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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United States

Daniel A Kracov

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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.

The United States has a public-private healthcare system, with major public healthcare programmes, such as Medicare, which provides healthcare coverage for the over-65 population and certain disabled individuals, and Medicaid, a federal/state health insurance programme for low-income individuals. The federal aspects of these programmes are administered by the Centers for Medicare and Medicaid Services. The Affordable Care Act (ACA) also ensures the availability of health insurance for a larger percentage of Americans, providing important protections, such as coverage of pre-existing conditions. The ACA is a complex and controversial system involving state exchanges, and insurance companies and employers remain central in healthcare coverage. Despite these controversies, it appears that the ACA will remain in place, although significant elements may be effectively repealed or blunted by legislation and litigation. The delivery of products for healthcare is handled through a complex system of wholesalers, pharmacy benefit management and logistics companies.

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?

The primary agency responsible for the regulation of medicinal products is the Food and Drug Administration (FDA), although the Drug Enforcement Administration (DEA) applies additional controls to scheduled FDA-approved drugs that are controlled substances. The FDA administers various frameworks for review and approval of medicinal products, as well as inspection and enforcement over violations of law. The agency determines whether products fall within categories of regulation, including combination products, based upon the definitions provided under the Federal Food, Drug, and Cosmetic Act (FDCA), the Public Health Service Act and the FDA's implementing regulations, guidance and case law.

Approval framework

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

For prescription drugs, the FDCA is the primary source of the FDA's authority over drug and medical device approvals, and the Public Health Service Act provides authority for licensing of biological products. The regulations implementing those statutes are found at Chapter 21 of the Code of Federal Regulations (21 CFR), and the FDA frequently issues non-binding, explanatory guidance. The standard for initial drug approval is 'substantial evidence', meaning sufficient data from one or more adequate and well-controlled studies demonstrating a safety and effectiveness (ie, a favourable benefit–risk balance for the product). Generic products, which are the subject of abbreviated new drug applications, must demonstrate that they are the same as the reference listed drug, and must be therapeutically equivalent to be substituted at the pharmacy level.

Medical devices, if not exempt from active regulation or subject to enforcement discretion, may be subject to 510(k) premarket notification and clearance by the FDA through a demonstration of substantial equivalence to medical devices on the market prior to 1976 or that have been the subject of a cleared 510(k) since that time. Devices not eligible for the 510(k) pathway may be required to be approved via a full premarket approval (PMA) application in which the applicant must provide a reasonable assurance of safety and effectiveness, typically via the submission of clinical studies. Products not falling within an existing classification can be down-classified to 510(k) status based on risk via the submission of a 'de novo' application.

All prescription drug products (including biologicals) are approved with physician labelling or instructions for use, which includes a full summary of the information relating to the safety and effectiveness of the drug, biological or device, including warning, precautions and contraindications, and many products also have labelling that provides a simpler recitation of the information on the drug product for patients. Some drugs and biologicals are also subject to Risk Evaluation and Mitigation Strategies, which may include measures known as Elements to Assure Safe Use intended to ensure that risks are understood and acted upon by physicians and patients.

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?

The Federal Food, Drug, and Cosmetic Act and implementing regulations found at Chapter 21 of the Code of Federal Regulations (21 CFR) Part

312 govern the process for obtaining and maintaining investigational new drug (IND) applications, and 21 CFR Part 812 governs investigational device exemptions (IDEs). The rules governing ethics committees – known as institutional review boards (IRBs) in the US – are found at 21 CFR Part 56, and informed consent obligations are addressed at 21 CFR Part 50. These regulations are part of a broad set of obligations to conduct ethical and compliant clinical studies under good clinical practices to ensure the protection of human subjects.

Reporting requirements

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

Unless subject to one of several very limited exceptions, most drug studies involving investigational drugs must be conducted under an IND cleared by the Food and Drug Administration (FDA). Similarly, most medical device studies must be the subject of an IDE, unless the IRB determines that the device study is a non-significant risk. In addition, most hypothesis-testing clinical studies by drug or device manufacturers are subject to registration and results reporting via the clinicaltrials.gov website maintained by the National Institutes of Health.

