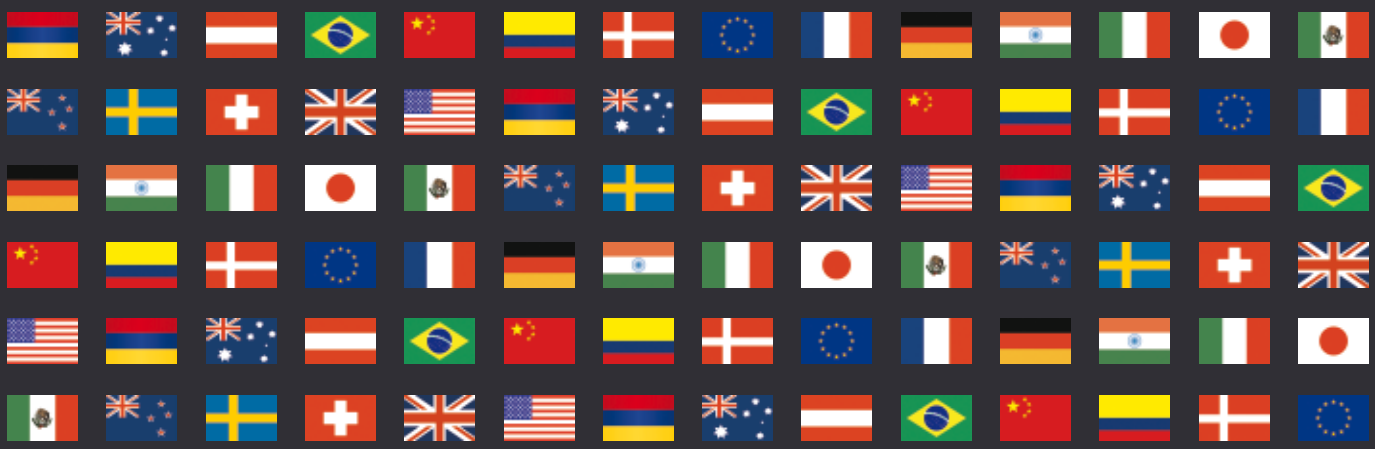
Pharma & Medical Device Regulation 2022

Contributing editors
Alexander Ehlers and Ian Dodds-Smith



LEXOLOGY
Getting The Deal Through

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Lexology Getting The Deal Through is delighted to publish the third edition of *Pharma & Medical Device Regulation*, which is available in print and online at www.lexology.com/gtdt.

Lexology Getting The Deal Through provides international expert analysis in key areas of law, practice and regulation for corporate counsel, cross-border legal practitioners, and company directors and officers.

Throughout this edition, and following the unique Lexology Getting The Deal Through format, the same key questions are answered by leading practitioners in each of the jurisdictions featured. Our coverage this year includes a new chapter on Armenia.

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Every effort has been made to cover all matters of concern to readers. However, specific legal advice should always be sought from experienced local advisers.

Lexology Getting The Deal Through gratefully acknowledges the efforts of all the contributors to this volume, who were chosen for their recognised expertise. We also extend special thanks to the contributing editors, Alexander Ehlers of Ehlers, Ehlers & Partner and Ian Dodds-Smith of Arnold & Porter, for their continued assistance with this volume.

LEXOLOGY®
Getting The Deal Through

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United Kingdom

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Arnold & Porter

HEALTH SERVICES FRAMEWORK AND COMPETENT AUTHORITIES

Healthcare bodies

1 Describe the bodies and their responsibilities (public and private sector) concerned with the delivery of healthcare and appropriate products for treatment.

Medicinal products and medical devices

The UK healthcare system comprises both public and private services. The UK provision of healthcare is devolved to the administrations of each of the UK's four constituent countries. Public healthcare is provided through the National Health Service (NHS) in England and by equivalent bodies in Northern Ireland, Scotland and Wales. The Secretary of State for Health and Social Care is ultimately responsible for the provision of medical services, but in England, discharges this role through the hospitals, clinics and related institutions contracted by NHS Trusts and Health Authorities and statutory bodies called clinical commissioning groups created under the Health and Social Care Act 2012. In addition, from 2021, integrated care systems in England will bring together providers and commissioners of NHS services with local authorities and other local partners to collectively plan health and care services to meet the needs of their population.

NHS England is an independent body. Its main role is to set the priorities and direction of the NHS and to improve health and care outcomes for people in England. Private healthcare may be provided for those individuals who take out such cover in parallel to the NHS. It is generally used as a complement to NHS services, in particular with respect to non-emergency services or elective procedures.

Competent authorities for authorisation

2 Identify the competent authorities for approval of the marketing of medicinal products and medical devices. What rules apply to deciding whether a product falls into either category or other regulated categories?

Medicinal products

The Medicines and Healthcare products Regulatory Agency (MHRA) is the competent authority responsible for the approval of marketing authorisations (MAs) for medicinal products. The MHRA is an executive agency sponsored by the Department of Health and Social Care, with the statutory responsibility to apply and enforce laws governing medicinal products and medical devices. It grants national MAs that are valid in the UK.

Medical devices

Although medical devices do not require an authorisation from the competent authority to be placed on the market, the MHRA is responsible for ensuring that devices placed on the market and put into service in the UK meet the regulatory requirements.

Under EU legislation, Notified Bodies (NBs) are private organisations that have been designated by an EU member state to assess whether manufacturers and their medical devices meet the requirements set out in the legislation. This certification allows manufacturers to place a European Conformity mark (CE mark) on their products, which in turn permits these products to be placed on EU market. In the UK, these bodies are called Approved Bodies, and NBs in the UK will continue to apply EU rules in relation to Northern Ireland.

Borderline products

The United Kingdom follows the EU law principle whereby a relevant product is ordinarily regulated under one legal regime. The MHRA publishes and regularly updates guidance to assist manufacturers and importers to distinguish the status of 'borderline products', and determines, through the MHRA Borderline Section, whether a product falls within the definition of medicinal product, medical device, cosmetic or food products, including, in particular, food supplements.

When the MHRA receives a question or a complaint about product classification, it assesses: the claims about what the product does, the product characteristics, the primary intended purpose of the product, whether there are any similar licensed or registered products on the market and their legal classification status, and how it is presented to the public through labelling, packaging or promotional communications and materials.

Approval framework

3 Describe the general legislative and regulatory framework for approval of marketing of medicinal products and medical devices.

Medicinal products

UK regulation of medicinal products derives from EU legislation, principally Directive 2001/83/EC (EU Directive 2001/83), and Regulation (EC) 726/2004 (EU Regulation). The key UK legislation is the Human Medicines Regulations 2012 (HMRs), which has been amended by Statutory Instruments on account of Brexit so that the UK can operate a stand-alone framework for the regulation of medicinal products. However, pursuant to the Withdrawal Agreement's Protocol on Ireland and Northern Ireland, Northern Ireland continues to follow EU rules. Therefore, in its regulation and approval of MAs which allow a product to be placed on the market in Northern Ireland, MHRA must apply the relevant EU pharmaceutical legislation.

The HMRs cover the requirements for the authorisation, manufacture, distribution, advertising and pharmacovigilance of medicines. The Regulations require all MAs to include the summary of product characteristics, labelling (internal and external packaging of the product) and package leaflet (or patient information leaflet).

Medical devices

UK regulation of medical devices derives from EU three EU directives (the Medical Device Directives):

- Council Directive 93/42/EEC on Medical Devices;
- Council Directive 90/385/EEC on Active Implantable Medical Devices; and
- Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices.

These directives are implemented in UK domestic law through the Medical Devices Regulations 2002/618 (UK Medical Devices Regulations).

The new EU Regulations on medical devices (Regulation (EU) 2017/745 on medical devices (EU MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (EU IVDR)) will not apply in Great Britain. They will, however, apply in Northern Ireland.

As of 1 January 2021, there is a new route to market, with an accompanying mark, to place a device on the Great Britain market – UKCA – which is based on the requirements derived from the current EU Medical Device Directives. EU CE marking will continue to be recognised in Great Britain, and certificates issued by EU-recognised NBs will continue to be valid for the Great Britain market, until 30 June 2023. Only UK Approved Bodies may conduct conformity assessments in relation to UKCA mark. They are not able to issue CE certificates other than for the purposes of the 'CE UKNI' marking, which is valid in Northern Ireland.

Under the terms of theNorthern Ireland Protocol, EU rules will continue to apply in Northern Ireland and EU CE marking is required. In addition, if the manufacturer chooses to use a UK NB for mandatory third-party conformity assessment for purposes of the Northern Ireland market, the UKNI mark must be applied in addition to the CE mark.

CLINICAL PRACTICE

Applicable rules

4 What legislation controls and which rules apply to ethics committee approval and performance of clinical trials in your territory for medicinal products and medical devices?

Medicinal products

The Clinical Trials Regulations 2004/1031 regulate clinical trials of medicinal products in the United Kingdom. Under these Regulations, clinical trials must be conducted in accordance with good clinical practice, the relevant clinical trial authorisation and ethics committee approval, and the terms of the trial protocol. These Regulations were originally made to implement the EU Clinical Trials Directive (2001/20/EC) and have been amended to reflect the UK's departure from the EU. The sponsor of a clinical trial, or its legal representative, should be based in the United Kingdom or a country on an approved country list, which includes EU and EEA countries.

