THE LIFE SCIENCES LAW REVIEW

SEVENTH EDITION

Editor
Richard Kingham

THE LAWREVIEWS

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This article was first published in March 2019
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Published in the United Kingdom
by Law Business Research Ltd, London
87 Lancaster Road, London, W11 1QQ, UK

www.TheLawReviews.co.uk

ISBN 978-1-83862-011-0

Printed in Great Britain by
Encompass Print Solutions, Derbyshire
Tel: 0844 2480 112

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ACKNOWLEDGEMENTS

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

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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

Chapter 33

UNITED KINGDOM

Grant Castle and Sarah Cowlishaw[1]

This chapter summarises the UK regimes governing medicines and medical devices. Since, at time of writing, the United Kingdom is still an EU Member State and has implemented the EU medicines and medical devices regimes, we will not repeat much of the substantive content of the European Union chapter. We will focus on unique features of the UK regimes and the chapter should be read in conjunction with the European Union chapter. As noted below, the regulatory position in the United Kingdom is likely to change significantly in the near future as a result of the United Kingdom's decision to leave the EU (Brexit), but the precise impact on the regulation of medicines and medical devices in the United Kingdom is unclear at this stage.

I INTRODUCTION

Medicines for human use are regulated primarily by the Human Medicines Regulations 2012 (the Medicines Regulations).[2] The Medicines Regulations implement Directive 2001/83/EC[3] 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[4] – 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 Directives[6] into UK law (pending the implementation of Regulation (EU) 2017/745[7] on Medical Devices, and Regulation (EU) 2017/746[8] on *In Vitro*

1 Grant Castle is a partner and Sarah Cowlishaw is an associate at Covington & Burling LLP.

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

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 The Medicines Act 1968 (Chapter 67), 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.

7 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.

8 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.

Diagnostic Medical Devices, which both entered into force on 25 May 2017 and, following a transition period, are anticipated to apply fully as of 26 May 2020 and 26 May 2022 respectively. For further details, see the European Union chapter).

The Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the Department of Health and Social Care, is the United Kingdom's national competent and enforcement authority for the regulation of both medicinal products and medical devices. However, the 'licensing authority' is responsible for the granting, renewal, variation, suspension and revocation of licences, authorisations, certificates and registrations under the Medicines Regulations. The licensing authority comprises either or both of the Secretary of State for Health and the Minister for Health, Social Services and Public Safety, acting on the advice of the MHRA. Likewise, the Secretary of State exercises certain powers under the Medical Devices Regulations. The 'enforcement authority' comprising relevant ministers is responsible for authorising inspectors and for bringing enforcement actions.

II THE REGULATORY REGIME

i Classification

The MHRA has primary responsibility for determining whether borderline products are medicinal products or medical devices. It does so case by case, having regard to the legal definition of a medicinal product and a medical device set out in EU law and implemented in the United Kingdom.

The MHRA's Borderline Section considers each product on its merits and any information that may have a bearing on the product's status; for example, its mode of action, pharmacological properties of the product's ingredients, the claims made for the product, whether there are any similar regulated products on the market, and how the product is presented through labelling, packaging, promotional literature and advertisements.

The Borderline Section provides informal, written advice on classification in response to specific enquiries about potential borderline issues. However, it will also exercise its enforcement powers following complaints about a particular product or based on its review of a product. In the latter scenario, the Borderline Section has a range of powers available to it to require removal of the product from the market (e.g., because it is an unlicensed medicine or a medical device that does not conform to the Medical Devices Regulations). However, the MHRA's usual approach is to serve a provisional determination notice advising that the MHRA considers the product a medicinal product or a medical device. A provisional determination must set out the reasons for the Agency's position and the options available to the person served with the notice should that person disagree with the determination. The options include the right to request an independent (advisory) review panel to review the determination and associated documentation. After considering the panel's advice, the MHRA makes a final determination. There is no right of appeal against a final determination, other than via the courts and judicial review. It is a criminal offence not to comply with the conditions of a final determination.

ii Non-clinical studies

The Animals (Scientific Procedures) Act 1986[9] implemented Directive 2010/63/EU[10] into UK law from 1 January 2013. It permits research involving animals only in premises licensed by the Home Office, by appropriately qualified staff and in accordance with procedures designed to minimise animal pain and suffering.

