Pharma & Medical Device Regulation 2022

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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.

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European Union

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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.

Primary responsibility for delivering and controlling healthcare services and products in the European Union is held by the EU member states. The EU institutions complement national policies by harmonising certain aspects of the legislation and services, such as for the evaluation and authorisation of certain medicines, and the procedures for placing medical devices on the EU or European Economic Area market.

The European Commission, supported in particular by the Directorate for Health and Food Safety, proposes healthcare-related legislation, provides financial support and coordinates health-related activities involving both medicinal products and medical devices.

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

Medicinal products are authorised through the centralised authorisation procedure at the EU level by the European Commission, which takes the decision based on the scientific evaluation carried out by the European Medicines Agency (EMA).

The Heads of Medicines Agency Coordination Group assists with the examination of any questions relating to the marketing authorisation (MA) of a medicine in two or more member states, and is involved in the coordination of assessment for nationally approved products via the mutual recognition or decentralised procedure.

Medical devices

Medical devices are regulated and authorised differently depending on the risk categorisation of the product. For higher risk devices, the quality systems and technical documentation should be reviewed by a Notified Body before the device can be placed on the market. A Notified Body is an organisation designated by the member state competent authorities to assess the conformity of certain products before being placed on the market.

There are a number of EU-wide organisations that seek to assist with the coordination between Notified Bodies and the competent authorities in the member state. For example, the Medical Device Coordination Group provides advice to the Commission and assists the Commission and the member states in ensuring harmonised implementation of the new medical devices regulations. The Competent Authorities for Medical Devices group seeks to enhance collaborative working, communication and surveillance of medical devices across Europe.

Borderline products

Sometimes, it may be unclear whether a product is a medicinal product, medical device, cosmetic, biocidal, food or another category of product. In the case of these 'borderline products', the decision on a product's classification is taken on a case-by-case basis based on both its function and its presentation. The starting point is the analysis of whether the product falls within the legal definition of any of these categories under EU law, and where there is doubt, the rules relating to medicines will apply. The European Commission has published numerous guidance documents to facilitate the demarcation between these categories of products, however, the decision is usually taken by member state authorities.

Approval framework

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

Medicinal products

The legal framework for the approval of medicinal products is primarily set out in Directive 2001/83/EC and Regulation (EC) No. 726/2004.

A marketing authorisation is required to place a medicinal product on the market in the EU. The assessment seeks to determine the medicinal product's safety, quality and efficacy based on the data submitted, and the competent authority determines a positive or negative risk-benefit balance.

There are four different routes or procedures for obtaining an MA for a medicinal product, three of which are European-level authorisation procedures for which there is coordination between member states (the centralised procedure, the decentralised procedure and the mutual recognition procedure), and the fourth being the national procedure, which is controlled by national legislation.

Under the centralised procedure, marketing authorisation holders (MAHs) may obtain a single EU MA. The product is assessed on an EU-wide basis and approved by the European Commission. The EMA, with the assistance of its committees, conducts the evaluation using scientific expertise from the member states. The centralised procedure is compulsory for some products, optional for others and not available for the rest.

The mutual recognition procedure and the decentralised procedure result in national MAs, although the procedure for assessment is coordinated across the EU. Mutual recognition must be used when a product is already authorised in at least one member state and the MAH wishes to obtain an MA for the same product in at least one other member state. The decentralised procedure may be used if the product is not already authorised in any member state, but the MAH is not able or does not want to use the centralised procedure.

Directive 2001/83/EC requires all MAs to include the approved product information: the summary of product characteristics, labelling (the internal and external packaging of the product) and package leaflet (or patient information leaflet). EU law determines the content, format and layout that applies to these documents.

Medical devices

The Medical Devices Regulation (EU) 2017/745 has been applicable since May 2021 and the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 is due to apply from May 2022. In addition, a number of devices continue to be on the EU market under CE marks and conformity assessment procedures carried out under the Directive 93/42/EEC concerning medical devices, Directive 90/385/EEC on active implantable medical devices, and Directive 98/79/EEC on in vitro diagnostic medical devices.