The EU Clinical Trials Regulation will not apply in Great Britain but will apply in Northern Ireland.

Medical devices

The Medical Devices Regulations 2002/618 regulate clinical investigations of medical devices in England, Wales and Scotland. Under these Regulations, the manufacturer of the device must give notice to the Medicines and Healthcare products Regulatory Agency (MHRA) of the investigation, and for certain devices, obtain a positive opinion on the relevant ethics committee.

In Northern Ireland, the EU Medical Device Regulation applies, although the procedures for clinical investigations are the same as in Great Britain.

Reporting requirements

5 What requirements exist for reporting the commencement of a trial and its results to the competent authorities or the public?

Medicinal products

The UK Clinical Trials Regulations include requirements relating to reporting the commencement and the results of clinical trials, and the favourable opinion of a research ethics committee is subject to the condition that the clinical trial is registered on a publicly accessible database. From 1 January 2021, clinical trials should be registered using established international databases such as ISRCTN registry or ClinicalTrials.gov. A clinical trial that involves both UK and EU sites should be registered on the European EudraCT database. Certain information about trials being conducted in the UK is made publicly available on the HRA research summaries website and the UK 'Be Part of Research' website.

The UK industry association, the Association of the British Pharmaceutical Industry (ABPI), Code of Practice requires member companies to disclose details of clinical trials in accordance with the International Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases, and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature.

There is currently no obligation under UK law for medical device manufacturers to publish information on clinical investigations.

Consent and insurance

6 Are there mandatory rules for obtaining trial subjects' consent to participate? Must sponsors arrange personal injury insurance to a particular limit?

Medicinal products

All trial subjects must give informed consent before being entered into a trial in the United Kingdom. Schedule 1 of the Clinical Trials Regulations describes the requirements for consent for clinical trials of investigational medicinal products. For each trial, specific consent documentation comprising a participant information sheet and consent form must be developed and approved by the ethics committee. Throughout the trial, the subject's willingness to continue participating in the trial should be reaffirmed periodically. If significant new information becomes available, subjects should be provided with revised consent documentation for approval.

With regard to personal injury insurance, it is a sponsor's responsibility to ensure there is provision for indemnity or compensation in the event of injury or death attributable to a study, and insurance or indemnity to cover the liability of the investigator and sponsor. It should be clear within the application for the clinical trial authorisation whether the insurance limit is capped for the study as a whole or per patient. The HRA, which provides ethical approval for clinical trials, will request justification from any sponsor not providing £5 million of insurance cover. In addition, for commercial studies, arrangements for no-fault compensation will normally be provided in accordance with the ABPI scheme.

Medical devices

The documentation submitted to the MHRA as part of the clinical investigation application form must include a copy of the patient consent form and confirmation of insurance of subjects. Similar to the position regarding medicines, for commercial studies, arrangements for no-fault compensation will normally be provided in accordance with the Association of British HealthTech Industries scheme.

MARKETING AUTHORISATION

Time frame

7 How long does it take, in general, to obtain an authorisation from application to grant, what fees are payable and what is the normal period of validity of the authorisation?

Medicinal products

The Medicines and Healthcare products Regulatory Agency (MHRA) is required to complete the assessment for a national marketing authorisation (MA) application within 210 days excluding procedural clock-stop. However, post-Brexit, the MHRA has introduced a 150-day assessment timeline for all high-quality MA applications.

MAs granted by the MHRA have an initial period of validity of five years. However, MAs cease to be valid if the product is not placed on the market within three years of the date of authorisation (the sunset clause). Once renewed, after the initial five-year period, the MA is valid for an unlimited period of time; however, if there are safety concerns, a five-year expiry date is given.

All current MHRA fees may be found on the MHRA website; the fee for a UK national MA is £92,753.

Medical devices

The MHRA does not perform conformity assessment procedures for medical devices where oversight by a third party is required. The classification of a medical device guides the conformity assessment procedure to be followed for the conformity mark to be affixed. A Notified Body (NB), or Approved Body (AB), is engaged in the conformity assessment if the device is considered higher risk. The timeline for completing the conformity assessment is agreed between the manufacturer and the designated NB or AB. CE markings are valid as long as the device meets the applicable legal requirements and no significant changes are made to the device. A UKCA mark is valid indefinitely and the underlying conformity assessment does not require renewal unless the specifications of the device change. The relationship between the manufacturer and NB, or AB, is contractual, and NBs and ABs set their own fees.

Protecting research data

8 What protection or exclusivities apply to the data submitted by originators to gain initial approval and, on variation or new application, to add indications or pharmaceutical forms?

Medicinal products

As set out in EU law, under the Human Medicines Regulations 2012 (HMRs), data submitted by originators to the Medicines and Healthcare products Regulatory Agency (MHRA) as part of an marketing authorisation (MA) application are protected for a period of eight years from the date of initial authorisation of the product. During the protection period, applications for generic versions of the product cannot refer to the preclinical and clinical data that were submitted to support the authorisation of the originator product. After this eight-year period, valid applications for generic products can cross-refer to the data for the originator product, meaning generic products can be authorised without having to submit independent preclinical and clinical data for the product. In addition, there is an additional period of two years of protection during which any authorised generic product cannot be placed on the market. The start of the protection period will depend on the type of authorisation and jurisdiction within the UK in which it is authorised.

The additional one-year protection set out in EU law for authorisation of one or more new therapeutic indications that, during the scientific evaluation prior to their authorisation, were held to bring a significant clinical benefit in comparison with existing therapies, or where an application is made in the UK for a new indication for a well-established substance, are also set out in the UK legislation.

A period of 10 years of orphan exclusivity will be granted for authorisations granted by the MHRA for Great Britain. In Northern Ireland, the EU orphan period of protection will apply.

Extensions to the orphan protection period (or to the Supplementary Protection Certificate in the case of products that are not orphan medicinal products) may be granted as a result of completing paediatric research.

Medical devices

Manufacturers are required to conduct a clinical evaluation on the characteristics and performance of the device under normal conditions of use. The clinical evaluation may be based on a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device or a critical evaluation of the results of all clinical investigations initiated by the manufacturer. Unlike medicinal products, the data underlying the critical clinical evaluation for a medical device is not protected by specific data or market rules. However, the data is treated as confidential and cannot be referred to by applications of equivalent products.

Freedom of information

9 To what extent and when can third parties make freedom of information applications for copies of research data submitted by applicants for authorisation to market medicinal products or medical devices?

Medicinal products

Third parties may request information about authorisations or applications held by the MHRA under the Freedom of Information Act 2000 (FOIA).

With regard to pending applications, the MHRA releases very little information. For completed procedures (that is, where the authorisation has been granted or rejected), the MHRA assesses each FOIA request on its own merits and decides the level of disclosure needed to comply with the FOIA, while respecting pharmaceutical companies' interests in limiting the disclosure of information relating to the products they are planning to place on the market.

Personal data, confidential information and commercially sensitive information may be redacted from the documents disclosed. The MHRA allows MA holders (MAHs) to comment on proposed redactions prior to their release.

Medical devices

UK Approved Bodies are private entities. Therefore, the FOIA provisions that are applicable to public bodies do not apply to them. The information relating to medical devices, including the technical documentation, belongs to the device manufacturer and remains confidential.

Once registered with the MHRA, a manufacturer's details are added to the MHRA Public Access Database for Medical Devices Registration. The database shows the name of the manufacturer, address, authorised representative or UK responsible person (if relevant), date of registration, MHRA reference number and type of device (code and medical device classification). Other information held by the MHRA could be requested under the FOIA, provided no exceptions apply.

Regulation of specific medicinal products

10 | Are there specific rules for approval, and rewards or incentives for approval, of particular types of medicinal products, such as traditional herbal and homeopathic products, biologicals and biosimilars, controlled drugs, orphan drugs and those for paediatric use?

The UK has updated its legislation to add UK-specific procedures for products that were previously covered by the EU regime. These procedures currently mirror the EU regime, although where possible, the UK has sought to simplify the EU regime. For example, 10 years of market exclusivity is granted to orphan medicinal products granted for the market in Great Britain, and full or partial refunds for MA fees may be available to encourage the development of orphan drugs. However, under the UK regime, there is no need to obtain orphan designation before the application for orphan medicinal products is made – the criteria will be assessed with the application. The EU regime continues to apply in Northern Ireland.

For paediatric medicines, a UK system of paediatric investigation plans (PIPs) has been put in place, with the same rewards being available for those completing the PIP. The scientific content and assessment required is similar to the current European Medicines Agency's (EMA's) guidance, and the MHRA will seek to recognise decisions of the EU's Paediatric Committee for products that are also covered by under the EU regime.

Post-marketing surveillance of safety

11 | What pharmacovigilance or device vigilance obligations apply to the holder of a relevant authorisation once the product is placed on the market?