The Good Laboratory Practice Regulations 1999[11] transpose Directive 2004/10/EC[12] into UK law. They require that all animal studies be conducted in accordance with sound standards of good laboratory practice. These standards reflect the Organisation for Economic Co-operation and Development requirements.

iii Clinical trials

Medicines

Clinical trials of medicines for human use are regulated under the Medicines for Human Use (Clinical Trials) Regulations 2004 (the Clinical Trial Regulations),[13] which implement Clinical Trials Directives 2001/20/EC[14] and 2005/28/EC[15] into UK law. Clinical trials of medicinal products in humans are generally only permitted if the MHRA has granted a clinical trial authorisation (CTA) and an ethics committee has issued a favourable opinion. A CTA is not required for 'non-interventional' trials, but the definition of a non-interventional trial is very narrow. It covers only trials involving approved medicines used on-label where there are no changes to routine medical care, including prescribing decisions or additional monitoring or information-gathering procedures.

CTA approval process

Applicants for a CTA must first have obtained a EudraCT number and must then submit the relevant application form, the investigational medicinal product dossier (IMPD) and supporting documentation to the MHRA. The MHRA aims to assess applications within 30 days from receipt of a valid application, but there are accelerated review times for certain studies. The Agency aims to review applications for Phase I trials in healthy volunteers within 14 days and there is also a 14-day notification scheme for clinical trials that involve an authorised medicinal product and meet certain conditions.

9 The Animals (Scientific Procedures) Act 1986 (Chapter 14), 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 The Good Laboratory Practice Regulations 1999 (SI 199/3106), as amended.

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

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

14 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.

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

Applications for a positive ethics committee opinion are usually considered in parallel with applications for a CTA and are made via the National Research Ethics Service, which is part of the Health Research Authority. Following the adoption of the new Clinical Trials Regulation (EU) No. 536/2014,[16] the United Kingdom is currently working towards the establishment of a system for the granting of a single approval for a clinical trial, encompassing both MHRA and ethics committee review.

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

Sponsors must submit reports of suspected unexpected serious adverse reactions (both United Kingdom and non-United Kingdom) relevant to a UK trial to the MHRA and the relevant research ethics committee. There is also a requirement to submit annual safety reports. They must provide investigators with information on safety issues relevant to whether they enrol patients or allow them to continue with the study.

The Clinical Trial Regulations require sponsors to provide adequate insurance or indemnity to cover liabilities that may arise in relation to the clinical trial. The MHRA expects that a sponsor's insurance policy or indemnity will reflect the form recommended by the Association of the British Pharmaceutical Industry (ABPI) Clinical Trial Compensation Guidelines. The ABPI has also published specific insurance and compensation guidelines for Phase I clinical trials.

Assessment process

The MHRA will assess the application within 30 days of receipt of a valid submission unless the applicant indicates that the study is eligible for the shorter 14-day assessment time.

Medical devices

Clinical investigations of medical devices are governed by the Medical Devices Regulations. In addition to obtaining research ethics committee approval, the manufacturer must notify the MHRA prior to the conduct of a clinical investigation involving a non-CE-marked medical device. The MHRA assesses notifications within 60 days of receipt of a complete notification.

There is a different process for performance evaluation of a non-CE-marked *in vitro* diagnostic medical device (IVD). Manufacturers must draw up a declaration and follow the procedure set out in Annex VIII of the IVD Directive 98/79/EC and must also register details of the IVD for performance evaluation with the MHRA.

Manufacturers must report serious adverse events involving a device under clinical investigation to the MHRA. The MHRA requires manufacturers to provide insurance for subjects in clinical investigations of medical devices.

16 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.

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[17] applies directly in the United Kingdom.