A medical device must have a CE mark before it can be placed on the market in the EU, and the procedure to obtain the mark will depend on the risk classification of the device. Each device must fulfil the relevant general safety and performance requirements applicable to it, and the manufacturer must demonstrate that its medical devices meet the requirements in the legislation by carrying out a conformity assessment. For some devices, the device can be self-certified without the involvement of a Notified Body. However, for higher risk devices, the conformity assessment involves an audit of the manufacturer's quality system by a Notified Body and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device.

The medical device directives established numerous requirements regarding the labelling and packaging of medical devices. However, the new medical devices regulations have implemented a large number of changes relating to the instructions for use, unique device identification requirements, serial and lot numbers, highlighting of the identity of the authorised representative, warnings and precautions on the label, medical device symbols and electronic information for use.

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

Clinical trials for medicinal products are currently governed by the Clinical Trials Directive 2001/20/EC. The sponsor of a clinical trial must obtain an authorisation from the competent authorities in the member states where the trial is being conducted to carry out the trial, together with a positive opinion from the relevant local ethics committee. These procedures are controlled by national legislation and procedures.

The Directive will be replaced by the Clinical Trials Regulation (EU) No. 536/2014 in January 2022, which aims to ensure a greater level of harmonisation in the European Union. In particular, the regulation will provide for a single EU database where the sponsor can make a single application for the clinical trial authorisation and ethics committee approval for all member states in which the trial will be conducted.

Medical devices

Both the medical device directives and the medical devices regulations require the manufacturer or person responsible for placing the medical device on the market in the European Economic Area to produce and maintain a clinical evaluation report for each device. The clinical evaluation involves the assessment and analysis of clinical data relating to a medical device in order to verify its safety and performance. This may include the need to conduct clinical investigations, but this is not a requirement of the Directives. Any clinical investigations that are carried out must be conducted in accordance with Annex X of the Medical Device Directive (or the equivalent Annex for other types of devices). As part of this process, the national competent authority will consider the application to conduct the clinical investigation, and the local ethics committee will provide an opinion on the investigation.

The new medical devices regulations place more focus on clinical evaluations, and the requirements for clinical investigations, although the procedures for the approval and performance of such investigations are similar to the procedures under the medical device directives.

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

Before commencing a clinical trial and before submitting an application to the national competent authority, the applicant must obtain a unique EudraCT number, which identifies the protocol for the trial. The EudraCT database is used by the competent authorities to collect information on clinical trials. It is the responsibility of the national competent authorities to update information about the trial in EudraCT, including the approval of the clinical trial, substantial amendments and the end of the trial.

Certain information in the EudraCT is made public and is searchable via the EU Clinical Trials Register.

Information on the results of trials are entered into the EudraCT database by the sponsors themselves and are published in the Register once the sponsors have validated the data. Commission guidance states that for all trials, result-related information should be supplied and made public within 12 months of the completion of the trial (not only after grant of the marketing authorisation), including a summary of the results and conclusions.

Under the Clinical Trials Regulation, the transparency obligations have been given a legislative setting, with more obligations being placed on sponsors of clinical trials to make information about the trials they conduct public.

Medical devices

Currently, there is a European central repository for information about medical devices: Eudamed2. Euramed2 is a secure web-based portal managed by the European Commission. It is restricted to national competent authorities; it is not publicly accessible. There are no obligations in relation to disclosure of information on clinical investigations. However, the medical device directives contain a general provision that clinical investigations should be conducted in line with the Declaration of Helsinki, which includes provisions on publication of results of investigations.

The new medical devices regulations provide for a much larger Eudamed database, some of which will be available to the public, including some information on clinical evaluations for certain devices. However, this does not include an obligation to routinely disclose information on clinical investigations for devices.

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

Both the Clinical Trials Directive and the Clinical Trials Regulation require informed consent from trial subjects to take part in a clinical trial. The consent must be written, dated and signed. It must be given freely after the subject has been duly informed of the trial's purpose, significance, implications and risks, and appropriately documented by any person capable of giving consent or, where the person is not capable, by his or her legal representative. If the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

With regard to personal injury insurance, the legislation obliges the sponsor to make provision for insurance or indemnity to cover the liability of the investigator and sponsor, without specifying a particular limit at the EU level. Such requirements are controlled at a national level.