Medicinal products

The HMRs oblige MAHs to keep the MA dossiers up to date to take account of scientific and technical progress. They are required to operate and audit appropriate pharmacovigilance and risk management systems in line with the EU Good Pharmacovigilance Practice, which is still referred to in the UK legislation and guidance. As part of this, the MAH must have an appropriately qualified person responsible for pharmacovigilance located in the EEA, although where that person does not reside and operate in the UK, they will need a national contact person for pharmacovigilance who resides and operates in the UK. The MHRA inspects MAHs to determine whether they comply with those obligations and takes necessary action if that is not the case.

Medical devices

Once a medical device has been placed on the UK market, the manufacturer is required to monitor and report any serious adverse incidents associated with the product. The MHRA operates the system for reporting and recording details of suspected adverse incidents relating to a medical device or in vitro diagnostic medical device that occur in the UK. Reporting of adverse incidents must be made via the MHRA Manufacturer's Online Reporting Environment. The MHRA investigates device-related adverse incidents and takes appropriate action where required.

Other authorisations

12 | What authorisations are required to manufacture, import, export or conduct wholesale distribution and storage of medicinal products and medical devices? What type of information needs to be provided to the authorities with an application, what are the fees, and what is the normal period of validity?

Medicinal products

The manufacture or assembly of finished medicinal products in the UK, or their importation from third countries (other than countries specified on a list of approved countries for importation, including EEA member states), requires a manufacturer's licence issued by the MHRA. Different types of manufacturer's licences are available depending on whether the activities involve licensed, unlicensed or investigational medicinal products.

An application for a manufacturer's licence should be accompanied by a site master file containing specific information about the production processes conducted at the manufacturing site. Manufacturers must demonstrate that they comply with good manufacturing practices (GMP), and the MHRA will only issue the licence following an inspection of the site. Manufacturers must also designate a Qualified Person who is responsible for ensuring each batch complies with the requirements of the marketing authorisation. The current application fee for a standard manufacturer's licence is £3,143, plus a £2,655 inspection fee.

Once granted, the manufacturer receives a licence document setting out the specific terms of the licence. Any changes to the information shown on the licence must be submitted to the MHRA for prior approval. Subject to payment of an annual fee (currently £468) manufacturers licences remain in force indefinitely until revoked by the MHRA or surrendered by the licence holder.

A wholesale distribution authorisation issued by the MHRA (also commonly referred to as a wholesale dealer's licence) is required to:

- procure, hold, supply or sell medicinal products for human use sourced in the United Kingdom to anyone other than members of the public;
- import medicinal products from a non-EEA member state for export to a non-EEA member state; or
- export medicinal products to a non-EEA member state.

This includes virtual operations where no physical handling of the products takes place. Wholesale distribution authorisation holders in the UK are also entitled to import medicines from countries on an approved country for import list (which includes EEA member states), subject to notifying the MHRA of their intent to do so and nominating a responsible person for importation activities.

Applicants for a wholesale distribution authorisation are submitted via the MHRA's online Process Licensing Portal. Wholesale distributors must demonstrate that they comply with good distribution practices (GDP), and the MHRA will only issue the authorisation following an inspection of the site. The current fee for a standard application for a wholesale distribution authorisation is £1,803, plus £1,936 inspection fees. There is an annual service fee of £288 (or £172 if reduced fees apply).

Once granted, the wholesale distributor receives a certificate of compliance with GDP detailing the types of products being handled for the relevant site. Wholesale distribution authorisations remain in force until revoked by the MHRA or surrendered by the authorisation holder.

Wholesalers in Northern Ireland can source medicines from Great Britain without additional regulatory importation controls (ie, under a wholesale distribution authorisation) until 31 December 2021, but thereafter will require a manufacturer's import authorisation.

Medical devices

Manufacturers of medical devices are not required to obtain a specific authorisation to manufacture. Manufacturers are required to register with MHRA in order to place the medical devices on the market in Great Britain. MHRA will only register devices where the manufacturer or their UK Responsible Person has a registered place of business in the UK; hence, manufacturers based outside the UK must appoint a UK Responsible Person having a UK place of business. A £100 statutory fee applies to registration and updating information. Medical devices registered with the MHRA before 1 January 2021, do not need to be re-registered. A grace period is available for compliance with the new registration process, the deadlines for this vary depending on the class of device being registered. Registration requirements differ for Northern Ireland.

Importers of medical devices into the United Kingdom from third countries are not required to obtain a specific authorisation but will instead become legally responsible under the UK Medical Devices Regulations for those devices.

Distributors of medical devices are not required to obtain an authorisation to engage in wholesale trade.

Sanctions

13 What civil, administrative or criminal sanctions can authorities impose on entities or their directors and officers for breach of the requirements concerning controlled activities?

Medicinal products

The MHRA is the competent authority that administers and enforces the law on medicinal products in the United Kingdom. It will take regulatory action where breaches of legislation are identified. This may take the form of adverse licensing action (ie, compulsorily making a variation to an existing licence), suspension or revocation of a licence or commencement of criminal investigations with a view to prosecuting those responsible for committing a statutory offence.

With regard to statutory offences, the UK HMRs provide for the imposition of penalties for breaches of the Regulations. These sanctions apply to breaches relating to the MAs as well as breaches of other specific requirements. A person guilty of an offence under the Regulations is liable on summary conviction to a fine not exceeding the statutory maximum; or on conviction on indictment, to an unlimited fine, to imprisonment for a term not exceeding two years or to both. In addition, the sanctions provided under the general consumer laws described below that apply to medical devices, also apply to medicines.

Those engaged in the imposition of sanctions examine each case on its own merits, and the preferred approach adopted by the MHRA would be to apply an incremental escalation in terms of the severity of the sanction. Any sanctions imposed by the MHRA seek to change the behaviour of the offender and to correct the harm caused by regulatory non-compliance where appropriate and are proportionate to the nature of the offence and the harm caused.

Medical devices

The MHRA administers and enforces the law on medical devices in the United Kingdom. It has a range of investigatory powers to ensure their safety and quality under the UK Medical Devices Regulations and under general legislation that is not specific to devices, as well as new powers under the Medicines and Devices Act 2021. If a company is considered to be in breach of the Regulations, the MHRA compliance unit will contact them to request further information. If the company fails to cooperate with the requests and continues to place non-compliant products on the market or there is a serious risk to public health, the MHRA will consider using its legislative enforcement powers. These powers include:

- a compliance notice to formally outline offences and request the company to correct a non-compliance and a restriction notice to restrict the availability of a medical device;
- prohibition notices to ban the supply of any goods that are considered unsafe or that do not comply with the regulations;
- notices to warn, which require a manufacturer to issue a warning at his or her own expense about any goods considered unsafe; suspension notices;
- forfeiture orders;
- notices to obtain information; and
- a notice requiring the manufacturer to organise the return of the product if the MHRA considers that the manufacturer has supplied a dangerous medical device to consumers.

If the MHRA considers the manufacturer to have committed a serious offence by failing to comply with the regulations or the conditions of a notice issued, the manufacturer may be subject to prosecution. Successful prosecution may carry a penalty of an unlimited fine or six months' imprisonment, or both.

Exemptions

14 What, if any, manufacture and supply of medicinal products is exempt from the requirement to obtain an approval to market?

Under the HMRs, a medicinal product must be subject to an MA before it is placed on the market, unless a limited exemption applies. The HMRs provide an exemption from the need for an MA for certain medicinal products commonly known as 'specials' (products provided to meet special needs pursuant to requests to supply that are unsolicited).

Other unlicensed medicinal products that are exempt in certain circumstances are:

- products prepared in a pharmacy;
- unlicensed herbal remedies;
- unlicensed homeopathic medicines prepared in a pharmacy;
- investigational medicinal products;
- intermediate products intended for further processing by an authorised manufacturer; and
- medicinal products for export to countries outside the European Economic Area.

Parallel trade

15 Are imports allowed into your jurisdiction of finished products already authorised in another jurisdiction, without the importer having to provide the full particulars normally required to obtain an authorisation to market? What are the requirements?

Medicinal products

The UK parallel import licensing scheme allows the holder of a parallel import licence (PLPI) to import medicinal products authorised nationally in an EEA member state and market them in the UK, as long as the imported product has no therapeutic difference from a product that is already authorised in the UK.

The procedure for obtaining a PLPI involves the submission of an application via the MHRA's online portal prior to importation. The applicant must identify the appropriate UK product upon which the application is based and provide mock-ups of all proposed labelling and the patient information leaflet. Fees range from £1,792 for simple applications where the products share a common origin, £6,663 for a standard application and up to £18,180 for complex applications where there is no common origin between the imported and UK reference product. If granted, a PLPI is valid for five years.

The holder of a PLPI must ensure that the imported product is manufactured to GMP standards and hold a wholesale distribution authorisation covering its importation, storage and sale. Any repackaging of the product must be carried out by the holder of an appropriate manufacturer's authorisation.

Parallel distribution notices issued by the EMA to distributors in Great Britain are no longer valid, but centrally authorised products and products authorised nationally in EU member states will still be able to be imported into Great Britain if the holder of the parallel distribution notice opts into a conversion process to be issued with a corresponding PLPI. Parallel distribution notices issued to distributors in Northern Ireland by the EMA remain valid, and no regulatory action is required to continue to market products directly imported from the European Union into Northern Ireland.