The MHRA's Early Access to Medicines Scheme (EAMS) provides another exemption to the requirement for a medicinal product to have a marketing authorisation prior to being placed on the market. The EAMS has been adopted to enable patients with 'life-threatening or seriously debilitating conditions' to have early access to medicines that have yet to receive a marketing authorisation. The process for joining the scheme involves a two-stage evaluation by the MHRA: step I is the promising innovative medicine (PIM) designation, and step II is the EAMS scientific opinion. For medicines to qualify for the EAMS, they must meet the following criteria:

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

Medical devices

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

The use of an individual non-complying medical device, for a single named patient, is permitted only in exceptional circumstances; for example, where no alternative CE-marked devices are available or where it has been demonstrated that the morbidity or mortality of

17 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.

patients is significantly reduced with the use of the device in question as compared to those using alternative available treatment. The MHRA requires that an application be made for each patient, which includes information from the manufacturer and relevant clinician.

v Pre-market clearance

Medicines

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

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

Medical devices

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

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

vi Regulatory incentives

Medicines

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

The additional data exclusivity provisions for 'orphan medicinal products' and for products with paediatric indications developed in accordance with an approved paediatric investigation plan under Regulation (EC) No. 141/2000[18] and Regulation (EC) No. 1901/2006,[19] respectively, apply directly.

In the United Kingdom, the Intellectual Property Office is responsible for granting supplementary patent certificates for medicinal products that meet the criteria under Regulation (EC) No. 469/2009.[20]

Medical devices

UK legislation does not provide specific regulatory exclusivity periods for medical devices. A device may be protected by a UK patent if it satisfies the requirements for patentability under the Patents Act 1977.[21] A UK patent is granted initially for four years and is renewable annually thereafter up to a maximum of 20 years from the filing date of the patent application.

vii Post-approval controls

The United Kingdom's post-approval controls over marketing authorisation holders for medicines and manufacturers of medical devices closely mirror the EU requirements.

Transfer of marketing authorisations for medicines

Marketing authorisation holders may apply to the MHRA to 'transfer' ownership of their marketing authorisations to third parties. If satisfied that the recipient is suitable to hold the approval, the MHRA will grant the transferee a new marketing authorisation. It will usually also allow the original authorisation to remain in force for a transitional period. This avoids interruptions in supply by allowing a product in the name of the original authorisation holder to be placed on the market until the new product is widely available.

Revocation, suspension or variation of marketing authorisations

The licensing authority, acting through the MHRA, has the power to revoke, suspend or vary a marketing authorisation. Companies that are unhappy with the proposal have the right to appeal to the appropriate committee, then to an independent review panel in accordance with Schedule 5 of the Medicines Regulations. However, these procedures do not apply when the product is centrally approved or has been subject to either the mutual recognition procedure, the decentralised procedure or an EU referral. Under those circumstances, the relevant procedures are governed by EU law.

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.

21 The Patents Act 1977 (Chapter 37), as amended.

viii Manufacturing controls

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

The MHRA regulates pharmaceutical manufacturing operations within the United Kingdom, although the licensing authority actually grants, suspends and revokes manufacturing authorisations. The MHRA will conduct inspections of manufacturing facilities before authorisation and periodically thereafter.

Changes to UK manufacturing and wholesale distribution authorisations require variations to be submitted to the MHRA. A change of name of the licence holder, if it remains the same legal entity, requires a simple administrative notification to the MHRA. Transfers of authorisations from one legal entity to another require submission of a change of ownership application signed by both the transferor and the transferee. The MHRA will only accept such change of ownership applications if there is no substantive change to premises, operations or personnel. If there are any substantive changes, the MHRA will treat the application as an application for a new licence.

ix Advertising and promotion

Medicines

The Medicines Regulations implement the EU advertising rules into UK law. These include the general requirements that advertisements should not be misleading, that they should be substantiated and that they should be accompanied by appropriate prescribing information. There is also a prohibition on pre-approval or off-label promotion of medicines, advertisements of prescription-only medicines to the general public, and illegal inducements to prescribe. Guidance from the MHRA, called the Blue Guide on Advertising and Promotion of Medicines in the UK (the Blue Guide), supplements the Regulations and is intended to provide additional clarification on the interpretation and application of the law. The MHRA is the statutory enforcement body for these rules and requires pre-vetting of advertising material in some circumstances, for example, new active substances granted marketing authorisations.