Medical devices

Clinical investigations with medical devices are expected to be designed, conducted and reported in accordance with international standards and the Declaration of Helsinki. The requirements regarding the collection of consent from trial subjects are, therefore, similar to those required for medicine-related trial subjects. Informed consent is required in all cases, and it must be given freely, written, dated and signed. There are no specific provisions on insurance, although many ethics committees will require such provision to be put in place.

The new medical devices regulations contain specific provisions on informed consent of subjects involved in clinical investigations, which are broadly in line with the requirements for medicinal products. In addition, the new medical devices regulations set out requirements for a 'system of compensation' to be put in place to compensate subjects for damage suffered as a result of participation in a clinical investigation. This system will be put in place on a national basis.

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

With regard to marketing authorisations (MAs) under the EU centralised procedure, the assessment of an application for a new medicine takes up to 210 'active days'. This time is interrupted by one or two 'clock-stops'. Overall, the assessment of a new medicine usually lasts around one year. MAs granted by the European Union have an initial period of validity of five years. The European Medicines Agency (EMA) charges fees for applications for MAs and for variations and other changes to MAs, as well as annual fees for authorised medicines. The EMA basic fee for an MA application for a human medicine starts at €296,500

Under the mutual recognition and decentralised procedures, the evaluation process may take up to 210 days after the submission of a valid application under the decentralised procedure, and 90 days under the mutual recognition procedure. Once all the member states involved in the procedure agree with the assessment, the procedure closes, and each member state must grant a national MA. This grant should occur within 30 days, but in practice, the national phase timelines and fees for MAs vary as these follow the national rules. MAs granted are also valid for an initial period of validity of five years.

Medical devices

It generally takes 12 to 16 weeks to get a CE marking for a medical device where this process requires the involvement of a Notified Body. Most Notified Bodies offer options for expedited reviews or dedicated on-site review of design dossiers and technical files. The EC Declaration of Conformity and CE mark are valid as long as the product meets the applicable legal requirements and no significant changes are made to the device.

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

Data submitted by originators is protected for a period of eight years from the initial authorisation of the reference product by a 'regulatory data protection' period. During this time, no generic applicant can refer to the data contained in the application dossier. After the expiry of this period, applications for generic products can be submitted that cross-refer to the preclinical and clinical data submitted to support the authorisation of the originator product, so the generic company does not need to generate its own data. In addition, there is a two-year period of 'market protection' during which authorised generic products, if authorised, cannot be placed on the market.

This 10 year-period (eight years regulatory data protection plus two years market protection) can be extended to a maximum of 11 years if, during the first eight years, the marketing authorisation holder (MAH) obtains an authorisation for one or more new therapeutic indications that, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

Where a change of classification of a medicinal product has been authorised on the basis of significant preclinical tests or clinical trials, the data summited to support that variation is protected by a standalone one-year period of data protection, during which a generic company cannot cross-refer to the data when seeking to make an application for a change in the classification of its product.

Where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data protection shall be granted, provided that significant preclinical or clinical studies were carried out in relation to the new indication.

Medical devices

There is no protection period for data submitted to support a CE marking. However, the data is usually considered to be confidential, and manufacturers of similar or follow-on products cannot access such data.

Medical device manufacturers may use a device that is already on the market to demonstrate equivalence of their own device to reduce the amount of data required to obtain a CE mark for its product. There are three equivalence criteria: clinical, technological and biological. The European Commission guidance provides details on how this should be documented and factors that could affect the demonstration of equivalence. Under the new medical devices regulations, manufacturers must have a contract in place allowing access to data for competitors' devices with which equivalence is claimed.

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

Regulation (EC) No. 1049/2001 provides EU citizens with a right to access documents held by EU institutions. This Regulation applies to the EMA, and to implement it, the EMA has put in place a policy on access to EMA documents. This right of access applies to documents received by the EMA or in its possession, such as research data submitted by applicants for MAs. The EMA's policy provides that it will ensure protection of commercial interests in accordance with the notion of commercially confidential information. The EMA policy defines it as 'any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information'.

Medical devices

Given that Notified Bodies are private entities, they are not subject to the freedom of information legislation. As such, there is very limited ability to request access to the technical information relating to an application for CE marking held by the Notified Bodies.

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?

