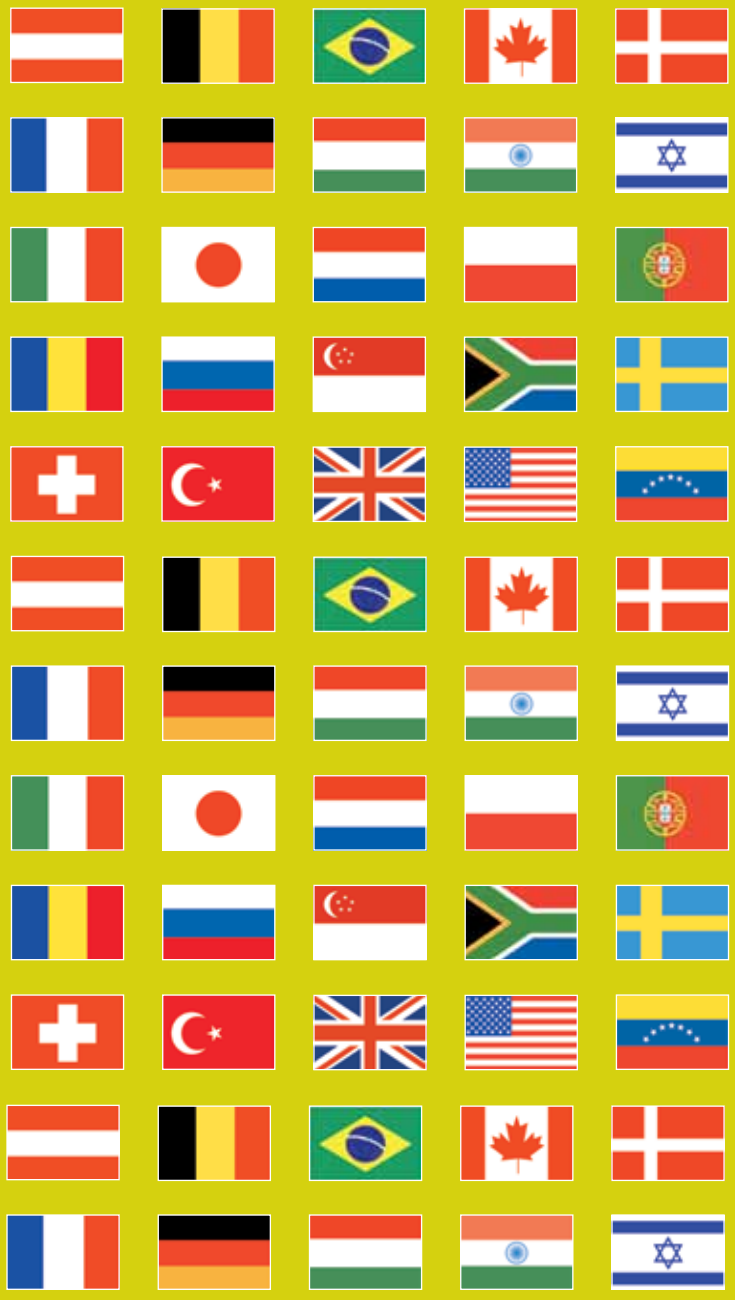
GETTING THE DEAL THROUGH

Life Sciences

in 25 jurisdictions worldwide

2012

Contributing editors: Alexander Ehlers and Cord Willhöft



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United States

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Organisation and financing of health care

1 How is health care in your jurisdiction organised?

The health-care system in the United States has evolved over the past 60 years through incremental public policy initiatives. These public policy changes have mainly been on the federal level.

The federal government is the largest single provider of health-care services in the United States. In 2010, there were approximately 4.4 million federal government employees, including temporary employees. The Federal Employees Health Benefits (FEHB) Program is administered through the Office of Personnel Management and manages the health insurance and retirement benefits for federal employees, retirees and their survivors. These employees have the widest selection of health plans in the country. An open enrolment period is conducted in the autumn of each year and employees can select plans ranging from fee-for-service, health maintenance organisations, consumer-driven health plans that offer catastrophic risk protection with higher deductibles, preferred provider organisations, health savings accounts and high-deductible health plans.