The statutory scheme is supported by a long-standing system of self-regulation based on the ABPI Code of Practice for the Pharmaceutical Industry (the ABPI Code). The ABPI Code is enforced by a self-regulatory body called the Prescription Medicines Code of Practice Authority (PMCPA), which adjudicates complaints by competitor companies and individuals, but can also bring proceedings itself.

The ABPI Code governs the advertising of prescription-only medicines to health professionals, relevant administrative staff and to the general public. It only applies to companies that are members of the ABPI or that have formally agreed to abide by the ABPI Code. The success of this self-regulatory scheme has meant that the MHRA has not needed to exercise its statutory enforcement powers against legitimate pharmaceutical companies for nearly 30 years.

The provisions of the ABPI Code are consistent with the Medicines Regulations and in some instances more stringent. For example, under the ABPI Code, promotional material must not be issued unless its final form has been certified on behalf of the company by a person that is a registered medical practitioner or a UK-registered pharmacist. It also significantly limits companies' ability to provide promotional aids and seeks to regulate certain company interactions with the National Health Service (NHS).

Medical devices

The United Kingdom has no specific device advertising legislation. Medical device advertising is subject to general advertising rules, requiring that advertisements be substantiated, factual, balanced and not misleading.

The Association of British Healthcare Industries (ABHI) has incorporated advertising guidelines into its Code of Business Practice (the ABHI Code). The provisions of the ABHI Code only apply to ABHI members and companies that have formally agreed to abide by the ABHI Code. There is a complaints procedure, but at the time of going to press, the Complaints Adjudication Panel has yet to hear a complaint.

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, the sale of a medicine without physically handling the product constitutes wholesale dealing, for which a distributor's authorisation is required.

The licensing authority, acting through the MHRA, is responsible for issuing, suspending and revoking wholesale dealers' licences in the United Kingdom. The MHRA will conduct inspections prior to the grant of such a licence and then periodically thereafter.

Consistent with EU law, the Medicines Regulations also regulate 'brokers', meaning persons who engage in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person. UK-based brokers must comply with GDP and must be registered with the MHRA.

Medical devices

The United Kingdom has no specific rules governing the distribution or wholesale of medical devices.

xi Classification of products

Medicines

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

There are two classes of non-prescription or over-the-counter drugs in the United Kingdom. Consumers must obtain pharmacy supply products bearing the designation 'P'

from pharmacies, where they are dispensed under the supervision of a registered pharmacist. General sale list products may be sold through general retail channels, such as supermarkets, convenience stores, petrol stations and the like. These products bear the designation 'GSL'.

Medical devices

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

xii Imports and exports

The United Kingdom's regulations governing the import and export of medicinal products reflect those at EU level. Unless products are intended only for trans-shipment via the United Kingdom, they must be imported by the holder of a manufacturer's authorisation. Products may only be exported by authorised manufacturers or distributors.

xiii Controlled substances

The Misuse of Drugs Act 1971[22] and subordinate legislation, including the Misuse of Drugs Regulations 2001,[23] implement the UN Single Convention on Narcotic Drugs 1961 and the UN Convention on Psychotropic Substances 1971 into UK law. A 'domestic licence' is required to produce, possess, supply or offer to supply any controlled substance. Any person that intends to import or export a controlled substance must also obtain an import or export licence for the particular consignment, as applicable. The Home Office is responsible for issuing controlled substances licences in England and Wales. A domestic licence holder may only supply controlled substances to persons authorised to possess such substances; for example, registered pharmacists.

xiv Enforcement

Medicines

A breach of the Medicines Regulations is in most cases a criminal offence, and the MHRA has an Enforcement Division that considers and manages prosecutions. When the MHRA identifies a potential breach of the legislation, a letter is sent to the individual outlining the Agency's provisional view. The letter will generally list the potential breach or breaches and any public health risk identified where appropriate, along with any action the MHRA requests the company to take. The process to resolve these issues tends to be informal, with individuals agreeing to take voluntary action, so prosecutions are rare. Offences under the Medicines Regulations are usually triable either way (i.e., in summary proceedings before magistrates or on indictment before a crown court judge and jury, depending on the seriousness of the breach). They usually carry a penalty of a fine on summary conviction, or an unlimited fine and the possibility of up to two years in jail on indictment. The historic limit of £5,000 for fines on summary conviction was removed for offences committed after March 2015.