EU law sets out requirements for certain specific areas, such as medicinal products for rare diseases (the Orphan Drugs Regulation (EC) No. 141/2000) or medicines for children (the Paediatrics Regulation (EC) No. 1901/2006). The basic procedures for authorisation of those medicinal products are the same as for standard products. However, there are additional requirements, or incentives, that may apply to such products.

For example, medicines must meet certain criteria if they are to be classified as orphan medicinal products. Medicines that have been granted an orphan designation benefit from protocol assistance (a form of scientific advice by the EMA) at a reduced charge; access to the centralised authorisation procedure; and 10 years of market exclusivity protecting the product from market competition from similar medicines with similar indications once they are approved.

Companies applying for designated orphan medicines also pay reduced fees for regulatory activities. Companies classified as micro, small and medium-sized businesses (SMEs) benefit from further incentives when developing medicines with orphan designation. These include administrative and procedural assistance from the EMA's SME office and fee reductions. Separately, the European Commission offers research grants for sponsors of orphan medicines.

MA applications for medicines must include consideration of use of that product in children. Medicines authorised in the European Union that include reference to the results of studies from an approved paediatric investigation plan included in the product information are eligible for an extension of their supplementary protection certificate (SPC) by six months, even when the studies' results are negative. If the product is an orphan product, the 10-year period of market exclusivity is increased to 12 years. The EMA offers scientific advice and protocol assistance free of charge for questions relating to the development of paediatric medicines. Medicines developed specifically for children that are already authorised but are not protected by a patent or an SPC are eligible for an MA for paediatric use (PUMA). If a PUMA is granted, the new data submitted to support authorisation of the product will benefit from 10 years of market protection.

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

Under the EU legal framework of pharmacovigilance, the MAH must monitor adverse events that relate to its product and seek to monitor and reduce the risk of those events. The requirements include risk management plans, post-authorisation studies, signal detection and management at the EU level, periodic safety update reports, and assessment and reviews of medicines through referrals. MAHs are also required to maintain a pharmacovigilance system master file that is permanently available for submission or inspection by the national competent authority.

The process of reporting adverse drug reactions is centralised through electronic submissions to the EudraVigilance database.

Medical devices

Manufacturers of medical devices are required to implement and maintain a post-market surveillance system that monitors the clinical performance and clinical safety of the device as part of their quality management system. There are also obligations on vigilance, whereby the manufacturer must collect and evaluate incidents and implement corrective action as 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

Manufacturers and importers (of medicines from third countries) located in the European Economic Area (EEA) must hold a manufacturing or import authorisation issued by the national competent authority of the member state where they carry out these activities. They must comply with EU good manufacturing practice (GMP) guidelines, which describe the minimum standard that a medicine manufacturer must meet in their production process. Importers are responsible for ensuring that the third-country manufacturers from whom they are importing comply with GMP. MA applicants must ensure that the proposed manufacturing sites included in the MA application comply with GMP.

To obtain a manufacturing or import authorisation, the applicant must specify the medicines that are to be manufactured or imported and the place where they are to be manufactured or controlled, and have at their disposal suitable premises and control facilities and the services of at least one qualified person. Fees vary per country. Both fees and the validity periods for manufacturing or importing authorisations are set out at a national level.

Possession of a manufacturing authorisation includes authorisation to distribute by wholesale the medicines covered by the authorisation.

Medical devices

Manufacturers or their authorised representative should be based in the European Union or EEA to place medical devices on the EU or EEA market. Importers of medical devices from outside the European

Union or EEA are not required to obtain an import authorisation but can become legally responsible under the medical devices legislation for those devices. The importer may choose either to sell the device under the name of the manufacturer as its authorised representative in the European Union, or to sell under the importer's own name (own brander), but the importer will then require an agreement with the manufacturer to ensure the importer has access to the technical documentation relating to the CE marking of the device, as the importer must ensure that the products that it places on the market comply with the applicable requirements. In this case, the importer must engage a Notified Body to obtain a CE mark under its own name. No authorisation is required to distribute medical devices that have been lawfully placed on the EU market.

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 enforcement of the pharmaceutical legislation is mainly carried out at a national level, although EU law states that in determining penalties, member states should ensure that they are 'effective, proportionate and dissuasive'. National penalties primarily involve administrative or, in some member states, criminal fines. Individuals who are involved in the commission of a breach may, depending on the country involved, be fined or imprisoned. At the EU level, Regulation (EC) No. 726/2004 provides for EU financial penalties, according to which the EMA may investigate and report on alleged breaches of the EU pharmaceutical rules by holders of an MA for centrally authorised products. The European Commission can then adopt decisions imposing significant financial penalties, of up to 5 per cent of their annual turnover, on infringing MAHs.

