products, including bulk product, from countries outside the EEA must hold a manufacturing authorisation. The holder of a manufacturing authorisation must retain the services of a qualified person, who will be responsible for ensuring that any imported product has undergone appropriate quality control testing prior to batch release onto the EEA market.

EU rules on the import of active pharmaceutical ingredients (APIs) require that APIs imported into the EEA must be manufactured in compliance with standards equivalent to EU GMP. Since July 2013, the competent authority of the exporting country has been required to confirm this compliance in writing. The written confirmation must accompany the imported APIs.

The definition of 'wholesale distribution' in Directive 2001/83/EC includes the export of medicinal products. An entity exporting medicinal products out of the EEA must therefore hold a wholesale distribution authorisation or manufacturing authorisation. As part of their import requirements, certain countries require medicinal products to be accompanied by an export certificate. These certificates confirm that the product or manufacturer to which the certificate relates has met statutory requirements in the country of export. Export certificates can take one of several forms, including a certificate of a pharmaceutical product, or a certificate of manufacturing status. The exact procedure for obtaining these certificates differs according to the laws of the country of export.

Medical devices

There are currently no EU-harmonised rules that govern the import or export of medical devices. When effective, Regulation (EU) 2017/745 and Regulation (EU) 2017/746 will introduce new obligations for entities importing medical devices from countries outside the EU, including verifying any device they place on the market is in conformity with the standards of the applicable regulations.

xiii Controlled substances

The United Nations (UN) Single Convention on Narcotic Drugs (1961) and the UN Convention on Psychotropic Substances (1971) codify internationally applicable control measures to ensure the availability of narcotic drugs and psychotropic substances for medical and scientific purposes. The individual Member States of the EU are all signatories to these UN Conventions. All signatories have a dual obligation to ensure that these substances are available for medical purposes and to protect populations against abuse and dependence.

The UN Conventions require signatories to require all persons manufacturing, trading (including exporting and importing) or distributing controlled substances to obtain a licence

from the relevant authority. Each individual export or import of a controlled substance must also be subject to an authorisation. Before the relevant authority can issue an export authorisation for a particular shipment, the exporter must provide the authority with a copy of the import authorisation issued by the relevant authority of the importing country.

xiv Enforcement

Medicines

The EMA is responsible for coordinating inspections to verify compliance with GCP, GMP, GLP and pharmacovigilance requirements for all centrally approved products. The EMA does not have any inspectors itself, but instead relies on inspectors from the national competent authorities to conduct inspections on its behalf. If an inspection identifies any non-compliance, typically corrective actions would be agreed with the marketing authorisation holder or other company inspected and, provided these were implemented, no further action would be taken. If the non-compliance gives rise to safety concerns about a particular product, the EMA could recommend to the European Commission that the authorisation be suspended or revoked.

In serious cases of non-compliance for centrally approved products, the European Commission could impose sanctions under the EU Penalties Regulation.²⁴ The European Commission can fine the marketing authorisation holder up to 5 per cent of the holder's EU turnover in the preceding business year. If the infringement continues, the European Commission may impose further daily fines of up to 2.5 per cent of the holder's average daily EU turnover in the preceding business year, until the infringement ceases. Non-cooperation with the European Commission's investigation of the infringement attracts an additional fine of 0.5 per cent of the holder's Community turnover in the preceding business year.

The national competent authorities are responsible for conducting inspections for products that are not centrally approved and in relation to manufacturing and distribution authorisations. The sanctions for non-compliance are determined by national laws.

Medical devices

Manufacturers of medical devices are not subject to regular inspections by competent authorities, although notified bodies will conduct surveillance audits as part of the ongoing conformity assessment procedures for many devices. National competent authorities are responsible for enforcing the medical device rules in their jurisdiction and sanctions are determined by national laws. Safeguard measures in the medical devices directives also allow Member States to restrict or prohibit the marketing of medical devices or to withdraw devices from the market where a device, although correctly marketed and used, may compromise the health and safety of patients, users or others.

24 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.

III PRICING AND REIMBURSEMENT

i Medicines

EU Member States are responsible for establishing and organising of their national social security schemes, including healthcare policies to promote the financial stability of their healthcare insurance systems.²⁵ 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/EEC²⁶ lays down a general procedural framework to increase the transparency of national pricing and reimbursement measures to limit the potential impact on these measures on the internal market for medicinal products. This Directive does not harmonise national pricing and reimbursement measures in the European Union, nor does it identify substantive criteria on which Member States must base their pricing and reimbursement decisions. This is in line with the limited competence of the European Union in the field of management of healthcare resources and the principle of minimum interference in the organisation by Member States of their domestic social security policies, as confirmed by European case law. For example, in *ABPI v. MHRA*,²⁷ the CJEU confirmed that public bodies forming part of a national public health service are not precluded from implementing prescribing incentive schemes that offer financial inducements to doctors to prescribe or switch patients to generic medicines, to achieve cost savings provided that the schemes comply with Directive 89/105/EEC.