When the PMCPA Panel rules there is a breach of the ABPI Code under the self-regulatory scheme, the company concerned must give an undertaking not to repeat the offending advertisement or activity. The company, whether a member of the ABPI or not, must also pay an administrative charge of £3,500 per matter (or £4,500 per matter for

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

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

non-members) where it accepts the Panel's decision that it breached the Code. The charge increases to £12,000 per matter (or £13,000 per matter for non-members) where the company appeals the Panel's decision and is unsuccessful. At the conclusion of a case, the PMCPA will also publish a detailed case report in its Code of Practice review and on its website.

Medical devices

The MHRA is responsible for ensuring compliance with the Medical Devices Regulations. For enforcement purposes, an offence under these Regulations is often treated as a breach of a safety regulation under the Consumer Protection Act 1987.[24] A person who contravenes the Medical Devices Regulations is liable for a penalty of six months' imprisonment or a fine per breach.

The main sanction under the ABHI Code for non-compliance is negative publicity. An administrative charge is also payable. However, there have been no complaints procedures under the Code and the level of the administrative charges payable has not yet been determined.

III PRICING AND REIMBURSEMENT

The NHS is primarily funded by general taxation. The NHS consists of four individual systems: NHS England, National and Social Care in Northern Ireland, NHS Scotland and NHS Wales. In England, the Department of Health and Social Care controls the NHS.

i Medicines

The NHS pricing and reimbursement process is essentially a free pricing model for innovative medicines. There are separate schemes for generic medicines. Manufacturers set the reimbursement price of products, usually having consulted the Department of Health. This price is published in the Drug Tariff. The Secretary of State has the power to impose price reductions under the National Health Service Act 2006, but most companies participate in the voluntary Pharmaceutical Price Regulation Scheme (PPRS) (for branded medicines), which provides for a system of price controls or rebates negotiated between the ABPI and Department of Health and Social Care. Companies that do not participate in the PPRS must participate in a statutory scheme whereby the Department of Health and Social Care imposes price reductions. In addition, the National Institute for Health and Care Excellence (NICE) assesses medicinal products to determine whether they are cost-effective and should be reimbursed by the NHS. NHS health service providers are expected to make funding available for products recommended by NICE.

ii Pharmaceutical Price Regulation Scheme

The PPRS is a voluntary arrangement negotiated between the Department of Health and Social Care[25] and the branded pharmaceutical industry represented by the ABPI. The ABPI negotiates the PPRS approximately every five years and agrees a price reduction or payment that participants must deliver during the term of the next scheme. The reduction is based largely on profits companies have generated on NHS sales. Historically, participants were

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

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

able to deliver the price reduction in a number of ways; for example, through uniform price reductions, by selectively reducing the price of certain products and even by making a payment in lieu of a proportion of the reduction. Under the most recent PPRS, which took effect on 1 January 2014, companies will be expected to deliver savings by making payments to the government.

iii National Institute for Health and Care Excellence

NICE performs technology appraisals of medicines and medical devices and draws up clinical guidelines to assist the NHS in England and Wales. There are analogous procedures for other parts of the United Kingdom.

Under the National Health Service Act 2006, NHS entities should reimburse medicines used in accordance with a favourable appraisal determination, but are not precluded from reimbursing products that NICE has not recommended.