Medical devices

The rules on medical devices are enforced at a national level. National competent authorities have a range of investigatory and enforcement powers to ensure the safety and quality of devices. Competent authorities assess allegations of non-compliance, monitor the activities of the Notified Bodies designated by them, investigate medical devices as a result of adverse incident reports and carry out proactive risk-based projects with other EU member states to identify emerging risks. As with medicines, national penalties may be imposed on individuals and entities found to be in breach of the legislation, and primarily involve administrative or, in some member states, criminal fines.

Exemptions

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

Directive 2001/83/EC provides certain exemptions from the requirement to obtain approval to market a medicinal product. These are:

- medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient (or magistral formula);
- medicines prepared in a pharmacy in accordance with a pharmacopoeia intended to be supplied directly to the patients served by the pharmacy (or officinal formula);
- intermediate products intended for further processing;
- radionuclides in the form of sealed sources;
- whole human blood or plasma;
- Advanced therapy medicinal products prepared on a non-routine basis and used in a hospital for an individual patient;
- industrially produced medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional (HCP) and for use by an individual patient under the HCP's direct personal responsibility to fulfil special needs; and
- temporary authorisations to distribute unauthorised medicines in response to the suspected or confirmed spread of pathogenic agents and other chemical or toxic agents that could cause harm.

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

Medicines authorised in both the EU member state of origin and the EU member state of destination may be parallel imported into the destination country, provided the imported product has the same composition of active substances, and there are no therapeutic differences from the corresponding product authorised in the member state of destination. Parallel importers must submit a notification of intention to parallel distribute to the EMA (for centrally authorised products) or an application to the national competent authority for a parallel import authorisation (for nationally approved products) prior to any importation. They must also hold a wholesale distribution authorisation covering importing, storage and sale of the relevant products. Any relabelling or repackaging activities will likely require a manufacturing authorisation.

EU law does not restrict individuals importing medicines into an EU member state from a third country provided they are strictly for use by that person or a member of their immediate family.

Medical devices

Once a medical device has been CE marked, it may be marketed anywhere in the European Union or EEA, as long as the requirements set out in the currently applicable medical device directives are met. A parallel importer would not normally be regarded as the manufacturer of the device unless that person repackaged the product and rebranded it so that the product is placed on the market under that person's name; or changes were made such that the device is no longer covered by the original CE mark, for example, if the parallel importer modifies the device in some way.

AMENDING AUTHORISATIONS

Variation

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

Medicinal products

Variations to the terms of marketing authorisations (MAs) are regulated by Commission Regulation (EC) No. 1234/2008 (the Variations Regulation). The procedure and requirements differ depending on the type of variation in question: type IA for minor variations, type II for major variations and type IB for those variations that are not type IA, type II, or an extension. An extension of an MA is a change that falls within the categories set out in Annex I of the Variations Regulation, mainly changes to the active substances and changes to strength, pharmaceutical form or route of administration.

Medical devices

If a manufacturer makes changes to a medical device that potentially affects its performance or safety characteristics, it must liaise with the relevant Notified Body and submit the necessary documentation to determine if the CE mark remains 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

MAs are renewable after five years upon application by the MA holder (MAH) to the relevant competent authority. Once renewed, the MA will be valid for an unlimited period unless the competent authority decides, on justified grounds relating to pharmacovigilance, to mandate one additional five-year renewal period. The MAH must apply for a renewal no later than nine months before the expiry date of the MA.

Medical devices

The EC Declaration of Conformity and CE mark are valid as long as the product 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

An MAH may transfer the MA to a new MAH. MA transfer applications for centrally authorised products, including mock-ups of the product information, must be submitted for each product. A transfer application follows a 30-day procedure following receipt of the application. When transferring the MA of a designated orphan medicinal product, the MAH must also transfer the orphan designation of the product.

Medical devices

A change of the manufacturer of a medical device will transfer all the obligations and requirements relating to the medical device to the new manufacturer. The new manufacturer must conduct its own conformity assessment procedure for the device, liaising with the corresponding Notified Body as required.