Medical devices

Medical devices that have been CE marked and placed on the market in the EU may, in principle, be imported into Great Britain and sold by a parallel importer without any specific authorisation to do so until 30 June 2023 (and indefinitely into Northern Ireland). From 1 July 2023, importing devices from the European Union and placing them on the market in Great Britain will be treated as a new placing on the market, with all the relevant UK manufacturer requirements applying to the parallel importer, including the requirement to register the device with the MHRA.

AMENDING AUTHORISATIONS

Variation

16 What are the main requirements relating to variation of authorisations for medicinal products and medical devices?

Medicinal products

The relevant sections of EU Commission Regulation (EC) No. 1234/2008 that apply to variations of purely national marketing authorisations have been incorporated into UK law, and the MHRA is responsible for the assessment of such variations. The Commission Variation Guidelines continue to apply in the UK. As under EU law, the requirements differ depending on the type of variation in question; these include type IA for minor variations to types IB and II for more complex changes, as well as extensions of marketing authorisations (MAs).

Medical devices

If a manufacturer makes changes to a medical device that would affect its performance or safety characteristics, it must liaise with the relevant Notified or Approved Body and submit the necessary documentation to determine if the CE or UKCA mark is still valid. For self-certified devices, this assessment is done by the manufacturer.

Renewal

17 What are the main requirements relating to renewal of authorisations for medicinal products and medical devices?

Medicinal products

Under the Human Medicines Regulations 2012 (HMRs), an MA is granted for up to five years. The MA holder (MAH) must renew it at least nine months before it expires. On first renewal, MAs are usually given unlimited validity but, if there are safety concerns, a five-year expiry date is given.

MAs for centrally authorised products converted into national MAs are treated as if they were granted in the UK on the date on which the corresponding EU MA was granted. The converted EU MA will, therefore, have the same renewal date in the United Kingdom as in the European Union.

In all cases where an application for renewal is made, the MA will remain in force until the MHRA notifies the MAH of its decision on the renewal application.

Medical devices

CE marks and UKCAs marks are valid as long as the device meets the applicable legal requirements and no significant changes are made to the device.

Transfer

18 How easy is it to transfer the existing approvals or rights to market medicines and medical devices? How long does this take in general?

Medicinal products

MAHs must apply to the MHRA for a 'change of ownership' to transfer a MA to a new MAH. Either the existing or the new legal entity taking over the MA must submit an application together with a series of supporting documents. A completed 'change of ownership' form should be sent via the MHRA online portal or via the Common European Submission Portal with the supporting documents.

The application can take up to 42 days to process from the date of submission. The expiry date on the current MA will remain the same when transferred unless it has less than six months remaining, in which case it will be given a minimum duration of six months. All pending submissions will be transferred over to the new MA. Pending MAs may not be transferred.

Medical devices

A change of the manufacturer of a medical device will transfer all the obligations and requirements relating to the medical device in question to the new manufacturer. The new manufacturer will need to demonstrate that they meet the relevant requirements to obtain a CE or UKCA mark, and will need to liaise with the corresponding Notified or Approved Body to update the technical documentation of the device, review the new entity's quality management system, and amend the product information and instructions for use, as needed in order to obtain a new CE or UKCA mark. In those cases where the medical device is registered with the MHRA, the MHRA should be notified of the new ownership. There is a fee of £100 for each registration change request.

RECALL

Defective and unsafe products

19 What are the normal requirements for handling cases of defective or possibly unsafe products, including approvals required for recall and communication with health professionals?

Medicinal products

Cases of potentially defective medicines are handled by the Medicines and Healthcare products Regulatory Agency (MHRA) Defective Medicines Report Centre (DMRC). This is a unit of the Inspection, Enforcement and Standards Division of the MHRA. The DMRC's role is to minimise the hazard to patients in these cases providing emergency assessment and communication systems between manufacturers, distributors, regulatory authorities and users. The MHRA website provides a DMRC email address for defect notifications as well as an electronic defect reporting form for healthcare professionals (HCPs), industry professionals and users to report suspected defective products to the DMRC (the Yellow Card Scheme reporting site) and a Guide to Defective Medicinal Products.

Where a product recall is required, the decision is taken in consultation with the relevant licence holder. Although the MHRA has regulatory powers to require a recall, these are rarely used. It is the licence holder's responsibility to ensure that a recall is carried out effectively throughout the distribution chain, but all stakeholders involved have responsibilities to carry out a recall. If necessary, the DMRC will issue a drug alert to support action taken by the licence holder. The holder of a manufacturer's licence must notify the DMRC immediately if its investigations identify a defect that could result in recall or other restrictions on supply.

Drug alerts are issued to a number of contacts for onward cascade to HCPs in the public and private sectors and are published in the MHRA website within one working day of issue. The MHRA uses an international agreed classification system for medicine recalls scaled from Class 1 (life threatening) to Class 3 (unlikely to cause harm), depending on the seriousness of the risk to health.

Medical devices

Cases of suspected defective medical devices or adverse incidents are handled by the MHRA. Medical device enforcement activities are carried out by the MHRA using powers under general legislation that is not specific to medical devices to ensure compliance with the Medical Devices Regulations 2002. Powers to recall, issue enforcement notices and impose civil sanctions were also introduced in Part 4 of the Medicines and Medical Devices Act 2021. These enforcement activities are undertaken in accordance with the statutory principles of the Regulators' Code. The MHRA has set out different reporting arrangements for manufacturers of medical devices and other stakeholders.

Manufacturers of medical devices must report an incident via the MHRA Manufacturer's Online Reporting Environment (MORE) or via email using the manufacturer Incident Report form; while HCPs and users or members of the public should report incidents using the MHRA Yellow Card Scheme. Once an incident has been reported, the MHRA will investigate it and, if necessary, will require the manufacturer to send a field safety notice (FSN) about the safety of a medical device and any Field Safety Corrective Action being undertaken to its customers. (Note: some specialised medical devices are subject to Device Specific Vigilance Guidance, which may include particular adverse incident reporting requirements.)

The FSN is a communication aimed primarily at the customers and users of the medical device to inform them of action being taken by the manufacturer to reduce the risk of death or serious deterioration in the state of health associated with the use of a medical device. In addition to the FSN, the MHRA may decide to issue a medical device alert. Manufacturers are encouraged to use the Medical Devices Safety Officer network to make the FSN exercise more efficient.

PROMOTION

Regulation

20 Summarise the rules relating to advertising and promotion of medicinal products and medical devices, explaining when the provision of information will be treated as promotional. Do special rules apply to online advertising?

Medicinal products

The advertising of medicinal products in the United Kingdom is controlled by a combination of legislation and industry codes of practice. The relevant legal framework is set out in the Human Medicines Regulations 2012 (HMRs); the changes to the HMRs as a result of Brexit have not affected the advertising of medicinal products and the rules applicable in the UK are currently consistent with the provisions of Directive 2001/83/EC. While, therefore, in accordance with the Northern Ireland Protocol, regulation of medicines in Northern Ireland continues to be subject to EU law, the rules governing advertising of medicinal products in Great Britain and Northern Ireland are currently aligned. The general provisions of the Bribery Act 2010 are also applicable in the context of advertising of medicinal products. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for supervision of advertising and issues guidance, mainly through the 'Blue Guide: Advertising and Promotion of Medicines in the UK', which was updated at the end of 2020. In addition to the legal requirements, most pharmaceutical companies operating in the UK agree to self-regulation in accordance with the relevant industry codes of practice. These mainly include the Association of the British Pharmaceutical Industry (ABPI) Code updated in July 2021 (administered by the Prescriptions Medicines Code of Practice Authority (PMPCA)) and the Proprietary Association of Great Britain (PAGB) Code, which regulate the advertising of prescription-only and over-the-counter medicines respectively. Both Codes reflect and, in certain respects, extend beyond the legal requirements.

UK law and the self-regulatory codes provide rules for advertising of medicines to the public and advertising aimed at HCPs. Advertising to the public is permitted for medicines that are not legally classified as prescription only, while advertising of prescription-only medicines may only be targeted at 'persons qualified to prescribe or supply medicines'. Advertising of unauthorised medicines or indications is not permitted. All medicines advertising must be consistent with the approved summary of product characteristics. Furthermore, where a product is only authorised in part of the UK (Great Britain *or* Northern Ireland), it may only be advertised in the territory where it is authorised. UK-wide advertising of a product is permissible only where the product is authorised in both Great Britain and Northern Ireland.

Under the HMRs, advertisement is defined broadly as 'anything designed to promote the prescription, supply, sale or use of a medicinal product'. This is stated to include: 'door-to-door canvassing, visits by medical sales representatives to persons qualified to prescribe or supply medicinal products; the supply of samples; the provision of inducements to prescribe or supply medicinal products by gift, offer or promise of any benefits or bonus, whether in money or in kind (except where the intrinsic value is minimal); the sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products; and the sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products, including payment of expenses'.