State and local governments also provide similar benefits to their employees. The trend at all levels of government, however, has been to raise the contribution levels of their employees. Through collective bargaining agreements, it had been rare for any government employee to contribute anything to their health benefits. However, the public sector has begun to follow the lead of the private sector in requiring increased contributions from their employees. This trend has been occurring in the private sector for approximately the last 20 years. More recently, an increasing number of government entities have begun to require their employees (policemen, firemen and teachers, to name a few) to begin to make contributions based on a percentage of the health benefits and their salary ranges.

The largest federal health programmes are administered through the Department of Health and Human Services (HHS). The HHS is the principal federal agency charged with protecting the health of all Americans and providing essential human services. The HHS budget in 2011 was US$81.3 billion and included the Centers for Medicare, Medicaid and the Children's Health Insurance Program (CHIP). State governments are responsible for the implementation of Medicaid and CHIP. The states contribute 50 per cent matching funds to their programmes for eligible state residents. Eligibility is based on the federal poverty level.

The Medicare programme's projected enrolment in 2011 is 48.9 million beneficiaries and it consists of three programmes: Medicare Part A Hospital Insurance, Part B Medical Insurance and Part D Prescription Drug Coverage. Medicaid is available only to certain low-income individuals and families who fit into an eligibility group that is recognised by federal and state law. Medicaid pays for medical services directly to health-care providers.

The most significant and controversial federal health-care reform legislation came with the passage of the Patient Protection and Affordable Care Act or the Affordable Care Act (ACA) in March 2010. (As will be discussed later, in November 2011 the United States Supreme Court announced that it would consider the constitutionality of various aspects of ACA. A decision is expected by the Supreme Court in the summer of 2012.) The intent of ACA is to reduce the number of people without health insurance by expanding eligibility for Medicaid and providing tax credits that make insurance more affordable for people buying coverage on their own through new Health Insurance Exchanges. The Congressional Budget Office projected that 32 million more people will have insurance by 2019 as a result of ACA.

ACA comes into effect in stages. Some provisions came into effect immediately, such as pre-existing condition insurance plans and Medicare rebates. As of September 2010, additional insurance reform provisions took effect, whereby insurance companies can no longer deny coverage to children based on pre-existing conditions, place lifetime limits on benefits or drop health coverage for an illness. Furthermore, young adults are permitted to stay on their parents' health plans until the age of 26.

Other major federal programmes are in the Department of Defense and the Veterans Health Administration, which provide health-care services to active members of the military, veterans and their families. The Veterans Health Administration has an integrated network of hospitals, physicians and medical staff located in 23 regions across the country.

The other health-care services provided in the United States are made up of non-profit and private, for profit, hospitals and facilities. The services at these health-care facilities are regulated by both federal and state government. Private providers deal with publicly traded and non-profit health insurance companies. Those companies determine what reimbursements private providers receive, except for the Medicare and Medicaid programmes whose reimbursement fees are determined by the federal and state governments.

2 How is the health-care system financed in the outpatient and in-patient sectors?

Health-care costs in the US account for 17 per cent of the country's GNP, and there has been a 3 per cent increase over the past 15 years. The current financial and reimbursement system is unsustainable, especially with the growing Medicare and Medicaid populations. Enrolment for Medicare coverage increased from 19.1 million in 1966 to a projected 48.9 million in 2011, a 156 per cent increase. On average, the number of Medicaid monthly enrollees in 2011 is about 56.1 million, with the largest group being children (28.3 million or 50.4 per cent). In 2008, roughly 19.9 per cent of the population was at some point enrolled in the Medicaid programme.

To change the existing health-system paradigm, ACA aims to help physicians, hospitals and other health- care providers improve the safety and quality of patient care and make health care more affordable. By focusing on the needs of patients and linking payments to outcomes, these delivery-system reforms are intended to improve

the health of individuals and communities, while at the same time slowing cost growth.