Directive 89/105/EEC lays down three key requirements with respect to national pricing and reimbursement decisions: (1) decisions must be made within a specific time frame (90 to 180 days); (2) decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria; and (3) decisions must be open to judicial appeal at national level.

ii Medical devices

There are no EU-harmonised rules governing the pricing and reimbursement of medical devices; this remains the competency of Member States. Directive 89/105/EEC does not apply to medical devices.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

i Medicines

Under EU law, it is possible to challenge directly, and in some instances indirectly, the decisions of the European Commission and EMA concerning medicinal products. Article 263 of the

25 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.

26 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.

27 *The Queen, on the application of Association the British Pharmaceutical Industry v. Medicines and Health-care Products Regulatory Agency* (Case C-62/09) [2010] ECR I-3603 (*ABPI v. MHRA*).

Treaty on the Functioning of the European Union (TFEU) permits direct challenges to the legality of EU acts and allows the EU courts²⁸ to review the legality of acts of EU institutions, bodies and agencies that are intended to produce legal effects against third parties.

For an EU act or decision to be successfully challenged, an application must satisfy certain basic requirements, including that the relevant act and body must be amenable to review, the applicant must have standing, and the application must be brought within the relevant time limit.

Article 263 TFEU sets out four specific grounds under which the EU courts may review an EU act: lack of competence, infringement of an essential procedural requirement, infringement of the TFEU provision or any rule of law relating to its application, and misuse of power. The EU courts have used these grounds as a framework through which to develop general principles and grounds for review under EU law by drawing on concepts found within national legal systems. These include fundamental rights (e.g., right to be heard, duty to give reasons, consultation and participation), proportionality, legitimate expectations, legal certainty, non-discrimination, transparency and, more recently, the precautionary principle. The same potential grounds of review apply to indirect challenges to EU acts under Article 267 TFEU.

Article 267 TFEU allows any court or tribunal of a Member State to make a preliminary reference to the CJEU in cases concerning: 'the interpretation of the Treaties' or 'the validity and interpretation of acts of the institutions, bodies, offices or agencies of the Union'. Thus, if an EU act addressed to a Member State or national competent authority requires specific action, an individual affected by that action may challenge the validity of the decision on which the action is based via the national courts.²⁹ Under Article 267(3) TFEU, a national court or tribunal has an obligation to make a preliminary reference to the CJEU where the court or tribunal considers that a decision on the question of EU law raised is 'necessary to enable it to give judgment'. The *Foto-Frost* doctrine³⁰ also requires that if a national court or tribunal entertains serious doubts as to the validity of an EU act, it must make a preliminary reference, as the CJEU has exclusive jurisdiction to declare EU acts to be unlawful.

Appeals and judicial reviews of decisions by national competent authorities are governed by the rules of the specific EU Member State.

ii Medical devices

The general administrative principles outlined in Section IV.i apply to challenges of decisions or acts of EU institutions, bodies or agencies that concern medical devices, such as an unfavourable decision by the EMA in relation to a medical device incorporating a medicine or a blood derivative. Appeals and judicial reviews of decisions by national competent authorities are governed by the rules of the specific EU Member State.

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

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

30 *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,³¹ if they are promotional.

If a communication is a genuine attempt to provide meaningful and relevant information that would assist the payer in making pricing, reimbursement or formulary or other positive listing decisions, then it is unlikely to be deemed promotional, even if the outcome might lead to an increased prescription or use of a particular product. On the other hand, any communication or activity intended simply to raise the profile of a product in the eyes of a payer may be promotional unless it contributes meaningfully to the payer's consideration of a medicinal product for pricing, reimbursement or formulary-listing purposes.

Companies should take particular care when communicating with non-healthcare professional representatives of payers. If communication with such individuals is promotional, the company may contravene the general EU prohibition on the advertising of prescription-only medicines direct to the public, as some medicine advertising regulators treat non-healthcare professional administrative staff within hospitals or health service providers as consumers. The general principle, therefore, is that information about medicines sent to payers should be non-promotional. Non-promotional information, as with promotional information, must be fair, balanced, capable of substantiation and not misleading.