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?

Yes, under 21 CFR Part 50, informed consent must be obtained from virtually all clinical trial subjects, although some exceptions are made – with additional safeguards – for situations in which informed consent cannot be obtained directly, such as in emergency procedures involving investigational products. Informed consent forms must be reviewed by an IRB. Although there is no federal requirement for personal injury insurance, states and institutions may apply such requirements, and the FDA forbids the use of exculpatory language in clinical trial subject informed consent forms.

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?

The review period for drugs and devices depends upon the commitments made by the Food and Drug Administration (FDA) as part of the enactment of user fee statutes. Currently, the target performance is the review of 90 per cent of standard drug applications within 10 months of a 60-day filing period, and for priority review applications (for serious conditions for which there is an unmet need), six months after the filing period. For device 510(k)s, the current typical review time is 120 days, and 315 days for premarket approval (PMA). Fees for applications vary by year, and type of product, and are governed by user fee statutes, which are reauthorised by Congress every five years, with associated FDA performance commitments. There is no limit on the validity of an authorisation, although applications may be withdrawn by the FDA under certain scenarios of non-compliance.

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?

In addition to patent protections, there are various statutory exclusivity periods available, including:

- five years of data exclusivity for the first approval of a drug that is a new chemical entity under a new drug application (NDA);
- 12 years of exclusivity for the first approval of a biological new molecular entity under a biologics licence application;
- three years of additional exclusivity for supplemental NDAs (eg, for new indications or dosage forms) for which one or more clinical studies conducted by the applicant and are essential to the approval;
- seven years of marketing exclusivity for the approval of a designated orphan drug to treat the designated rare disease or disorder;
- six months of add-on data exclusivity for fulfilling an FDA written request for the conduct of a paediatric study; and
- five years of additional data exclusivity for the approval of a specially designated antibiotic product.

Other incentives, known as priority review vouchers, which permit a more rapid FDA review of products not otherwise eligible for such review, may also be granted if a company obtains designation and achieves approval of a product for a rare paediatric disease, material threat countermeasure or neglected tropical disease. Such vouchers are transferable under certain conditions.

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?

Any party may submit a request for such data under the Freedom of Information Act (FOIA), but FDA regulations and exceptions under the FOIA for trade secret information limit the release of certain proprietary data. Nonetheless, significant information regarding approved applications and FDA reviews may be obtained via the FOIA. For investigational products, the FDA will not acknowledge the existence of an investigational new drug or an investigational device exemption if the applicant has not made the information public, and information in such submissions is generally not available for public release.

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?

Herbal products that only bear claims relating to an impact on bodily structure or function and contain permitted ingredients may be marketed as dietary supplements without FDA approval. New ingredients used in such products must be the subject of an FDA clearance. However, herbal products with disease or disorder claims are generally subject to the same process for drug approval as purified chemical drugs, with adaptations for the botanical nature of the product.

Homeopathic drugs are permitted under the Federal Food, Drug, and Cosmetic Act (FDCA), but must be marketed in a manner consistent with the Homeopathic Pharmacopoeia and the traditional formulation and labelling constraints for such products.

Biological products are regulated under both the Public Health Service Act and the FDCA, and the process is largely the same as the process for review of NDAs. Biosimilars and interchangeable biological products are licensed under the Public Health Service Act as amended by the Biologics Price Competition and Innovation Act. Such products must demonstrate that they are highly similar or interchangeable with a reference licensed biological product. To date, only one interchangeable biological product has been licensed by the FDA.

Innovator biologic products receive 12 years of data exclusivity, and four years from approval before a biosimilar application may be filed. The first licensed interchangeable biologic receives one year of marketing exclusivity vis-à-vis other interchangeable products that may be licensed.

Orphan drugs are approved in the same manner as other drug and biological products, although they must be designated as an orphan product prior to application submission, and must be approved for the rare disease for which designation was obtained. Similarly, paediatric drugs are approved through normal processes, although additional data on the paediatric population may be required. Orphan drugs may receive seven years of market exclusivity if approved for the designated orphan indication.