NICE appraises individual or multiple products, technologies and procedures and develops guidelines on the instructions of the Department of Health and Social Care or the Welsh Assembly government. Where necessary, it commissions an independent academic centre known as an assessment group to review available evidence, including submissions by manufacturers, and prepare an evaluation report. A NICE appraisal committee then produces an appraisal consultation document (ACD), which includes NICE's provisional view on the cost-effectiveness of a product and its recommendations. NICE has a fairly rigid approach to assessing cost-effectiveness. It determines the quality-adjusted life year (QALY) associated with a technology and uses that to calculate the cost per QALY saved (i.e., incremental cost-effectiveness ratio (ICER)). NICE will favour interventions with a lower ICER. If the ICER is less than £20,000, NICE will usually recommend reimbursement. For ICERs up to £30,000, it will often exercise its discretion to recommend a product, but above this threshold, it is unlikely to recommend a product unless there are extenuating circumstances. Stakeholders and commentators have four weeks to comment on the ACD. After considering comments on the ACD, the appraisal committee makes its final recommendations in the final appraisal determination (FAD). Stakeholders can appeal against the final recommendations in the FAD to the NICE Appeal Panel. If there are no appeals, or an appeal is not upheld, the final recommendations are issued as NICE guidance.

NICE has developed a highly specialised technology (HST) process, which is a variation of its existing processes designed to evaluate technologies for extremely rare conditions, essentially ultra-orphan medicines. NICE will recommend funding for HSTs with an ICER of less than £100,000 per QALY gained, but a medicine can only be appraised through the HST process if it satisfies narrow criteria. These include not only that the product is ultra-orphan but also that treatment is concentrated in very few centres in the NHS.

Finally, a partnership between NHS England, NICE, Public Health England and the Department of Health and Social Care also operates the Cancer Drugs Fund (CDF). NICE can recommend a drug for use in the CDF if it has the potential to satisfy the criteria for the standard health technology assessment process, but where there is significant clinical uncertainty that needs further investigation (i.e., through data collection in the NHS or clinical studies). The CDF provides an interim funding mechanism, often while a company gathers additional data to demonstrate the cost or clinical effectiveness of its drug.

NICE is currently contemplating whether to move to a more flexible 'value-based' approach to health technology assessment, perhaps for medicines for small patient populations.

iv Medical devices

There is no formal scheme in the United Kingdom that governs the pricing and reimbursement of medical devices. Some devices are listed in the Drug Tariff, but these are largely consumable devices used by outpatients. Many other devices are reimbursed as part of the cost of NHS procedures under the Payment by Results system of tariffs. However, NICE performs some technology appraisals of medical devices.

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

It is possible to challenge the decisions of national public authorities, such as the MHRA or NICE, by judicial review. This is a procedure by which courts examine the decisions, actions or failures to act of a public body, subject to general principles of administrative law. Before seeking judicial review, the applicant must have exhausted all other avenues of redress, such as internal or administrative appeal procedures. In addition, the relevant act and body must be amenable to review, the claimant must have 'sufficient interest in the matter to which the application relates',[26] or legal standing, and the claim must be commenced 'promptly and in any event not later than three months after the grounds to make the claim first arose'.[27]

The grounds for judicial review are constantly evolving but, in general, the courts will consider whether decisions or acts of a public body are illegal, irrational or procedurally unfair.[28]

There are three specific discretionary remedies for judicial review proceedings: quashing orders, prohibiting orders and mandatory orders. A claimant may also seek a declaration, a stay or injunction and, in certain circumstances, damages. Claimants typically seek a quashing order to set aside the public body's decision, together with a mandatory order directing the public body to take the decision again in accordance with the court's judgment.

Where national judicial review proceedings involve matters of EU law, national courts may refer questions of EU law to the Court of Justice of the European Union (CJEU). The CJEU will issue a preliminary ruling, which the national court can use as a basis for its judgment.

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

i Medicines

Regulations 293 to 300 of the Medicines Regulations implement into UK law the EU rules on the promotion of medicinal products and interactions between pharmaceutical companies and healthcare professionals. The legal position concerning communications or activities of pharmaceutical companies involving prescribers and payers is therefore the same in the United Kingdom as in the European Union, and contains a broad prohibition on the offer to healthcare professionals of unlawful inducements to prescribe. However, the prohibition excludes financial trade practices, such as discounts, that were in common use in the industry before 1 January 1993.