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

The European Medicines Agency (EMA) coordinates the assessment of reports of product quality defects of centrally authorised products. Marketing authorisation holders (MAHs) and manufacturing authorisation holders are obliged to report to the EMA any product quality defect that could result in a recall or abnormal restriction on supply. This includes any new information that may influence the evaluation of the product risk-benefit or any restriction imposed by the competent authority of any country.

In addition, MAHs must notify the national competent authorities of the country where the suspected defective product is distributed. If the nature of a product quality defect presents a serious risk to public health, national competent authorities inform each other through the rapid alert system, and a recall mechanism may be activated. The relevant MAH is encouraged to discuss communications they intend to send to healthcare professionals (HCPs) with the authorities before they are issued.

Medical devices

Post-marketing obligations are overseen by the national competent authorities in the member states, although the European Commission can undertake a coordination role where a product is withdrawn from the market. Corrective action may need to address any incident identified with a device, and this may include the recall or withdrawal of a device to reduce the risk of death or serious injury. The manufacturer of the device must assess the need for the recall and work with the competent authorities to ensure appropriate information is provided to HCPs.

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 promotion of medicinal products in the European Union is controlled by a combination of legislation and self-regulation through the industry codes of conduct, mainly the European Federation of the Pharmaceutical Industry Association (EFPIA) Code of Practice (the EFPIA Code), which covers the promotion of medicines to healthcare professionals (HCPs) and interactions with HCPs, healthcare organisations (HCOs) and patient organisations (POs). The EFPIA Code is designed to be implemented by its national member associations. In practice, the interpretation of the legislation and EFPIA guidance is determined at a national level.

Advertising to the public is permitted for medicines legally classified as non-prescription, 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 medicine advertising must be consistent with the approved summary of product characteristics.

Under Directive 2001/83/EC, advertising is defined as 'any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products'. Corporate or financial information describing a company's area of business and progress in research will likely fall outside the definition, provided it is not presented in a promotional style and includes no claims in relation to medicinal products or medical treatments and does not encourage patients to ask their doctors to prescribe a particular product.

Online advertising is regulated under the same provisions and controls as traditional advertising, although the various industry codes of practice have been updated in recent years to add provisions specifically aimed at use of the internet by the industry, including the use of online platforms and social media.

Medical devices

The EU laws governing the promotion and advertising of medical devices are less detailed than those established for medicines, although EU general consumer legislation on misleading advertising also applies. The medical devices regulations contains a requirement

concerning promotional claims that expressly prohibits the making of claims, when promoting a medical device, that may mislead the user or the patient with regard to the device's intended purpose, safety or performance.

In addition, the largest medical device manufacturer's industry association, MedTech Europe, issues a Code of Business Practice (the MedTech Code), which is obligatory for its member associations and member companies, and regulates their interactions with the medical community and other stakeholders. This also covers online advertising.

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

Directive 2001/83/EC prohibits the supply, offer or promise of gifts, pecuniary advantages or benefits in kind to persons qualified to prescribe or supply medicines where medicines are being promoted, unless they are inexpensive and relevant to the practice of medicine or pharmacy. This prohibition is reflected in the national laws of all member states. Hospitality extended to HCPs is considered acceptable in the context of promotional events, provided it is limited to the main purpose of the event and offered to HCPs only.

The EFPIA Code reflects these restrictions, prohibiting gifts for the personal benefit of HCPs, HCO members and PO representatives (either directly or indirectly). Providing cash or offering cash, cash equivalents, promotional aids (non-monetary items given for promotional purposes) or personal services is also prohibited. Personal services are any type of service unrelated to the profession and that confer a personal benefit to the recipient. Donations and grants to HCOs and POs are allowed under strict conditions, but donations and grants to individuals are not permitted.

Medical devices

The legislation requires Notified Bodies to carry out their assessments and verifications with the highest degree of professional integrity and free from all pressures and inducements, particularly financial, which might influence their judgement, especially from persons with an interest in the results of the verifications.