As noted previously, while traditional health-care policies in the United States have been employer-funded, the premium increases over the years have driven employers to require their employees to contribute a greater share towards their insurance plans. Benefit consultants believe that employees will soon be contributing at least 50 per cent of the premium for their health-care plans. This trend may shift the country's health-care coverage from an employer-based one to a consumer direct purchase, whereby Americans will begin to purchase their coverage directly and select the benefits based on their individual and family needs.

Compliance – pharmaceutical manufacturers

3 Which legislation governs advertisement of medicinal products to the general public and health-care professionals?

The Food and Drug Administration (FDA) oversees and regulates promotional labelling and advertising for prescription drug products aimed at both the general public and health-care professionals. Generally, product promotion includes any materials or communications issued by or any programmes or events developed by or on behalf of a company, that inform, solicit or make representations to the general public or the medical community about company products. The Federal Trade Commission (FTC) regulates over-the-counter drug advertising to consumers.

Prescription drug advertising is governed by the Food, Drug and Cosmetic Act (FDCA) (21 USC subsection 301 et seq) and the FDA Promotional Regulations (21 CFR parts 201 and 202). The FDCA prohibits the introduction of a misbranded drug into interstate commerce. A drug may be deemed 'misbranded' if the labelling is false or misleading, or if the labelling does not contain adequate directions for use (for its intended uses) and appropriate warnings. A drug may also be misbranded as a result of unlawful advertising. The FDA Promotional Regulations set forth requirements for prescription drug advertising. For example, promotional communications must not be false or misleading; must be consistent with approved labelling; must be supported by substantial evidence or clinical experience; and must include information about the drug's side effects and effectiveness, also known as 'fair balance'. Fair balance is a 'reasonably comparable' balance between information relating to side effects and contraindications and information relating to effectiveness of the drug.

In addition to regulations, the FDA has issued several guidance documents related to prescription drug promotion. These include 'FDA Guidance for Industry: Presentation of Risk Information'; 'FDA Draft Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements'; and 'FDA Guidance for Industry: Consumer-Directed Broadcast Advertisements'. While these guidance documents are not binding, they do represent the FDA's current thinking on the topic.

The FDA's Office of Prescription Drug Promotion (OPDP) (formerly Division of Drug Marketing, Advertising and Communications – DDMAC) monitors pharmaceutical company communications regarding investigational new drugs, regulates and monitors post-approval promotion, and issues warning letters or untitled letters to industry members when violations occur. With an untitled letter, also known as a notice of violation, the FDA generally requires a company to withdraw the violative pieces and other pieces containing similar claims and presentations. Warning letters also generally require a company to develop an action plan for the 'prompt dissemination of accurate and complete information' to the audiences that received the misleading messages. In other words, the company must engage in corrective advertising. Failure to correct violations cited in a warning letter can result in FDA regulatory action, including seizure or injunction, as well as other sanctions.

Industry guidance, while also not binding, provides a method for self-regulation by the life sciences industry. The Pharmaceutical Research and Manufacturers of America (PhRMA) is a trade organisation representing leading pharmaceutical research and biotechnology companies in the United States. In 2009, it released 'Guiding Principles on Direct to Consumer Advertisements About Prescription Medicines' (PhRMA Principles) to express the commitment of its members to deliver direct-to-consumer communications that are a 'valuable contribution to public health'. The PhRMA Principles incorporate existing law relating to direct-to-consumer advertising, but also extend beyond legal requirements. For instance, the PhRMA Principles suggest that companies establish a waiting period after a new drug is approved to facilitate physician education about it.

4 What are the main rules and principles applying to advertising aimed at health-care professionals?

Prescription drug promotion aimed at health-care professionals must not be false or misleading; must include information about the drug's side effects and effectiveness (ie, 'fair balance'); must be supported by substantial evidence or clinical experience; and must be consistent with approved labelling. Similar standards apply to advertising aimed at the general public.

An advertisement for a prescription drug is false or otherwise misleading, and can therefore constitute misbranding, if it contains a misleading or unsubstantiated efficacy or comparative claim; or if it minimises, omits or misleadingly presents risk information or other material facts; or if the claim broadens, misinforms or inadequately communicates the indication, use or administration of the product. An advertisement is lacking in fair balance and similarly can constitute misbranding if it includes information about the effectiveness of the drug but does not include important information about side effects and contraindications in a reasonably comparable manner.