The Blue Guide and the ABPI Code clarify or establish additional requirements governing interactions with payers and prescribers. For example, the ABPI Code also governs

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

27 The Civil Procedure Rules 1998 (SI 1998/3132), Part 54.5(1).

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

the offer of inducements to administrative staff and prohibits promotional aids, except for inexpensive items for patient support. The ABPI Code also contains guidelines governing certain interactions between companies and NHS entities.

ii Medical devices

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

The ABHI Code includes guidelines and a question-and-answer document on the minimum standards device companies should comply with when interacting with healthcare professionals, including payers. The provisions of the ABHI Code are based on the EU code of practice (the Eucomed Code) and therefore the national principles reflect the EU position on ethical communications and interactions with prescribers and payers.

iii Anti-bribery legislation

Most healthcare professionals, administrative staff and payers in the United Kingdom are government officials, employees or contractors. Companies should therefore also be mindful of anti-bribery legislation, such as the UK Bribery Act 2010.[29]

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

i Medicines

With the exception of a specific vaccine injury compensation scheme and the implementation of EU rules governing compensation for clinical-trial related injuries, there are no specific pharmaceutical injury compensation rules in the United Kingdom.

The Vaccine Damage Payments Act 1979 (VDPA)[30] provides a statutory compensation scheme for individuals who can demonstrate that they have suffered a severe mental or physical disability caused by a vaccination against a specific disease. The VDPA scheme applies only to vaccinations for specified diseases listed in the VDPA or diseases recommended by the Secretary of State for Health as falling under the scope of the VDPA scheme.[31] The diseases are typically those for which vaccination is recommended.

Under the VDPA, individuals must show that they were at least 60 per cent disabled by the vaccination to be entitled to a tax-free payment of £120,000. The scheme is rarely used because of the requirement for 60 per cent disability before a claim can be made and limitation periods under UK law.

ii Medical devices

There is no national scheme or system to compensate individuals injured by medical devices.

29 The Bribery Act 2010 (Chapter 23).

30 The Vaccine Damages Payments Act 1979 (Chapter 17), as amended.

31 Section 2 of the VDPA.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

Since the United Kingdom is an EU Member State and because the provisions of the UK Competition Act 1998 closely reflect those found in Articles 101 (anticompetitive agreements) and 102 (abuse of dominant market position) of the Treaty on the Functioning of the European Union, many of the considerations and issues outlined in the European Union chapter apply equally in the United Kingdom.

The Competition and Markets Authority (CMA) is the body with responsibility for policing activities that affect trade within the United Kingdom, or regions within the United Kingdom. The CMA has recently been reviewing certain pricing practices in the pharmaceutical industry, particularly the practice of de-branding (or genericising) drugs so that they are no longer subject to price regulation through normal control mechanisms, such as the PPRS. For example, at the end of 2016, the CMA fined pharmaceutical companies Pfizer and Flynn Pharma nearly £90 million for abusing their dominant position by charging excessive prices to the NHS for an anti-epilepsy drug. At least three other investigations relating to excessive and unfair prices are in train in the United Kingdom. The CMA has also focused on 'pay-for-delay' agreements, issuing its first pay-for-delay infringement decision on 12 February 2016. It fined GlaxoSmithKline (GSK), Generics UK Limited (GUK), Merck KGaG (GUK's former parent company), Actavis UK Limited, Xellia Pharmaceuticals ApS and Alpharma LLC a total of £45 million for delaying market entry of generic versions of GSK's anti-depressant Seroxat (paroxetine) in the United Kingdom. The decision has been appealed to the UK Competition Appeal Tribunal, which has made a referral to the European Union Court of Justice. The CMA is also investigating a discount scheme that Merck Sharp & Dohme has operated for its product Remicade, among suggestions that it might restrict competition for 'biosimilar' versions of infliximab.