The MedTech Code prevents member companies from offering and providing educational grants to individual HCPs with certain exceptions, and has phased out the provision of financial or in-kind support directly to individual HCPs to cover costs for their attendance at third-party organised educational events (with the exception of procedure training). It also sets out transparency obligations with regard to all interactions with HCPs, in terms of notification to the HCP's superiors or relevant health institutions before the interaction may take place, disclosure of payments (made as educational grants) and a centralised platform for the approval of conferences and other events (the Conference Vetting System).

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

EU law does not set out requirements for recording or publishing the details of transfers of value (ToV) to HCPs by pharmaceutical companies. Requirements are, however, imposed by the national legislation of some European countries and by the self-regulatory codes.

The EFPIA Code provides for disclosures of ToV made to HCPs and HCOs, whether directly or indirectly. When deciding how a ToV must be disclosed, member companies, must, wherever possible, identify and publish relevant information at the individual HCP level (rather than the HCO level) as long as this can be achieved with accuracy and consistency and in compliance with applicable laws and regulations. The items to be disclosed are those ToVs relating to donations and grants (to HCOs), contribution to costs related to events and fees for service and consultancy. Where certain information cannot reasonably be allocated to one of these categories or cannot be disclosed on an individual basis, member companies must disclose the information on an aggregate basis. Research and development ToVs must also be disclosed on an aggregate basis. Disclosures must be made pursuant to the national code of the country where the recipient has its professional address and on the company's website or on a central platform, depending on national requirements.

Medical devices

There are no legal provisions at the EU level requiring medical device companies to disclose payments to HCP, HCOs or POs. However, there are requirements to disclose certain ToVs under the national laws of some member states and under the MedTech Code.

Under the MedTech Code, member companies must document and publicly disclose all educational grants in accordance with the Code's disclosure guidelines. Educational grants include support for third-party organised educational events, grants for public awareness campaigns and scholarships and fellowships. Each member company must disclose all payments related to their educational grants to HCOs based in Europe without limitation of value. Amounts paid to each recipient HCO will be aggregated on a category-by-category basis but will need to be itemised upon request from the competent authorities. The disclosure may be made on the MedTech Europe website or on the national platform, if one is set up under national rules.

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.

The enforcement of the EU provisions regarding advertising of medicinal products and medical devices is undertaken at a national level by the national competent authorities or the national self-regulatory bodies.

Sanctions

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

Sanctions for breach of national legal provisions on advertising vary from fines or imprisonment of responsible individuals under a criminal law framework to administrative fines in certain jurisdictions. Sanctions may escalate if the breach of the advertising provisions is linked to an illegal inducement of a healthcare professional (HCP) and the matter falls within the remit of the national anti-bribery law or there has been a breach of the antitrust rules.

Under the self-regulatory systems, sanctions for breach of national self-regulatory codes include fines, publication of cases, issuance of corrective notices to HCPs, audits and ultimately suspension

or cancellation of the company's membership to the relevant national industry association and potentially of corresponding European industry associations.

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?

The controls on pricing of medicines and medical devices and decisions regarding reimbursement of these products by national social security systems applicable to manufacturers, distributors and pharmacists are established exclusively at a national level. EU law only contains certain provisions requiring the transparency of such national controls and how they are applied.

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

EU legislation does not prevent healthcare professionals (HCPs) from prescribing or using products outside their authorised indication of use (off-label) under their own responsibility, but national controls may exist. Professional rules and codes of conduct may describe the criteria and conditions that should guide HCP practice.

However, the EU advertising rules prevent pharmaceutical companies from drawing the attention of HCPs to potential off-label uses or promoting their medicines in a manner that is not consistent with the summary of product characteristics (SmPC). Not all the information contained in an advertisement needs to be identical to that in the SmPC, provided the claims are consistent with the information in the SmPC.

Pharmaceutical companies may, however, discuss such use with HCPs in a reactive manner, in response to specific unprompted questions from HCPs or in a strictly non-promotional context, as part of a legitimate exchange of scientific information.

Medical devices

EU law does not prevent HCPs from using medical devices off-label, and such use will be at the risk of the HCP.

Any promotion of a device by the manufacturer should be limited to the intended purpose and CE mark. The legislation and the MedTech Code of Business Practice do not contain provisions on providing information about off-label uses. However, all information about a device should be accurate, balanced, fair, objective and unambiguous. The medical devices regulations expressly prohibit the making of claims, when promoting a medical device, that may mislead the user or the patient with regard to the device's intended purpose, safety or performance by suggesting uses for the device other than that are part of the intended purpose for which the conformity assessment was carried out.