Directive 2001/83/EC also provides rules restricting the supply of medicine samples, promotional aids, gifts and hospitality to healthcare professionals. There is a general prohibition on inducements to prescribe and companies may only supply inexpensive gifts to healthcare professionals. Companies may provide reasonable hospitality to healthcare professionals provided that it is strictly limited to the main purpose of a promotional or scientific meeting and never extended to persons other than healthcare professionals. Since most healthcare professionals in the EEA are also government employees or contractors, companies must also consider anti-bribery laws.

The provisions of Directive 2001/83/EC are supplemented at EU level by the EFPIA Code on the promotion of prescription-only medicines to, and interactions with, healthcare professionals (the EFPIA HCP Code), which provides additional guidance to companies on problematic compliance areas, including gifts, sponsoring of healthcare professionals and hospitality.³²

ii Medical devices

There is no EU harmonised legislation that governs the interaction of medical device companies with prescribers and payers. MedTech Europe, the European medical device trade association, however, has published the Medtech Europe Code of Ethical Business Practices that provides detailed guidance on this issue.

The MedTech Europe Code is intended to assist medical device companies to comply with general anti-bribery and corruption law concepts by setting minimum standards that companies and their representatives should adhere to when interacting with healthcare or

31 See Section II.ix.

32 EFPIA HCP Code, updated June 2014.

other government officials. However, the MedTech Europe Code is not designed to supplant or supersede national laws or other professional or other business codes (including company codes), which may have stricter requirements.

The MedTech Europe Code provides specific guidance on some key compliance areas, including gifts, engaging healthcare professionals as consultants, sponsoring scientific meetings and the level of subsidy, entertainment and hospitality associated with such events. The provisions of the MedTech Europe Code are enforced through a self-regulatory regime operated mainly at national level. Where no dispute resolution mechanism exists under a national applicable code, the MedTech Europe Compliance Panel may rule on the dispute. MedTech Europe members should require that third-party intermediaries, who interact with healthcare professionals in connection with the sale, promotion or any other activity involving their products, comply with standards equivalent to the MedTech Europe Code.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

i Medicines

There is no pan-European scheme to compensate individuals injured by medicinal products. However, EU legislation on clinical trials requires the provision of an indemnity or insurance to cover the liability of the investigator or sponsor for the death or study-related injuries of subjects.³³

Directive 85/374/EEC³⁴ harmonises the EU rules on strict liability for defective products and provides that a 'producer' is liable for damage 'caused by a defect in its products'. A product is considered defective when it 'does not provide the safety which a person is entitled to expect'. In defining the term 'producer', Directive 85/374/EEC seeks to ensure that an injured party will always have someone within the European Union against whom they can bring a claim. The term includes any manufacturer of finished products, raw materials or parts within the European Union; importers of products from outside the European Union; and any person who places their name or mark on a product (which would include a product's marketing authorisation holder). It also includes any intermediate suppliers of products, which could include distributors, retailers, healthcare professionals and their employers. However, intermediate suppliers are only liable under the Directive if they fail to identify any other producer further up the supply chain within a reasonable period.

Separately, Directive 2001/83/EC provides that in the event of a public health emergency (e.g., an influenza pandemic), companies should not have civil or administrative liability in respect of the supply or use of unapproved medicinal products or use of approved medicines outside their authorised indications, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. The effect of this provision is that, in circumstances where a national competent authority recommends or requires the use of a medicinal product pre-approval or off-label in response to an emergency

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

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.

threat, the company has statutory immunity from liability in negligence or contract for the consequences of that use. Strict liability under Directive 85/374/EEC, however, will remain as a cause of action for persons injured by the product.³⁵

ii Medical devices

There is no EU-level scheme or system to compensate individuals injured by medical devices, but the principles of strict liability under Directive 85/374/EEC apply to devices.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The European Commission (the Commission) has continued to focus on patent settlement agreements. In 2013, the Commission found that Lundbeck's settlement agreements relating to its citalopram drug restricted competition by object and infringed Article 101 TFEU.³⁶ Shortly thereafter, the Commission found that Servier's reverse payment patent settlement agreements restricted competition both by object and by effect (the Commission also concluded that Servier's commercial strategy was an abuse of dominance under Article 102 TFEU).³⁷ The General Court delivered its judgment in *Lundbeck* in September 2016 confirming the Commission's decision and upholding the fines that the Commission imposed on Lundbeck and the generic companies (totalling €146 million).³⁸ Lundbeck and the generic companies have appealed the General Court's judgment to the European Court of Justice. Conversely, the General Court ruled in *Servier* that the Commission had failed to prove the relevant market was limited to the drug perindopril, and therefore did not uphold that Servier had abused its dominant position.³⁹