Controlled substances are also approved under the general new drug application (NDA) processes; however, such substances are subject to a scheduling recommendation by the FDA and a scheduling determination via notice and comment rule-making by the Drug Enforcement Administration, which may delay product approval, subject to certain statutory constraints.

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?

Post-marketing safety reporting requirements for human marketed drug and biological products are found at Chapter 21 of the Code of Federal Regulations (21 CFR) sections 310.305, 314.80, 314.98, 600.80 and 600.81. Such regulations require that post-marketing safety reports be submitted to the FDA for serious and unexpected adverse experiences from all sources (domestic and foreign), and for spontaneously reported adverse experiences that occur domestically and that are serious and expected, non-serious and unexpected, and non-serious and expected.

The Medical Device Reporting Regulation at 21 CFR Part 803 imposes mandatory requirements for manufacturers, importers and device user facilities to report certain device-related adverse events and product problems to the FDA. Manufacturers are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury, and must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Importers are required to report to the FDA and the manufacturer when they learn that one of their devices may have caused or contributed to a death or serious injury. The importer must report only to the manufacturer if their imported devices have malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. In addition, 'device user facilities' (ie, hospitals, ambulatory surgical facilities, nursing homes, outpatient diagnostic facilities or outpatient treatment facilities (that are not a physician's office)) must report a suspected medical device-related death to both the FDA and the manufacturer, and a medical device-related serious injury to the manufacturer, or to the FDA if the medical device manufacturer is unknown.

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?

Various requirements apply. Drug, biologicals and device manufacturers must register their establishments with the FDA and list the products associated with each facility.

Application fees for NDAs and BLAs are currently over US$2.5 million and a PMA for a device is subject to a fee in the range of US$320,000. Establishment and programme fees may apply to certain classes of products, and certain exceptions also may apply.

The content of applications varies depending on the type of product, but, in general, applications for approval contain extensive information on the content and manufacturing of the product, as well as all of the various in vitro, animal and clinical data developed to support a finding of safety and effectiveness or other regulatory standard. For drug products, an NDA submission also includes the listing of patents, which may be the subject of certification by applicant for the generic and abbreviated new drug application and subsequent litigation with the reference listed drug application holder.

Drug and device distributors may be subject to state licence or permit requirements, which typically require providing various information regarding the company and products, paying a relatively small fee, and, in some cases, posting a bond.

Although the Department of Health and Human Services is pursuing plans to allow broader importation of products, at present drugs generally can only be imported into the United States by the manufacturer. Manufacturers and those in the drug distribution chain must also comply with drug track and trace requirements, which mandate the passing of a pedigree and investigation of reports of suspect or illegitimate products.

In general, applications remain in effect and are subject to fees and other requirements until discontinued or withdrawn by the manufacturer, or withdrawn by the FDA via a formal process, which is rarely undertaken by the agency.

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?

Violations of the FDCA can result in misdemeanour and felony convictions and imprisonment, as well as fines; civil penalties are also available for certain violations. The FDA also has authority, working with the Department of Justice, to seek a court injunction to prevent further violations, or to detain or seize certain products in commerce. Those committing fraud in the drug application process may be subject to debarment from working with companies submitting applications to the FDA. In addition, other laws governing the submission of claims for government payment for biomedical products, such as the False Claims Act, may result in both huge civil settlements and the imposition of corporate integrity agreements by the Department of Health and Human Services Office of Inspector General, and exclusion from government healthcare programmes.

Exemptions

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

Certain over-the-counter (OTC) drug products may be marketed without FDA approval if they comply with FDA regulations, known as 'OTC monographs', that provide permitted active ingredients, indications and instructions for use, as well as current good manufacturing practice (cGMP) requirements. Products that do not fall within OTC monographs may be deemed OTC via the full NDA or NDA supplement process. The 2020 enactment of the Over-the-Counter Monograph Safety, Innovation, and Reform Act has recently streamlined processes for seeking changes to existing monographs.