All promotional claims and information must be supported by 'substantial evidence', meaning support by at least two 'adequate and well-controlled' studies. Claims based on in vivo or in vitro studies, retrospective data, post-hoc analyses or results that were not predefined endpoints generally do not constitute substantial evidence.

In the United States, it is unlawful for a drug company to promote its drugs for 'off-label' uses or arrange for others to do so. Off-label promotion is the promotion of products for uses, indications, dosing, administration or a patient population not included in the approved labelling. Under current FDA policy, companies may disseminate information on unapproved uses in response to specific, unsolicited requests for this information, provided that the company maintains documentation concerning the nature of the request and there is no evidence that the request was, in any way, solicited by the company.

5 What are the main rules and principles applying to advertising aimed at the general public?

The FDA, FTC and various consumer protection laws regulate advertising aimed at the general public, or direct-to-consumer (DTC) advertising. Pharmaceutical manufacturers may also follow private codes of conduct, either voluntarily or due to corporate integrity agreements with the government, or adopt industry group standards, such as PhRMA's code of conduct.

The laws distinguish between advertising and labelling of pharmaceuticals. Advertising consists of advertisements in published journals, magazines, newspapers and other periodicals, as well as radio, television, internet and telephone communication systems. Promotional labelling, on the other hand, consists of any written material about the drug or that accompanies the drug as it is sold and describes, explains or otherwise supplements the product. Brochures, sales aids, websites, catalogues and health-care professional letters

are examples of promotional labelling. Only advertising is addressed in this section.

Food and Drug Administration

The FDA governs DTC advertising of prescription drugs and medical devices. While the FDA laws are complex and address numerous aspects of the format and content of the advertisements, the laws, in general, prohibit false or misleading statements and require disclosure of warnings and risk information in advertisements. As mentioned above, advertisements must:

- not be false or misleading;
- be consistent with approved labelling or the package insert;
- be supported by substantial clinical evidence; and
- include information about the drug's side effects and effectiveness.

More specifically, print advertisements must include a 'brief summary' that provides information about side effects, contraindications, warnings, precautions and side effects and contains specified information from the package insert. In addition, print advertisements must contain prescribing information and contact information for FDA MedWatch for reporting of adverse events, all in patient-friendly language. Broadcast advertisements require a 'major statement' and must provide a brief summary or allow for the adequate provision of prescribing information (the 'adequate provision' requirement). A major statement is a description of the drug's major risks (21 CFR 202.1).

Certain types of advertisements are exempt from many of these requirements provided they meet the specified criteria. For example, 'disease state communications' may discuss only the disease that the drug treats, may not reference a drug's established name or the specific drug class if there is only one approved product for the class and may not have the same or similar 'look or feel' as the branded material. Similarly, 'reminder advertisements' contain only the name of the product and do not imply the indication or provide the dosing of the drug. Reminder advertisements are not permissible for certain types of drugs (ie, drugs that bear 'boxed warnings') (21 CFR 202.1(e)(2)(i)).

In addition to required content, prescription drug advertisements must conform to certain formatting rules, including the mandate that the established name of the product is half the size of the font of the product's brand name and those relating to location of risk information in connection with the use information.

Until recently, DDMAC oversaw the enforcement of FDA laws governing advertising and review of advertisements. As noted, the FDA was recently reorganised and DDMAC is now known as the OPDP. The OPDP has established the following mission statement, available on the FDA's website (www.fda.gov):

> *To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program and by fostering better communication of labelling and promotional information to both health-care professionals and consumers.*

Among other tasks, the OPDP reviews drug advertising and promotional labelling submissions, provides comments to sponsors on proposed promotional pieces, reviews complaints about alleged promotional violations (made by competitors, health-care providers or consumers) and initiates enforcement actions on promotional materials that are found to be false or misleading.