Pay-for-delay agreements have also attracted regulatory scrutiny from the national competition authorities (NCAs). The United Kingdom's Competition and Markets Authority (CMA) issued its first pay-for-delay infringement decision on 12 February 2016, fining GlaxoSmithKline (GSK), Generics UK Limited (GUK), Merck KGaG (GUK's former parent company), Actavis UK Limited, Xellia Pharmaceuticals ApS and Alpharma LLC a total of £45 million for delaying market entry of generic versions of GSK's anti-depressant Seroxat (paroxetine) in the United Kingdom.⁴⁰ The decision has been appealed to the UK Competition Appeal Tribunal, which has made a referral to the CJ.

NCAs have also begun to scrutinise excessive pricing. In October 2016, the Italian Competition Authority fined Aspen over €5 million for excessive pricing of its anti-cancer drugs Alkeran (melphalan), Leukeran (chlorambucil), Purinethol (mercaptopurine) and Tioguanine (thioguanine).⁴¹ Shortly thereafter, in December 2016, the CMA found that Pfizer and Flynn Pharma had abused their dominant positions by charging excessive and unfair prices for phenytoin sodium capsules (drugs used to treat epilepsy) in the United

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

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].

39 Case T-691/14 *Servier v Commission* [2018]

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

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

Kingdom.⁴² An appeal was brought to the UK Competition Appeal Tribunal, which ruled against the CMA's decision. The CMA has received permission to appeal the UK Competition Appeal Tribunal's decision to the UK Court of Appeal. At least two other investigations relating to excessive and unfair prices charged are under way in the United Kingdom. In a related vein, public health authorities have increasingly litigated, seeking compensation for overspending as a result of alleged illegal behaviour by pharmaceutical companies.

Several other types of behaviour have been investigated and continue to be scrutinised by the NCAs. Market sharing has remained on the agenda, with the Italian *Lucentis/Avastin* case having been referred by the Italian Council of State to the ECJ in March 2016. Beyond this, at least one NCA is investigating whether cross-distribution arrangements amount to market sharing. Finally, while the Commission concluded its inquiry into the pharmaceutical sector in 2009, a number of NCAs have since pursued sector inquiries (e.g., the Italian Competition Authority announced on 25 May 2016 the results of its sector inquiry into 'Markets for vaccines of human use' and the Danish Competition Council published its analysis on competition between pharmaceutical wholesale suppliers in October 2016).

ii Transactional issues

EU competition law prohibits agreements that have as their object or effect the prevention, restriction or distortion of competition within the European Union. The European Commission has issued a series of block exemptions, which grant an automatic exemption to certain categories of agreement, provided that the market shares for the products covered by the agreement are below the specified threshold, and the agreement does not contain any 'hard-core' restrictions, such as resale price maintenance or prohibitions on unrelated research and development. Two block exemptions are particularly relevant to in-licensing and collaboration agreements in the pharmaceutical and medical device sectors: the R&D Block Exemption,⁴³ which provides for a market share threshold of 25 per cent in the case of agreements involving competitors, and the Technology Transfer Block Exemption,⁴⁴ which provides for a market share threshold of 20 per cent in the case of agreements involving competitors and 30 per cent for those involving companies that are not competitors.

Since the approval of the competent authorities is required to transfer marketing authorisations and other pharmaceutical licences, including manufacturing authorisations, medicinal product divestments and other transactions structured as asset deals need to take into account the delay between agreeing to transfer the product or business and completion of the regulatory procedures necessary to give effect to the transfer. This delay can be many months or even years, so it is common for parties to enter into transition services agreements, determining how the parties will market, distribute and perform the regulatory tasks associated with the products during this transitional period.

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

43 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.

44 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.