Further, if a device is not placed on the market, information can be provided about it if it is clear that it is not officially launched and does not have a CE mark. Devices may be 'shown' at trade fairs, exhibitions, demonstrations, etc, when they do not have a CE mark. This is provided that a visible sign clearly indicates that the device cannot be marketed until it does comply.

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 manufacture, importation and supply of unauthorised medicines is controlled at a national level. Directive 2001/83/EC expressly allows member states not to apply its authorisation procedure to industrially manufactured products that are required to meet 'special needs'. The CJEU case law states that such 'special needs' must be therapeutic and not motivated by price. There is, otherwise, no harmonisation of the rules controlling 'special needs' supply at the EU level.

Member states may temporarily authorise the distribution of unauthorised medicines or authorised medicines for non-approved indications in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation. Unauthorised products may also be manufactured, imported and supplied in the context of medical research, or as part of compassionate use programmes for unlicensed medicinal products.

Medical devices

Medical devices should not be imported or placed on the market if they do not have a valid CE mark. Medical devices that are custom-made for individual patients or used for clinical investigations do not need a CE mark.

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 make certain medicines regulated under that Regulation available for compassionate use. This means making those medicines available to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product.

The medicinal product concerned must be either the subject of an application for a marketing authorisation in accordance with this Regulation or undergoing clinical trials. The Committee for Medicinal Products for Human use of the European Medicines Agency may adopt opinions (non-binding on national authorities) on the conditions for use of such products, distribution and the patients targeted, after consulting the manufacturer or the applicant. The applicant, in respect of the compassionate use programme is obliged to ensure that the patients taking part also have access to the new medicine during the period between authorisation and placing on the market.

Medical devices

There are no provisions covering medical device compassionate use programmes under EU law. Compassionate use programmes are, however, not prohibited. The European Commission recognises in its guidance that, in exceptional cases, major benefits may justify relatively high levels of uncertainty, and access to the market may be granted on the basis of limited clinical evidence, such as experience available from compassionate use programmes. Medical device compassionate use programmes may, therefore, be coordinated and implemented by EU member states according to national legislation and guidance.

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

When a marketing authorisation for a medicinal product is granted at the EU or national level, the conditions and restrictions under which the medicinal product should be made available to patients (the 'legal status' of the medicine) must be included as part of the authorisation.

Directive 2001/83/EC sets out levels of categories in relation to legal status. The medicine is first classified either as subject to medical prescription or not. For products subject to medical prescription, member states may use a second level: medicines subject to special medical prescription, medicines subject to restricted medical prescription and medicines subject to renewable or non-renewable delivery.

In addition, the summary of product characteristics of the product may include an explanation on how the medicine should be supplied to patients (ie, to be administered in a hospital setting or prescribed by specialists only) or on the specific type of care required during the treatment of a chronic disease.

Medical devices

The dispensing, sale and use of medical devices is set out in the device's labelling and instructions for use, which will specify, for example, if the device should be used by a healthcare professional.

Online supply

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

EU law does not prevent the dispensing, sale and supply of medicines or medical devices online. However, patients are encouraged to only use online retailers registered with the national competent authorities in the EU member states, to reduce the risk of buying substandard or falsified medicines and medical devices.

The EU requires the use of a common EU logo for legally operating online pharmacies in EU countries. The logo links to the website of the national competent authority listing all legally operating online pharmacies so users can confirm the website is legitimate and that the retailer is registered. Thenational flagand thetextare an integral part of the logo; a logo that displays the EU flag is not authentic.

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?

Medicinal products

While the Clinical Trials Regulation was adopted in April 2014, it will not come into operation until January 2022.

The Commission is intended to propose new legislation in relation to orphan and paediatric medicines in 2022 and there are ongoing consultations whereby the Commission is seeking views of stakeholders on proposed changes.

Medical devices

The new medical devices regulations applied from 26 May 2021, and the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 will apply from May 2022. Despite the amount of detail in the new regulations, there are many areas where additional guidance is needed. Notified Bodies are also completing the designation procedure to ensure they can accept applications under the new medical devices regulations and that products can be placed on the market.

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