Corporate or financial information describing a company's area of business, including progress in research will likely fall outside this definition, provided it includes no product claims and is directed towards an appropriate audience.

Online advertising is subject to the same provisions and controls as traditional advertising, although the ABPI and PAGB Codes include provisions specifically directed towards advertising through the internet and the use of online platforms and social media. The PMCPA has published guidance on digital communications, which includes advice on how companies can use digital communication tools such as Twitter, Facebook, Pinterest and Wikipedia, whilst complying with the restrictions under the ABPI Code. In addition, the new 2021 ABPI Code has been updated throughout to address digital communications. The MHRA's Blue Guide also contains information relevant to this, and confirms that material posted on UK websites (including social networking sites, blogs and discussion forums) and/or aimed at a UK audience is subject to UK medicines advertising legislation.

Medical devices

Legislation concerning medical devices is principally provided by the Medicines and Medical Devices Act 2021 and the Medical Devices Regulations 2002. These contain few provisions relating to the

advertising of medical devices, save to provide that a device must be covered by an appropriate marking as required in the relevant part of the UK before it may be advertised to any audience. Advertising of medical devices is also subject to the general laws relating to consumer products advertising including the Consumer Protection from Unfair Trading Regulations 2008 (business-to-consumer practices) and the Business Protection from Misleading Marketing Regulations 2008 (business-to-business practices).

In accordance with the Northern Ireland Protocol, the EU Medical Devices Regulation 2017 (EU MDR) is also applicable in Northern Ireland. Advertising of medical devices in Northern Ireland is therefore subject to the EU MDR prohibition on the use of misleading claims in the advertising of medical devices.

The Advertising Standards Authority (ASA) is the UK's independent regulator for general advertising across all media. The Committee of Advertising Practice (CAP) is the body responsible for writing and maintaining the CAP Codes. The CAP Codes apply to advertising of products to consumers but not to advertising addressed solely to HCPs and provide specific rules controlling advertisements of medical devices. They cover all media including all electronic media, online and other media, but there are no longer specific rules for distance selling.

From a self-regulation perspective, the Association of British HealthTech Industries (ABHI) Code of Ethical Business Practice sets out the minimum standards that should apply to members' UK business practices in connection with promotion addressed solely or primarily to HCPs. The ABHI Code implements the provisions of the MedTech Europe Code of Business Practice and regulates various activities, including interactions with HCPs, advertising and promotion, unlawful payments and practices, data privacy, and compliance and enforcement. The requirements of the ABHI Code apply to advertisements in electronic media, including, but not limited to, online advertisements.

In addition, the PAGB (which represents UK manufacturers of self-care medical devices) issued a new Medical Devices Consumer Code of Practice for advertising of self-care medical devices products for PAGB members in 2019. The PAGB defines self-care medical devices as those that treat or prevent self-treatable conditions.

Inducement

21 What regulations exist to discourage the provision of inducements to healthcare professionals to prescribe, sell, supply or recommend use of a particular medicinal product or medical device?

Medicinal products

The HMRs prohibit the supply, offer or promise of gifts, pecuniary advantages or other benefits to HCPs in connection with the promotion of medicinal products unless they are inexpensive and relevant to the practice of medicine or pharmacy. These provisions apply to advertising, price promotions, loyalty schemes and bonus schemes. Inexpensive items are considered to be those which do not cost a company more than £6 (excluding VAT) and represent a similar value to the recipient; while the criterion of 'relevance' is only met by items that have a clear business use. The prohibition of inducements explicitly excludes measures or trade practices relating to prices, margins or discounts that were in existence on 1 January 1993. Hospitality to HCPs is considered acceptable in the context of events for professional or scientific purposes provided this is limited to the main purpose of the event and offered to HCPs and appropriate administrative staff only. The general provisions of the Bribery Act are also applicable.

The ABPI Code goes further than the HMRs in prohibiting the supply, offer or promise of any gift, pecuniary advantage or benefit to members of the health professions or to other relevant decision-makers in connection with the promotion of medicines or as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. Promotional aids are no longer permitted save for inexpensive notebooks, pens and pencils for use at company organised meetings. Such items must not bear the name of any medicine or provide any information about medicines, but may bear the name of the company providing them. No individual attendee should receive more than one pen or pencil or one notepad. HCPs may be provided with items that are to be passed on to patients in accordance with the conditions contained in the ABPI Code.

These restrictions do not prevent the provision of educational or promotional material to HCPs or other relevant decision makers in the form of inexpensive memory sticks and the like. In appropriate circumstances, independently produced medical or educational publications, such as textbooks may be given to healthcare organisations as a grant or a donation; they must not be given to individuals.

Medical devices

The Medical Devices Regulations 2002 do not address the question of inducements offered to HCPs to prescribe sell, supply or recommend use of a particular medical device or to offer the relevant device company any other benefit. Such activities are however prohibited as a result of the Bribery Act 2010.

The EU MDR, which is applicable in Northern Ireland, prohibits the offer of inducements that might influence the judgment of conformity assessment bodies. This requirement is also reflected in the Guidelines on the appointment of UK Conformity Assessment Bodies certifying for the GB and NI market from 1 January 2021, issued by the Department for Business, Energy and Industrial Strategy.

From a self-regulation perspective, the ABHI Code, in line with the European MedTech Code, prohibits member companies from providing financial or in-kind support directly to individual HCPs to cover costs of their attendance at third-party organised educational events with the exception of procedure training meetings or pursuant to a consulting agreement with a speaker for a satellite symposium. It also sets out clearer transparency obligations with regard to all interactions with HCPs, in terms of notifications to the relevant health institutions before the interaction may take place.

Reporting transfers of value

22 What requirements apply to recording and publishing details of transfers of value to healthcare professionals and organisations by companies marketing medicinal products or medical devices?

Medicinal products

UK law does not require the recording or publishing of the details of transfers of value (ToV) made directly or indirectly to HCPs and, other relevant decision makers, healthcare organisations (HCOs), patient organisations or others by pharmaceutical companies. These requirements are imposed by the self-regulatory Codes.

The ABPI Code has implemented the EFPIA Code requirements for disclosure of ToV to HCPs, HCOs and other relevant decision makers on an annual basis. It defines a ToV as 'a direct or indirect transfer of value, whether in cash, in-kind or otherwise, made, whether for promotional purposes or otherwise, in connection with the development or sale of medicines.' The Code requires companies to document and publicly disclose ToV on an annual basis, relating to collaborative working, donations and grants, contractual services, sponsorship of attendance by HCPs at meetings, fees and expenses paid to HCPs, and contributions made towards the costs of meetings paid to HCOs. Where ToV have been made to individual HCPs, the disclosure should identify the HCPs concerned (unless precluded by legal reasons). Where individual HCPs may not be identified, ToV should be disclosed on an aggregated basis.

The ABPI Code also requires member companies to disclose ToV to POs and also to disclose contracted services provided by members of the public, including patients and journalists.

Companies making ToV must publish a note summarising the methodologies used in preparing the disclosures and identifying each category of transfer of value. The note, including a general summary and/or country specific considerations, must describe the recognition methodologies applied and should include the treatment of multi-year contracts, VAT and other tax aspects, currency aspects and other issues relating to the timing and amount of transfers of value for the purposes of the Code.

The provisions and requirements are summarised in the European Union chapter.

Medical devices

There are no legal requirements for medical device companies to disclose payments to HCPs, HCOs, POs or others.

However, under the ABHI Code, member companies are required to document and publicly disclose all educational grants provided to HCOs based or registered in Europe. ToV not related to educational grants are not within the scope of the disclosure obligation.

Educational grants shall be disclosed on an aggregate basis for each recipient for the reporting period (annually, each calendar year). Itemised disclosure must be made available upon request by the relevant recipient or the relevant authorities, or both. 'Educational grants' means those grants made to support third-party organised events (including support for HCP participation at the event) and other educational grants made to HCOs (including scholarships, fellowships and grants for public awareness campaigns).

Disclosure shall be made within six months of the end of the relevant reporting period and will be made public on 31 August of the year of the relevant time of disclosure. Disclosure should be made in English using the template set forth in the Annex to the ABHI Code.

ENFORCEMENT OF ADVERTISING RULES

Enforcers

23 Describe the bodies involved in monitoring and ensuring compliance with advertising controls for medicinal products and medical devices, distinguishing between any self-regulatory framework and control by the authorities.

Medicinal products

The Human Medicines Regulations 2012 (HMRs) provide a means of enforcement and include both criminal and civil sanctions. The HMRs provide that it is an offence for 'any person' to breach the Regulations. This allows enforcement action to be taken against all stakeholders involved in the promotion, including marketing authorisation holders, publishers and advertising agencies.

Enforcement of the advertising provisions of the HMRs is the responsibility of the Enforcement Group of the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA prefers to resolve complaints quickly and informally, with companies agreeing to take voluntary action to amend their advertising and, in some cases, to issue a corrective statement. Details of cases resolved informally are posted on the MHRA's website.

Complaints under the Association of British Pharmaceutical Industries (ABPI) Code are considered by the Prescriptions Medicines Code of Practice Authority (PMPCA) Code of Practice Panel.