As described previously, DDMAC enforced the drug advertising laws through 'untitled' or 'warning' letters to manufacturers, in which DDMAC identified violative content or formatting in drug advertisements. The FDA laws also allow for imposition of civil penalties and criminal prosecution.

Many pharmaceutical companies advertise their products on the internet and other social media. DDMAC advised that it would issue guidance to the industry on the use of social media. In the meantime, drug manufacturers continue to look to the current statutes and regulations governing more traditional types of advertising.

Regardless of the medium through which the advertisement is presented, the laws require that all advertisements and promotional labelling for a particular drug product be submitted to the FDA at the time of initial publication or dissemination (21 CFR 314.81(b)(3)(i)).

Federal Trade Commission

The FTC focuses on protecting consumers against false or misleading advertisements. Its laws prohibit unfair and deceptive trade practices. Methods of enforcement include claims for injunctive relief to prohibit the offending advertisement and potential civil penalties for making false or unsubstantiated statements through endorsements or failing to reveal a manufacturer's material connections to endorsers. The FTC also publishes guidance documents related to advertising, some of which are applicable to the pharmaceutical industry.

Private codes of conduct

Certain jurisdictions within the United States require pharmaceutical manufacturers to adopt a code of conduct that addresses, among other things, marketing of pharmaceutical products. As noted, PhRMA adopted guiding principles for DTC advertisements, and several pharmaceutical companies have adopted the industry group's principles.

While not voluntary, many companies have adopted codes of conduct as conditions of deferred prosecution agreements or corporate integrity agreements with the federal government and particular states, or both.

Other rules and sources of guidance

States have their own laws that apply to advertising of pharmaceutical drugs and devices. The states often invoke their consumer protection laws to enforce DTC advertising violations that constitute deceptive trade practices. In addition, the False Claims Act prohibits the knowing submission of false or fraudulent claims for payment by the federal government and is often used as a basis to challenge off-label promotion of drugs (31 USC section 3279 et seq). Finally, the Securities and Exchange Commission (SEC) has issued regulations that impact DTC prescription drug and device advertising, as well as guidance on use of company websites.

6 What are the most common infringements committed by manufacturers with regard to the advertisement rules?

Based on a review of FDA untitled and warning letters sent to pharmaceutical manufacturers throughout 2010 and 2011, DDMAC issued letters to manufacturers most frequently for the following violations of the promotion and advertising rules:

- minimisation, omission or misleading presentation of risk information or material fact;
- misleading or unsubstantiated efficacy claims;
- misleading or unsubstantiated comparative claims; and
- broadening, misinformation or inadequate communication of indication, use or administration.

Manufacturers also face trademark infringement and other challenges by their competitors, as well as false claims allegations for off-label promotion and charges of consumer protection violations by state governments.

7 Under what circumstances is the provision of information regarding off-label use to health-care professionals allowed?

To protect the public health and encourage industry to subject products and uses to the scientific rigours of a controlled clinical trial, United States law generally prohibits off-label promotion of unap-

proved products or uses. The law does not, however, prohibit health-care providers from prescribing products for off-label uses. In fact, for many pharmaceutical products, off-label usage constitutes the medical standard of care. Because of the inherent benefits of scientific exchange and the possible value in health-care providers prescribing approved products for unapproved uses, under certain circumstances drug or medical device manufacturers may disseminate information that discusses off-label uses for approved products to health-care professionals and health-care entities.

This exception is rooted in the now-lapsed Food and Drug Administration Modernization Act (FDAMA) at section 401 (section 401). Pursuant to FDAMA section 401 at 21 USC section 360aaa(6), and under current FDA policy, companies may disseminate information on unapproved uses in response to specific, unsolicited requests for off-label scientific information. That is, if a company receives a directed question from a health-care provider regarding an off-label use of its product, it may respond to the question, provided the answer and materials disseminated in response are not false or misleading in any respect. To provide a certain level of protection, companies responding to such requests should maintain documentation concerning the nature of the requests and should not engage in a pattern of repeated dissemination of materials. Further, such requests should not be solicited by the company in any way.