VIII CURRENT DEVELOPMENTS

In May 2017, the EU adopted new legislation to revise the regulatory framework for medical devices. Directives 90/385/EEC and 93/42/EEC will be repealed and replaced by Regulation (EU) 2017/745 with effect from 26 May 2020, while Directive 98/79/EC will be repealed and replaced by Regulation (EU) 2017/746 with effect from 26 May 2022. Importantly, unlike directives that must be implemented into national laws, the regulations will be directly applicable in all EU Member States. The regulations do not set out a radically new system but clearly envisage, among other things, stricter controls of medical devices, including strengthening of the conformity assessment procedures, increased expectations as regards clinical data for devices and pre-market regulatory review of high-risk devices. The regulations also envisage greater control over notified bodies and their standards, increased transparency, more robust device vigilance requirements and clarification of the rules for clinical investigations. Under transitional provisions, medical devices or IVDs with notified body certificates issued under one of the directives prior to the effective date of the applicable regulation may continue to be placed on the market for the remaining validity of the certificate, until 27 May 2024 at the latest. There are no transitional provisions for devices or IVDs whose conformity assessment has not involved a notified body, so unless the devices have been CE marked in accordance with the new requirements of the applicable regulation, such devices may no longer be placed on the market after the effective date of the applicable regulation. However, at the time of writing, only one notified body has been designated under Regulation (EU) 2017/745. We are not aware of any notified body that has yet been designated under Regulation (EU) 2017/746, meaning in practice it is not yet possible to bring an *in vitro* medical device to market, and likely to be difficult to quickly bring any other medical devices to market under the new regulations if notified body input is necessary.

The Clinical Trials Directive 2001/20/EC is also to be repealed and replaced with a Regulation on clinical trials on medicinal products for human use, which was adopted in early 2014.⁴⁵ The Clinical Trials Regulation will revise current rules, in particular as regards the authorisation procedures, introduce new principles, such as co-sponsoring, and increase clinical trial transparency.

The Regulation has the same scope as Directive 2001/20/EC but amends some existing definitions (clinical trial, non-interventional clinical trial) and introduces new definitions, such as ‘clinical study’, ‘low-intervention clinical trial’ and ‘auxiliary medicinal product’. The new rules show a risk-based approach to clinical trials and distinguish between low-intervention clinical trials and other clinical trials. The Regulation also introduces a new streamlined single authorisation procedure via an EU portal linked to an EU database managed by the Commission, although an ethics committee review will still be needed in each Member State in which the trial will be conducted. The EU database will provide public access to protocol information and clinical trial results, suggesting greater clinical trial transparency in the European Union. Overall, the new regime should reduce administrative costs for industry, better reflect the variety of clinical trials, and increase clinical-trial transparency. The new Regulation is now expected to come into effect in 2020, once the new EU portal and database are fully operational. There will be a transitional period of three years, during which the rules under the Clinical Trials Directive will continue to apply to existing clinical trials.

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.

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 public the data submitted in support of marketing authorisation applications once a product has been approved, subject to the deletion of personal data. The EMA has recently placed online clinical trial data for the first products subjected to its proactive release policy.

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.

ABOUT THE AUTHORS

GRANT CASTLE

Covington & Burling LLP

Grant Castle is a partner in the London office of Covington & Burling LLP, practising in the areas of life sciences regulatory law, with an emphasis on pharmaceutical and medical device regulation and associated compliance issues. He has assisted clients with a wide range of regulatory and compliance issues and has participated in formal and informal advertising, commercial practices, good manufacturing practices, good clinical practices, drug safety and pharmacovigilance proceedings before the European Medicines Agency, national authorities, courts and self-regulatory bodies.

He speaks and lectures frequently on compliance issues in both the pharmaceutical and medical device areas at the University of Surrey, the University of Wales and Cranfield University. He received a BSc in chemistry with first-class honours from Imperial College of Science, Technology and Medicine in London in 1991 and a PhD in organic chemistry from Trinity College, University of Cambridge in 1994.

ROBIN BLANEY

Covington & Burling LLP

Robin Blaney is a partner in the life sciences practice of Covington & Burling LLP, dividing his time between the firm's London and Brussels offices. He advises pharmaceutical, biotechnology, medical device and cosmetic manufacturers and trade associations on a wide range of regulatory, compliance, transactional and legislative matters, as well as the full range of commercial agreements that span the product life cycle in the life sciences sector. His expertise includes clinical trial agreements, manufacturing and supply agreements, distribution and other marketing agreements, regulatory services agreements and tenders. He has particular experience of structuring and documenting transitional arrangements relating to product acquisitions and EU distribution structures. Mr Blaney writes and speaks regularly on subjects such as medical device regulation, pharmacovigilance and clinical trials.

COVINGTON & BURLING LLP

265 Strand
London WC2R 1BH
United Kingdom
Tel: +44 20 7067 2000
Fax: +44 20 7067 2222
gcastle@cov.com
rblaney@cov.com

www.cov.com



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