The two systems, statutory and self-regulatory, are regarded as 'complementary and synergistic' (memorandum of understanding between the MHRA, ABPI and PMCPA). Both bodies may hear complaints from any source, but the MHRA generally refers inter-company complaints to the PMCPA and routinely declines to investigate cases where it is aware that these are under investigation by a self-regulatory body. The Serious Fraud Office (SFO) is responsible for enforcement of alleged examples of bribery and corruption but will generally intervene in matters concerning advertising of medicinal products only where it considers that the self-regulatory regime is not effective or the potential sanctions that may be imposed are inadequate (memorandum of understanding between the SFO, ABPI and PMCPA).

Medical devices

The MHRA's enforcement powers in relation to medical devices derive principally from the Medical Devices Regulations 2002 and general powers that are not specific to devices. In addition, the Medicines and Medical Devices Act 2021 seeks to consolidate and expand the enforcement regime for medical devices, so that enforcement provisions and powers are contained solely in the 2021 Act.

Under these provisions, the MHRA can investigate any business activity that is covered by the regulations and is empowered to assess allegations of non-compliance, to monitor the activity of Notified or Approved Bodies and to investigate medical devices as a result of adverse incident reports.

Under the self-regulatory system, compliance with the ABHI Code is mandatory for ABHI members and those who have accepted the jurisdiction of the ABHI Complaints Adjudication Panel. The Code is administered by the ABHI Secretariat in conjunction with the chair of the Panel. The Panel is not an investigatory body and the complainants have the burden of proving their complaint. The Panel is responsible for resolving complaints made under the Code and may also assist in arranging for conciliation or mediation between companies. There is no appeal procedure against the Panel's rulings; however, this procedure does not preclude recourse to courts or other tribunals.

Sanctions

24 What are the possible financial or other sanctions for breach of advertising and promotional controls for medicinal products or medical devices?

Medicinal products

The MHRA has the power to issue notices prohibiting the publication of specific advertisements. Where the MHRA notifies a company that it considers an advertisement to be in breach of the HMRs, the company has the right to make representations to the MHRA Review Panel. If the MHRA issues a final notice determining that an advertisement is in breach, the company has no further right to appeal and will commit a criminal offence if it proceeds to publish the advertisement. The company may also be asked to issue a corrective statement. Companies may challenge the legality of the MHRA final notice by judicial review.

A person or company that contravenes the legislation may be subject to an unlimited fine. In addition, or alternatively, where individuals are involved in the publication or use of unlawful advertising, a period of up to two years' imprisonment may be imposed. Where directors are convicted of a criminal offence, they may also be disqualified. Fines are imposed according to the offence in question.

While there are only a few precedent decisions concerning the level of fines imposed, it is clear that the fine may be a substantial amount that is calculated to send a message to the defendant's shareholders (in cases where the defendant is a company rather than an individual). Fines must be paid directly by the person or company convicted, and cannot be insured. In addition, the MHRA's costs in bringing the proceedings are typically borne by the defendant, if convicted.

When a company is found in breach of the ABPI Code, an administrative charge is imposed: £3,500 per matter for ABPI member companies, and £12,000 if the matter is unsuccessfully appealed. The

charges increase to £4,500 and £13,000 respectively for non-members. In addition, the Panel and the Appeal Board have the power, in serious cases, to require an audit of the company's promotional procedures or to refer the matter to the ABPI Board of Management, which may suspend or expel the company from the ABPI, with the result that the company becomes subject to direct supervision by the MHRA.

The PAGB does not impose any financial sanctions but it may expel a company if it has failed to comply with the PAGB Code.

Medical devices

Upon completion of an investigation, the MHRA may impose a range of sanctions, including the issuance of a warning letter or a formal caution. The enforcement options include prohibition, suspension, compliance and restriction notices.

At present, most offences under the medical devices legislation are summary offences, meaning that penalties are generally lower than those that may apply to offences relating to medicines. The ABHI operates a similar enforcement system to that of the ABPI and the PMCPA, whereby member companies may ultimately be expelled from the ABHI. However, the Medicines and Medical Devices Act 2021 provides the Secretary of State with the ability to impose civil sanctions as an alternative to criminal prosecution and seeks to create a bespoke criminal offence that clarifies which contraventions of the Medical Devices Regulations 2002 could result in prosecutions. In particular, the Act provides the Secretary of State with powers to impose a monetary penalty on a person (where the Secretary of State is satisfied beyond reasonable doubt that the person has committed an offence) and accept an enforcement undertaking (where the Secretary of State has reasonable grounds to suspect a person has committed an offence and that person offers the undertaking).

PRICING AND REIMBURSEMENT

Pricing

25 What are the controls imposed on pricing of medicines and medical devices and reimbursement by national social security systems that are applicable to manufacturers, distributors and pharmacists?

Medicinal products

Pricing

The UK National Health Service Act 2006 provides the statutory basis for controlling the prices of health service medicines.

The prices of branded health service medicines (originator products, branded generics and biosimilars) are controlled under the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) or the parallel Statutory Scheme. In addition to these measures, the prices of medicines are controlled through public procurement procedures and limitations on reimbursement.

VPAS

The VPAS is a voluntary scheme, not binding under the laws of contract, negotiated between the Department of Health and Social Care and the Association of the British Pharmaceutical Industry.

The VPAS controls the prices of branded medicines indirectly, by limiting the profits that may be made by manufacturers and suppliers on such products on their National Health Service (NHS) business, by reference to a target rate of return on NHS sales, based either on total sales or capital. A margin of tolerance (MOT) of 50 per cent is permitted around the target level of profit. However, if a company exceeds the profit limit by more than the MOT, it will be required to do one or more of the following:

- repay excess profits over and above the MOT;
- reduce prices charged to the NHS to bring profits down to an acceptable level based on available forecasts; or
- delay or restrict agreed price increases.

The VPAS also imposes a budget cap on total expenditure on branded medicines by the NHS, with scheme members required to make scheme payments to the Department of Health and Social Care (calculated as a percentage of eligible net sales) in respect of excess expenditure. The payment percentage for 2019 was set at 9.6 per cent, for 2020 at 5.9 per cent and for 2021 at 6.6 per cent.

New branded health service medicines introduced by VPAS member companies following the grant of an EU or UK new active substance marketing authorisation are generally subject to free pricing, as are new products based on the same active substance that are line extensions, launched within 36 months of authorisation of the initial indication in the United Kingdom. The Department of Health and Social Care must be notified of the proposed price prior to launch and will confirm whether the product may be priced freely. The maximum price or NHS List Price of new branded health service medicines supplied by VPAS member companies that do not contain a new active substance must be approved by the Department of Health and Social Care prior to launch.

No VPAS member may increase the NHS List Price of a relevant medicinal product without the Department of Health and Social Care's prior approval. Where a company wishes to increase the price, it should provide at least eight weeks' notice, stating the amount of the proposed increase and the reasons in sufficient detail to satisfy the Department that the increase is justified. A price increase will only be agreed if the scheme member's estimated and forecast profits for the current and following financial years are below 50 per cent of the target level. No scheme member will be awarded a price increase within 12 months of a previous agreed increase.

Statutory Scheme

If a company that supplies branded medicines to the NHS is not a member of the VPAS (around 10 per cent of such companies), it is regulated by the parallel Statutory Scheme, currently set out in the Branded Health Service Medicines (Costs) Regulations 2018. The Statutory Scheme is applicable only to branded health service prescription-only medicines. Since 1 April 2018, it has involved a payment scheme, calculated as a percentage of net sales, similar to the scheme payments required under the VPAS. Payments are made on a quarterly basis, and the payment percentage was 9.9 per cent in 2019, 7.4 per cent in 2020 and 10.9 per cent in 2021.

The maximum or NHS List Price of new branded medicines supplied by Statutory Scheme members is directed by the Secretary of State, taking into account factors similar to those under the VPAS, including whether the product includes a new active substance.

A Statutory Scheme member company may apply to the Secretary of State to increase the maximum price of a medicine. Any such application by a manufacturer or supplier must be in writing and must specify the presentations to which it relates, the reasons justifying the increase and the proposed new price.

There is no formal system of international reference pricing in the UK, although the cost of the presentation in other markets is specifically mentioned as a factor for consideration under both the VPAS and the Statutory Scheme.

Unbranded generic medicines

Unbranded generic medicines may be priced at the discretion of the manufacturer, with the expectation that prices will be controlled by competition. Where the price charged for a specific unbranded medicine is viewed as excessive, the Secretary of State has power under the

National Health Service Act 2006 to issue a specific direction in relation to the price of that product.

Reimbursement

There is no formal reimbursement step or 'decision' that has to be undertaken in the UK. Once the price of a medicine has been notified to or agreed by the Department of Health and Social Care, the product is, in principle, available to be prescribed and reimbursed, unless it is listed in Schedules 1 or 2 to the National Health Service (General Medical Services Contracts) (Prescription of Drugs etc) Regulations 2004, which provide that certain medicines may not be prescribed using NHS prescriptions and others may be prescribed only for certain conditions (the 'black' and 'grey' lists). In practice, however, reimbursement is controlled through local formularies and national commissioning policies.