FDAMA also states that a manufacturer can proactively disseminate 'written information concerning the safety, effectiveness or benefit of a use not described in the approved labelling of a drug or device' so long as certain requirements were met (21 USC section 360aaa(a)). For example, manufacturers can distribute a full, unabridged, unedited, unmarked and peer-reviewed reprint or copy of an article or reference publication provided that it was not false or misleading, was accompanied by a disclaimer and met certain other requirements, including that the manufacturer had applied to the secretary of the HHS to distribute such information.

A string of lawsuits brought in federal court challenging section 401 on the ground that it violated the First Amendment (commonly referred to as the 'Washington Legal Foundation Decisions') led to the FDA's issuance of a notice that clarified its interpretation of the narrow circumstances allowing for off-label distribution of medical and scientific information set forth by section 401. According to the notice, section 401 established a 'safe harbour' to ensure that certain conduct would not be used against manufacturers in misbranding and intended use enforcement actions.

While section 401 lapsed in 2006, in 2009 the FDA issued a guidance document, 'Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices' (the Reprint Guidance). Guidance documents, unlike statutes or regulations, are not binding; rather, they represent the FDA's current thinking and position on a particular topic. The Reprint Guidance echoes the spirit of section 401, but differs in several respects. Generally, journal articles and reference publications distributed:

- must not be false or misleading;
- must not pose a significant risk to the public health, if relied upon; and
- should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety and effectiveness of the drug or device.

There are several additional guidelines that pertain specifically to journal articles, as well as recommendations that pertain specifically to reference publications.

Furthermore, pursuant to the Reprint Guidance, the medical and scientific information distributed should be unmarked or unhighlighted in its full form and accompanied by the product's approved label, a comprehensive bibliography of publications discussing adequate and well-controlled studies published about the product (if such information exists), a representative publication that reaches different or contrary conclusions (if such information exists) and a disclaimer statement. All medical and scientific information should be disseminated separately from promotional information. The Reprint Guidance provides additional supplementary details and standards regarding the dissemination of off-label medical and scientific information.

8 Which legislation governs the collaboration of the pharmaceutical industry with health-care professionals? Do different rules apply regarding physicians in the in-patient and outpatient sector?

Many federal, state and local laws impact interactions between health-care professionals and members of the life sciences industry. At the federal level, the FDA, Drug Enforcement Administration, Centers for Medicare and Medicaid Services, Office of Inspector General (OIG) of the HHS and other federal authorities regulate the life sciences industry and collaboration between companies and health-care professionals. At the state and local level, various agencies and governmental bodies impact these interactions, including departments of health and boards of licensure. The laws and regulations that most often impact the interactions between industry and health-care professionals include, but are not limited to, federal and state anti-kickback statutes, federal and state False Claims Acts, the federal Prescription Drug Marketing Act (PDMA), the FDAMA, the FDCA and similar state laws, the federal Health Insurance Portability and Accountability Act of 1996 and state privacy laws, various FDA regulations, federal and state health-care programme requirements, and federal and state compliance requirements.

Health-care fraud and abuse and anti-corruption laws

Many life sciences companies' products are reimbursed under federal and state health-care programmes, including Medicare, Medicaid, Department of Veterans Affairs and state pharmaceutical assistance programmes. Federal and state laws commonly referred to as 'anti-kickback' laws are designed to prevent fraud and abuse under these programmes and prohibit pharmaceutical companies from offering valuable items or services to customers or potential customers to induce them to buy, prescribe or recommend a company's products.

Under the federal anti-kickback statute, it is illegal to offer, pay, solicit or receive any remuneration to induce, or in return for purchasing or ordering, or recommending the purchase or order of, a reimbursable service, or referring an individual for an item or service reimbursed under a federal health-care programme. The Department of Justice (DOJ) enforces the criminal provisions of the federal anti-kickback statute, whereas the OIG of the HHS enforces its civil and administrative provisions. Severe sanctions for violating the statute may be imposed, including criminal or civil fines, or both, against the offending company and individual employees, imprisonment of individuals and possibly exclusion of the company's products from eligibility for reimbursement under federal health-care programmes. The anti-kickback statute is broadly constructed and may implicate legitimate and appropriate activities. Specific statutory exceptions, or 'safe harbours', have been carved out to insulate legitimate activities from anti-kickback liability. In particular, the 'personal services' safe harbour is especially relevant for industry-health care professional collaboration. Following the requirements of the personal services safe harbour can protect legitimate service arrangements (eg, consulting agreements) between companies and health-care professionals.