Under the Compounding Quality Act, certain medicinal products may be compounded by pharmacies on a per-patient basis or produced in outsourcing facilities for more general use, without FDA approval. Such parties must comply with pharmacy compounding or cGMPs, respectively, and otherwise stay within the boundaries for such products. For example, such pharmacies and outsourcing facilities may not produce products that are essentially the same as commercially available approved drug products.

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?

Under current US law, drug and biological products may be imported into the United States solely by the application holder for the approved product. Medical devices may be imported if compliant with any required 510(k), PMA or exemption.

AMENDING AUTHORISATIONS

Variation

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

Changes to an approved drug or biological that could have an impact on safety and effectiveness, including even minor changes in manufacturing processes or equipment, may require the submission of a supplement to the original application, although changes presenting lesser risk may be the subject of 'changes being effected' submissions, under which the changes may be instituted prior to Food and Drug Administration (FDA) approval (eg, adding a new warning) or reporting in an annual report. For medical devices, the manufacturer must engage in appropriate analyses to determine whether modifications to existing products must be subject to a 510(k) seeking changes to the originally cleared product (to determine if it is still substantially equivalent to the predicate product), or, for approved devices, if a premarket approval (PMA) supplement is required.

Renewal

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

In general, the drug and device authorisations are not subject to renewal per se; rather, they are the subject of ongoing obligations – registration, listing, payment of fees, cooperation in inspections, submission of reports, etc – under applicable law. A failure to comply with such requirements may result in enforcement and, in extreme situations, an effort by the FDA to either enjoin continued shipment of products or to seek withdrawal of approval.

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?

In general, the transfer of existing approvals or rights is an administrative process involving an exchange of letters, filings with the FDA and appropriate changes to registrations. However, if the transfer involves changes in the products, the manufacturing facilities or processes for approved products, or the oversight of quality systems, approval and prior inspection by the FDA may be required prior to initiation of the change.

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?

The Food and Drug Administration (FDA) requires that companies engage in a health hazard assessment of defective or possibly unsafe products to determine if a recall is required, and the extent of the recall generally depends on the risk presented. Although the FDA may mandate recalls for certain products, in general, recalls are conducted voluntarily in consultation with the FDA, and companies carry out the recalls with reporting to the FDA on the effectiveness of the effort. In cases of significant risk, the FDA may mandate a recall and implement its own communication plan. The FDA's regulations governing product recalls may be found at Chapter 21 of the Code of Federal Regulations Part 7, subpart C.

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?

For prescription drugs and restricted devices (those subject to restrictions via regulation or Food and Drug Administration (FDA) approval due to risk), the Federal Food, Drug, and Cosmetic Act is the primary source of the FDA's authority over promotion via labelling (promotional materials) or advertising (print or broadcast), whether to payers, physicians or direct-to-consumer (DTC). The Federal Trade Commission (FTC) has a subsidiary role, but can still police certain aspects of advertising by prescription drug manufacturers. However, the FTC has primary jurisdiction over monograph over-the-counter drug and non-restricted device advertising. State laws also have a role, to the extent they are not pre-empted by the federal framework. There are also private rights of action for addressing competitor disputes, including under the Lanham Act. In addition, the False Claims Act provides for 'relator' actions seeking to recoup government payments for false claims induced by marketing or other violations, with a 'bounty' for the relator filing the case. Industry associations also maintain codes of conduct focused on pharmaceutical marketing and sales, including payments to physicians.

There is a wide array of requirements for such advertising, including for prescription drugs, routine submission of promotional materials to the FDA (and in limited scenarios, pre-clearance) and:

- avoiding any claims that are false or misleading, including by implication or depiction;
- not making claims beyond the approved indications and labelling; although such restrictions are now under scrutiny and somewhat relaxed due to recent First Amendment case law recognising pharmaceutical free speech rights pertaining to communication of off-label truthful and non-misleading information;
- ensuring appropriate support for product claims, including comparisons and claims of superiority;
- adequately communicating safety information and balancing the presentation of the benefits and risks generally; and
- providing contact information to enable the provision of full labelling, responses to questions and reporting of adverse events.