In England, most new medicines (and new indications for existing products) undergo health technology appraisal or highly specialised technology evaluation by the National Institute for Health and Care Excellence (NICE), which assesses their clinical effectiveness and cost effectiveness compared with standard care in the UK, and issues guidance to the NHS on use of the new product or indication. NHS bodies in England have a legal obligation to make funding available for treatments recommended by NICE following such assessments, usually within three months of guidance being published. NHS England conducts a prioritisation assessment that determines which specialised services (medicines, medical devices and other health interventions), which have not been assessed by NICE, will be funded on an annual basis. Other medicines, which are not specialised services and have not been assessed by NICE, undergo assessments at local level. Similar assessments to those carried out by NICE are undertaken by designated bodies in Scotland and Wales. Medicines that have not been recommended following an appropriate assessment are unlikely to be routinely available for patient treatment.

Medicines supplied in hospitals are not subject to any co-payment arrangements. However, for products supplied in primary care in England, patients must pay a fixed price for each NHS prescription dispensed, unless they fall within one of the exempt categories (eg, children, the elderly and persons suffering from certain chronic diseases) or the prescription is exempt (eg, certain contraceptives). The overwhelming majority of prescriptions are dispensed free of charge to persons in an exempt category. The current prescription charge is set at £9.15, which, in some cases, exceeds the price of the medicine dispensed. Prescription charges are not levied in Scotland, Wales or Northern Ireland.

Community pharmacies purchase medicinal products from wholesale distributors or directly from manufacturers. They are reimbursed by the NHS Business Services Authority for the products they dispense in the course of providing pharmaceutical services for the NHS, in accordance with the amounts set out in the Drug Tariff, published monthly in England in accordance with the National Health Service (Pharmaceutical and Local Pharmaceutical Services) Regulations 2013/349. Similar regulations provide for equivalent drug tariffs in Scotland and Northern Ireland. Where medicinal products are not listed in the Drug Tariff (most medicines that are still subject to patent protection) or are prescribed by brand, the pharmacy contractor will generally be reimbursed at the manufacturer's NHS List Price.

Medical devices

Pricing

Medical devices and in vitro diagnostic tests may be priced at the discretion of the manufacturer. However, as with medicines, prices may be controlled through public procurement procedures and control of reimbursement.

Reimbursement

The reimbursement of a medical device depends on the context in which it is used. Many medical devices used in hospitals are reimbursed under tariff systems where the price paid to the hospital by the relevant clinical commissioning group for the overall treatment includes the cost of the device, which may in turn be purchased under public procurement tenders. Certain high-cost medical devices are, however, paid for separately outside the tariff system.

Medical devices may undergo health technology assessment under one of NICE's parallel programmes, either on the application of the manufacturer or following referral by NHS bodies or clinicians. These will all involve assessment of the clinical use of the medical device and some will also include consideration of economic evidence. In general, the content of NICE's recommendations and briefings on use of medical devices is advisory only, although intended to avoid the need for repetitive assessment at local level. However, a NICE recommendation for use of a medical device following technology appraisal carries with it the requirement for NHS bodies to provide funding for the device to be available as an option for patients, as described above.

Alternatively, medical devices used in specialised services may be assessed by NHS England under its prioritisation procedure, involving consideration of both benefits and costs and comparison with a range of other health technologies, to determine which should be prioritised for NHS commissioning. In some cases, where the clinical data are viewed as inadequate to reach a conclusion on NHS use, a commissioning through evaluation approach is adopted, where use of the device in a limited number of patients over a specified period of time (usually two years) is funded by the NHS and data are collected for the purposes of a final commissioning decision at the conclusion of the process. High-cost medical devices may be purchased through NHS Supply Chain, which negotiates with manufacturers on behalf of all NHS purchasers collectively.

In primary care, medical devices, such as appliances and dressings, incontinence appliances, stoma appliances and chemical reagents, are routinely dispensed through the NHS if a reimbursement price, agreed with the NHS Business Services Authority, is listed in the Drug Tariff. The reimbursement price is principally determined by comparing the device with the prices of similar products on the market. If there are no comparable devices or the applicant submits evidence to support a different price, the reimbursement price will be determined by negotiation between the parties. Applications must meet three criteria, supported by evidence: the products are safe and of good quality (generally assumed for all CE-marked products); they are appropriate for general practitioners and, if relevant, non-medical prescribing; and they are cost effective (eg, as determined by NICE).

OFF-LABEL USE AND UNLICENSED PRODUCTS

Off-label use

26 | May health professionals prescribe or use products for 'off-label' indications? May pharmaceutical companies draw health professionals' attention to potential off-label uses?

Medicinal products

Certain healthcare professionals (HCPs) may prescribe or use products off-label, where this is considered appropriate, including for certain categories of patient (eg, children) or in certain therapeutic areas (eg, oncology and dermatology), where there may be no treatment authorised for the required clinical indication. Guidance issued to prescribers by the Medicines and Healthcare products Regulatory Agency (MHRA) states that the responsibility that falls on HCPs when prescribing an unlicensed medicine or a medicine used off-label may be greater than when prescribing a licensed medicine within the terms of its licence, and

reminds prescribers to pay particular attention to the risks associated with using an unlicensed medicine or a licensed medicine off-label.

The reimbursement of an unlicensed medicine or a licensed medicine used off-label (where this can be determined) depends on applicable National Health Service (NHS) commissioning policies.

Pharmaceutical companies may not advertise unlicensed medicinal products or off-label indications for licensed medicines or otherwise draw the attention of HCPs to potential uses of their medicines in a manner that is not consistent with the summary of product characteristics (SmPC). These provisions do not, however, preclude the provision of information in response to a specific, unsolicited enquiry or in a strictly non-promotional context, as part of a legitimate exchange of scientific information at, for example, an international meeting held in the UK.

The guidance of the MHRA and the provisions of the Association of the British Pharmaceutical Industry (ABPI) Code reflect the Court of Justice of the European Union (CJEU) decision in the *Novo Nordisk* case (C-249/09) recognising that, although claims that conflict with the SmPC are not permitted, not all of the information contained in an advertisement needs to be identical to that in the SmPC, provided the claims are consistent with the content of the SmPC. Advertisements may, therefore, include additional information, provided that this confirms or clarifies the content of the SmPC and is compatible with it. Any such additional information must also meet the various other requirements of the UK Human Medicines Regulations 2012, such as being presented objectively, faithfully and in such a way as to allow independent verification, and not being exaggerated, misleading or inaccurate. In addition, the ABPI Code permits certain limited activities that may take place prior to the grant of a marketing authorisation (MA) or approval of a new indication for an existing product in order to assist the NHS with financial planning. Such information must be directed towards those responsible for policy decisions on budgets and not to prescribers and is limited to non-promotional, factual information in circumstances where the new product or indication is likely to impact local NHS expenditure.

Medical devices

The use of a medical device by an HCP or patient in a way or for a purpose inconsistent with the CE/UKCA mark (off-label use) is not prohibited by UK law. Guidance issued by the MHRA, however, advises HCPs that off-label use of a medical device, without the manufacturer's approval, will be at their own risk and may result in civil claims for damages if such off-label use results in injury to patients. Off-label use in the context includes reuse of single-use devices, modification of medical devices that are not intended to be modified or failure to make modifications (including software updates) where advised by the manufacturer.

A manufacturer may not promote a medical device in a way inconsistent with its CE/UKCA mark.

Unlicensed products

27 What rules apply to the manufacture and importation and supply to healthcare providers of unlicensed medicines or medical devices?

Medicinal products

The Human Medicines Regulations 2012 (HMRs) provide a number of exemptions to the requirement for an MA.

The 'special needs exemption' applies to medicinal products supplied in circumstances where all the following conditions are met: the product is supplied in response to an unsolicited order; it has been manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber; and the product is for use by a patient for whose treatment the above-specified person is directly responsible, in order to fulfil the special needs of that patient. The CJEU has confirmed, in *Commission v Poland* (Case C-185/10), that 'special needs' must be construed as special clinical needs and not costs. In the interest of public health, this exemption is narrowly drawn because these products, unlike licensed medicines, have not been assessed as meeting criteria of safety, quality and efficacy.

The 'pharmacists exemption' applies to a medicinal product prepared or dispensed in a registered pharmacy, hospital, care home or health centre by or under the supervision of a pharmacist in accordance with a prescription given by an appropriate practitioner.

The 'doctors' and dentists' exemption' covers a medicinal product manufactured or assembled (otherwise than on a large scale or using an industrial process) by a doctor or dentist and supplied by that doctor or dentist, or a member of the same practice, to a patient during the course of treatment.

Herbal medicinal products prepared by a person (otherwise than on a large scale or using an industrial process) for use by a specific patient and that do not include prohibited substances or substances in excess of permitted quantities.

The UK may also temporarily authorise the distribution of unlicensed medicines in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation.

In addition, investigational medicinal products supplied in the context of medical research under the provisions of the UK Medicines for Human Use (Clinical Trials) Regulations 2004 may be supplied to healthcare providers.