The CMA's predecessor, the Office of Fair Trading (OFT), also brought a number of proceedings against companies in the life sciences sector. For example, the OFT found that Genzyme abused its dominant position by bundling the list price of its drug Cerezyme with the price of home-care services. The OFT imposed directions requiring that the NHS list price for Cerezyme be a stand-alone price for the drug, exclusive of any home-care services, and that the price at which the drug was supplied to third parties be no higher than the stand-alone price for the drug.

Napp Pharmaceuticals and other manufacturers have been investigated for fixing the prices of opiate drugs. The OFT found that Napp abused 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 European Union chapter apply equally in the United Kingdom.

VIII CURRENT DEVELOPMENTS

In March 2017, the United Kingdom issued a formal notice in accordance with Article 50 of the Treaty on the Functioning of the European Union that put the United Kingdom on course for Brexit on 29 March 2019.

Brexit is likely to have significant implications for the pharmaceutical and medical devices industries in the United Kingdom and for international companies operating in the United Kingdom. Its impact will very much depend on the form a post-Brexit United Kingdom will take, the relationship that the country chooses to have with the European Union, and indeed the relationship that the European Union is willing to accept.

The European Union (Withdrawal) Act 2018 (the Withdrawal Act)[32] received royal assent on 26 June 2018. In overview, the Withdrawal Act will repeal the European Communities Act 1972[33] at 11pm on 29 March 2019, with generally all 'Direct EU-legislation' and 'EU-derived domestic legislation' (each as defined within the Withdrawal Act) that is operative as part of UK law the day before continuing to have effect in the United Kingdom on and after Brexit until otherwise amended or repealed by the UK Parliament to reflect any negotiated Brexit outcome.

A draft withdrawal agreement (the Draft WA),[34] representing the proposed agreement reached between the United Kingdom and EU negotiating parties, and proposed political declaration on the future relationship between the United Kingdom and EU,[35] were both published by the UK government and the European Commission in November 2018. The Draft WA sets out a proposed transition period between the date the agreement enters into force (upon the United Kingdom's exit from the EU), until 31 December 2020, during which time EU law will 'be applicable to and within' the United Kingdom. The Draft WA also details that the United Kingdom must transfer all documentation relating to ongoing procedures led by a UK competent authority in accordance with Directive 2001/83/EC, and, if reasonably requested by the European Medicines Agency or an appropriate Member State authority, make available any UK-authorised medicinal product marketing authorisation dossier to that authority before the end of the transition period. Similarly, the relevant Member State authorities must also make available to the United Kingdom any medicinal product marketing authorisation dossier approved by that body, when requested by the United Kingdom before the end of the transition period. UK conformity assessment bodies must also make available the information they hold (such as in relation to medical devices) to any notified body of a Member State as indicated by the certificate holder before the end of the transition period.

While the Draft WA was endorsed by the 27 EU Member States on 25 November 2018, it was recently rejected in a UK parliamentary vote on 15 January 2019. At time of writing, the exact nature of Brexit continues to be debated, and very significant uncertainty remains regarding the eventual post-Brexit relationship between the European Union and the United Kingdom. EU and UK regulators are continuing to plan for all eventualities, as are

32 The European Union (Withdrawal) Act 2018 (Chapter 16).

33 The European Communities Act 1972 (Chapter 68).

34 Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, as endorsed by leaders at a special meeting of the European Council on 25 November 2018.

35 Political Declaration setting out the framework for the future relationship between the European Union and the United Kingdom (published 25 November 2018).

companies that Brexit may affect. Since August 2018, both the Department of Health and Social Care and MHRA have published a series of 'no Brexit deal' guidance and proposed contingency planning (available on the UK government website). However, there is now a growing acceptance that potentially affected pharmaceutical companies must move regulatory approvals and adjust pharmaceutical supply chains in preparation for a potential 'hard' Brexit. That means the United Kingdom will not join either the EEA or the European Free Trade Association, and the extent to which the United Kingdom continues to participate in the EU regulatory schemes will need to be defined in bilateral trade agreements.

Appendix 1

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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.

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ISBN 978-1-83862-011-0