Similar rules apply to DTC advertising, but there is more of an emphasis on the appropriateness of claims, balance (including in visual representations), providing extensive and prominent safety information and providing methods to obtain the full labelling. The FDA has also issued guidance on the application of the above principles in the context of the internet, and social media particularly, providing information on when such information is attributed to the manufacturer, how required risk information can be conveyed in character-limited social media such as Twitter, and how companies can seek to correct misinformation in social media. Finally, the pharmaceutical and medical device trade associations maintain codes of conduct relating to DTC advertising.

Not all communications by manufacturers are subject to such restrictions and requirements. Communications that are not promotional (eg, investor communications and bona fide scientific exchanges (such as responding to a physician's unsolicited questions)) are not within the FDA's jurisdiction. However, certain communications, such as press releases, may have investor, scientific and promotional audiences, depending on how they are utilised. Companies typically maintain review processes and compliance controls to delineate between such types of communications in a consistent and compliant manner.

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?

The primary authority governing such inducements is the Anti-Kickback Statute (AKS), which prevents 'kickbacks' to providers that could influence the practice of medicine and prescribing. However, it is a very wide-ranging and ambiguous statute, and thus, relationships with providers and institutions that submit claims to payers, particularly federal healthcare programmes, need to be examined carefully and should be well documented in agreements based on unclear 'safe harbours' developed over years of interpretation and advisory opinions. The setting of care and relevant payment frameworks will have an impact on such analyses. The AKS is a criminal statute, and it is administered by the Department of Health and Human Services Office of Inspector General and the Department of Justice. In addition to the AKS, which is intended to prevent undue remuneration to physicians that induce prescribing in the US, transfers of value to physicians and institutions outside of the US may come under scrutiny under the Foreign Corrupt Practices Act (FCPA). The FCPA prohibits bribery of foreign officials, including certain physicians and institutions affiliated with governments, and addresses accounting transparency requirements under the Securities Exchange Act of 1934. Companies typically maintain extensive compliance programmes to ensure adherence to these requirements, and ensure that all payments to healthcare practitioners and institutions are bona fide in nature and based on fair market value.

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?

Payments to US physicians and teaching hospitals (and, from 2022, to advance practice nurses and physician assistants as well) are subject to a reporting scheme under the Physician Payments Sunshine Act, under which such transfers of value – including indirect payments – by manufacturers are routinely reported and posted on a government-run Open Payments website in considerable detail.

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 Food and Drug Administration maintains three centres for regulating drug, biological and medical device products:

- the Center for Drug Evaluation and Research, which includes the Office of Prescription Drug Promotion, which regulates most drug and biological promotion;
- the Center for Biologics Evaluation and Research, which includes the Advertising and Promotional Labeling Branch, which regulates the promotion of certain biological products, such as cell and gene therapies, blood products and vaccines; and
- the Center for Devices and Radiological Health, which maintains a similar function for device promotion.

These organisations develop guidance, review complaints, conduct surveillance on promotion (eg, at scientific meetings, in social media), review materials when submission is required and pursue enforcement when appropriate. The Federal Trade Commission's Division of Advertising Practices has a primary role with respect to monograph over-the-counter (OTC) drug products and non-restricted medical device advertising.

While the primary trade associations in this area – such as PhRMA and AdvaMed – maintain various compliance codes, they do not operate self-regulatory systems for adjudicating promotional disputes. The National Advertising Division of the Better Business Bureau does maintain such mechanisms, but it is largely focused on consumer product claims, such as for OTC drugs and devices.

Sanctions

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

In most cases, agency findings relating to non-compliant promotion are the subject of an enforcement letter and remediation by the recipient. However, in cases of significant violations, the consequences can include civil and criminal penalties, imprisonment, exclusion from government healthcare programmes, including corporate integrity agreements, and liability under statutes such as the False Claims Act due to inducement of claims for government payment.