The release of unlicensed medicinal products or 'specials' should be by the quality controller or a nominated deputy. Adequate precautions should be taken to ensure that the product is of the quality required for its intended purpose and that it complies with any standards described in relevant pharmacopoeia monographs.

Companies holding a 'specials' manufacturing licence may advertise that they make up individualised remedies to order for HCPs. It should be clear that these remedies are not available for supply directly to the public. It is only appropriate to advertise this facility to HCPs who are authorised to have specials supplied to them. Specials manufacturers must not advertise or otherwise solicit orders for specific unlicensed products. This does not preclude them from sending out simple price lists to HCPs to whom the price of specials may be relevant, such as potential customers and budget managers. Price lists can be sent out at reasonable intervals or in response to an enquiry and must not include product claims.

The importer of an unlicensed medicinal product (a special) into Great Britain must hold a wholesale dealer's licence (if the product is to be imported from a country on the approved list (currently countries in the European Economic Area (EEA)) or Northern Ireland) or a manufacturer's (specials) licence (if the product is to be imported into Great Britain from outside the EEA). The holder of the wholesale dealer's licence or manufacturer's licence must comply with certain obligations, and that notification is given to the MHRA at least 28 days in advance of the intended import. If the MHRA issues an objection to importation, this cannot take place.

The Medicines for Human Use (Clinical Trials) Regulations 2004 require all interventional clinical trials to be authorised by the MHRA and ethically approved, including the arrangements for the supply of investigational medicinal products. Such products may currently be imported into Great Britain by holders of a wholesale dealer's licence (if the product is to be imported from the EEA or Northern Ireland) or a manufacturer's licence (if the product is to be imported from outside the EEA).

Medical devices

A medical device may only be placed on the market or into service if it is CE/UKCA marked or satisfies one of the exemptions under the Medical Devices Regulations 2002. These exemptions include:

- single-use combination products regulated as medicinal products;
- custom-made medical devices and devices intended for clinical investigation;
- supply of non-compliant devices under an authorisation from the MHRA in the interest of the protection of health, where there is no legitimate alternative available; and
- in vitro diagnostic medical devices intended for performance evaluation in a laboratory.

MHRA guidance advises HCPs to use CE/UKCA marked medical devices as this shows that the relevant device has met the requirements for safety, quality and performance if used as the manufacturer instructs.

Medical devices that are custom-made for individual patients are defined under the UK Medical Devices Regulations as medical devices manufactured specifically in accordance with a written prescription of a registered medical practitioner, or other person authorised to write such prescriptions, which gives under his or her responsibility, specific characteristics as to its design and intended for the sole use of a particular patient. The MHRA has issued specific guidelines to assist manufacturers with understanding compliance requirements for the manufacture of custom-made medical devices (including active implantable medical devices).

Compassionate use

28 | What rules apply to the establishment of compassionate use programmes for unlicensed products?

Medicinal products

Regulation (EC) No. 726/2004 allows member states to exempt certain medicines from the requirement for an MA (those that must be authorised under the Regulation and those that are eligible for authorisation via this route) so that they can be made available for compassionate use by groups of patients with chronically or seriously debilitating diseases or whose diseases are considered be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The unlicensed product must either be the subject of an application for an MA in accordance with the Regulation or be undergoing clinical trials.

There is no formal implementation of this provision in the UK. However, a programme for access to certain medicines prior to grant of MA may be established through the MHRA's early access to medicines scheme (EAMS). This involves a two-step evaluation process comprising: an application for a promising innovative medicine designation, which gives an indication that a product may be eligible for the EAMS based on early clinical data; followed by an early access to medicines scientific opinion on the benefit-risk balance of the medicine. The scientific opinion is based on the data submitted at the time of application and lasts for a year. Following a positive early access to medicines scientific opinion, the MHRA will publish a public assessment report and the EAMS treatment protocol on the UK government website. Company promotion of the EAMS is not permitted. Application for EAMS is conditional upon the manufacturer providing the medicine free of charge to the NHS during the EAMS period (defined as after the award of a positive scientific opinion and up to the granting of the MA) and those patients receiving a free of charge medicine during this EAMS period continuing to do so up to the point of a positive funding decision (eg, Human Tissue Authority guidance, national funding policy and local funding arrangements).

For products that are not assessed under EAMS arrangements or do not qualify, individual patients may receive treatment prior to grant of MA in the context of clinical trials or in accordance with the special needs provisions.

Medical devices

The Medical Devices Regulations 2002 provides that the MHRA may approve exceptional use of a non-compliant device to protect a patient's health if there is no legitimate alternative available. These provisions, commonly known as supply on 'humanitarian grounds' are available only in exceptional circumstances following an application by the manufacturer. The key conditions are that the clinician responsible for the patient's treatment supports the manufacturer's application, there is no alternative CE-marked device available for this treatment and it can be demonstrated that mortality or morbidity is significantly reduced if the device is used compared with compliant alternatives.

A separate application is required for each patient on a case-by-case basis. If the application is approved, the decision will also include details of any associated obligations for the manufacturer or clinician.

SALE AND SUPPLY

Regulation

29 | Are there special rules governing the dispensing or sale of particular types of medicinal products or medical devices?

Medicinal products

All medicinal products marketed in the UK are classified according to one of the three following categories:

- prescription-only medicines, which are available only by prescription from a doctor or other authorised health professional, and must be dispensed from a pharmacy or other specifically licensed premises;
- pharmacy or over-the-counter medicines, which are only available in pharmacies under the supervision of a pharmacist; and
- general sale list (GSL) medicines, which are available in general retail outlets, such as supermarkets.

The classification of a medicinal product is determined by its marketing authorisation and determines the level of control over how it is supplied. In part, classification rests on how much input from healthcare professionals is needed to diagnose and treat the conditions for which the medicine might be used. The underlying principle for classification is to maximise timely access to effective medicines while minimising the risk of harm from inappropriate use.

Medical devices

There are three main types of medical devices:

- general medical devices;
- active implantable medical devices; and
- in vitro diagnostic medical device (IVD).

Medical devices are also given a classification depending on the level of risk associated with their use. Classification depends on factors such as intended purpose, duration of use and whether it is invasive or surgically invasive, implantable or active, or contains a medicinal product.

The categories for general medical devices and active implantable devices are Class I (low risk), Classes IIa and IIb (medium risk) and Class III (high risk). All active implantable medical devices fall under the highest risk category.

IVDs are categorised into four main groups based on whether they are general IVD medical devices, intended for self-testing, or classified under Lists A or B in Part IV of the UK Medical Device Regulations 2002.

All medical devices placed on the market in Great Britain must be registered with the MHRA. A UK Approved Body ensures manufacturers

have followed the appropriate conformity assessment route and comply with the UK regulations, including reviewing clinical and scientific data, manufacturing processes and the quality management system. If they comply then the UK Approved body will issue a UKCA certificate, which manufacturers can place on their device to show that it has passed the conformity assessment.

Online supply

30 What laws and guidelines govern online dispensing, sale and supply of medicinal products and medical devices?

Online retailers may only sell GSL products unless they are registered pharmacies. With regard to medical devices, the MHRA advises buyers to look for the UKCA mark on medical devices as an indicator that they have been approved to be placed on the market in Great Britain. Online pharmacies and clinics are regulated by bodies such as the General Pharmaceutical Council and the Care Quality Commission.

The online supply of both medicines and medical devices must also comply with the Electronic Commerce (EC Directive) Regulations 2002 (as amended by the corresponding Brexit statutory instrument).

UPDATE AND TRENDS

Forthcoming legislation and regulation

31 Is there any current or foreseeable draft legislation or other rules that will affect the regulation of pharmaceuticals and medical devices? What is likely to change, and what steps need to be taken in preparation?

The regulation of medicines and medical devices in the United Kingdom was previously governed by EU law as transposed into UK domestic law, and the UK legislation has been substantially amended to take into account the fact that the UK is no longer part of the EU medicines regime. In addition, the Medicines and Medical Devices Act 2021 grants broad and wide-ranging powers to the Secretary of State to amend the existing regulatory framework for human medicines, clinical trials and medical devices, which is intended to enable the UK regime to be amended as necessary. The Act also establishes a Patient Safety Commissioner for England, as recommended in the Independent Medicines and Medical Devices Safety Review, which delivered its report in July 2020.

The Medicines and Healthcare products Regulatory Agency (MHRA) is undertaking a number of consultations on the new regime that should apply in the UK. This is particularly the case for medical devices, where the UK will continue to recognise EU CE-marked devices until June 2023, but the EU Medical Devices Regulations do not apply in Great Britain. A consultation on the new regulatory framework in the UK for medical devices was published in September 2021.

The MHRA has also stated that it intends to amend the UK clinical trials regime in order to align with the EU Clinical Trials Regulation 'where that makes sense'. Initial changes are due to be introduced so they are effective by the end of 2021, in line with the date of application of the EU Regulation, with more substantial consultation planned for 2022.

The EU medicines and devices regimes continue to apply in Northern Ireland, and the authorisation, supply and oversight of products in Northern Ireland and the relationship between the EU and UK continues to cause complications for companies, and industry continued to lobby the government to clarify the position. The requirements are subject to ongoing political discussion.

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