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?

This varies greatly in the US. While there are complex systems governing issues such as providing best price and rebates on pricing in certain government programmes, and government programmes may consider data in coverage and reimbursement decisions, many such programmes are obligated to pay for all covered drugs, while controlling use via formulary reviews, tiering and other mechanisms. Some, particularly in the device area, may utilise health technology assessment processes. In commercially run insurance programmes, consideration of cost-effectiveness and associated analyses has become routine, and various formulary and other mechanisms are used to control use accordingly. A particular current focus is the development of value-based arrangements with payers, in which the manufacturer and payer share risk, and payment is based on product performance in the relevant patient population. Congress is currently considering various proposals for reforming drug pricing in the United States.

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?

Yes, health professionals may prescribe products 'off-label' in the practice of medicine, although that does not ensure that the product will be subject to coverage and reimbursement for that use, and medical malpractice liability is also a constraint. Pharmaceutical companies generally must refrain from communicating off-label information to physicians in a manner that suggests an off-label intended use, or is false or misleading. However, there are significant protections under the First Amendment to the US Constitution for speech by pharmaceutical and medical device companies, and some companies rely on such protections to communicate truthful and non-misleading off-label information. In addition, the Food and Drug Administration (FDA) has liberalised aspects of its regulatory guidance in response to development First Amendment case law, and now permits, under certain parameters, (1) broad communication of information that is not found in an approved label but is nonetheless consistent with the approved label; and (2) communication to payers of information regarding unapproved products and uses, albeit without claims. In addition, companies can communicate off-label information in scientific exchange settings, such as by presenting data at scientific meetings or responding to unsolicited requests from health practitioners. The FDA has recently proposed a new rule defining 'intended use' for medical products, which could also have an impact on the parameters of manufacturer communications relating to products.

Unlicensed products

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

Companies can communicate information regarding their pipeline to healthcare practitioners, and may present such information in scientific exchange settings, such as bona fide scientific meetings. However, there is a general prohibition against promoting or commercialising investigational products or uses prior to approval. More information can be provided to other audiences, such as payers and investors.

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Compassionate use

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

There are two pathways for compassionate use. The first is compliance with FDA rules for providing expanded access to a patient under an investigational new drug (IND), found at Chapter 21 of the Code of Federal Regulations section 312.310. Such an IND may be sponsored by the company or the patient's physician, but the regulations generally reserve compassionate use for patients with serious or life-threatening conditions who are not eligible for clinical trials. The second is providing access under the Right to Try Act framework adopted in 2018, which has rarely been utilised owing to the lack of any IND requirement or FDA oversight.

SALE AND SUPPLY

Regulation

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

Beyond general prescription status, drug products may be subject to special restrictions, known as Risk Evaluation and Mitigation Strategies, that may – to maintain the benefit-risk balance for the product – require adherence to various controls over prescribing, dispensing and patient access, including registries, training and agreements. Controlled substances are also subject to special restrictions at both the federal and state level, which may vary depending on how they are scheduled by the Drug Enforcement Administration. Medical devices may also be made subject to certain dispensing or sale restrictions or conditions of use as part of approval.

Online supply

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

Drug and device products dispensed online are not exempt from the general rules relating to prescribing prescription products, and such products must be subject to appropriate regulatory approvals and clearances. Foreign online pharmacies may not ship drug products into the

United States. Various federal and state laws apply to online pharmacies and suppliers, including associated telemedicine functions, such as a federal prohibition on the prescribing of controlled substances online, and a wide array of rules at the state level relating to valid prescriptions, licensing, practice of pharmacy, reciprocity among jurisdictions, and other areas.

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?

At present, the primary legislative and regulatory focus is on drug pricing but it remains unclear if any such legislation will be enacted as part of pending budget legislation. Prior proposals relating to importation and international reference pricing are no longer a significant factor. In the coming year, the various Food and Drug Administration user fee statutes, which often include additional substantive regulatory changes, will be considered.

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