In addition to the federal anti-kickback law, many states have similar laws that apply to items and services reimbursed under Medicaid and other state-funded programmes. Some states have anti-kickback laws that are even broader in scope, covering reimbursement of items and services not only under government-funded programmes but also by private insurers.

'False claims' laws prohibit the submission of false or fraudu-

lent information to state or federal government reimbursement programmes, or causing, assisting or encouraging a company's customers to submit false claims for payment to these programmes. Violations of these laws may result in significant penalties against the responsible employee and the company, including jail sentences, large fines and exclusion of the company's products from reimbursement under federal and state programmes. False claims laws have been applied to pharmaceutical manufacturers where the company took action that may have 'caused' its customer, the health-care professional, to submit a false claim. Companies must be particularly careful about reimbursement relating to their products or any statements related to off-label information.

The Foreign Corrupt Practices Act (FCPA), state and local anti-corruption laws, and laws adopted under relevant international treaties prohibit gifts to non-US government officials, as well as union officials and employees. The FCPA is a federal law that prohibits corrupt or improper payments to foreign officials. The FCPA consists of two primary sections: the anti-bribery provision and the record-keeping provision. The DOJ enforces the anti-bribery sections and the SEC enforces the record-keeping requirements. Violations of the FCPA may subject a pharmaceutical company and its individual employees to criminal and civil penalties.

The anti-bribery section of the FCPA prohibits US-based companies from offering, paying, promising to pay or authorising payment of anything of value to a foreign official with the intent of influencing the official or gaining improper advantage. The statute broadly includes 'anything of value', which consists of cash payments, gifts, meals or any other item that may have value to the recipient. An item of value may also include forgiveness of indebtedness or favourable terms to a loan. Further, the definition of foreign official includes any officer or employee of a foreign government (any department, agency or instrumentality) or public international organisation. Health-care professionals at government-owned hospitals, for example, may qualify as foreign officials under the FCPA.

Compliance laws

The federal government and several states have enacted laws that require life sciences companies to report certain gifts, payments and other expenditures provided to health-care professionals and organisations. At the federal level, section 6002 of the Patient Protection and Affordable Care Act, commonly known as the Sunshine Act, requires pharmaceutical companies to disclose annually, beginning in 2013, many payments made to United States physicians and teaching hospitals. Information about these payments will be posted on a public website, making the interactions and payments among life sciences companies and physicians publicly available information.

Some state and local laws also restrict the provision of gifts to and interactions with health-care professionals. For example, under Vermont law, meals may not be provided by pharmaceutical companies to health-care professionals during educational presentations. Under Massachusetts law, meals are permitted at those presentations only if the interaction occurs in the office or hospital setting. Minnesota law limits companies to providing only up to US$50 worth of gifts and meals per year to an individual health-care professional.

9 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with health-care professionals?

In addition to the federal and state laws and regulations that impact collaboration and interaction between industry companies and health-care professionals, several principles and guidance documents provide direction to pharmaceutical companies. In particular, the OIG of the HHS published in 2003 its 'Compliance Program Guidance for Pharmaceutical Manufacturers'. Additionally, PhRMA and the Advanced Medical Technology Association (AdvaMed) are two industry groups that have provided codes of conduct for industry, both of which were revised and restated in 2009.

OIG guidance

The OIG 'Compliance Program Guidance for Pharmaceutical Manufacturers' provides guidance to the industry on how to create a compliance programme or update an existing programme. The OIG states that:

> *a compliance program may not entirely eliminate improper conduct from the operations of a pharmaceutical manufacturer. However, a good faith effort by the company to comply with applicable statutes and regulations as well as federal health care program requirements, demonstrated by an effective compliance program, significantly reduces the risk of unlawful conduct and any penalties that result from such behavior.*

Specifically, the guidance provides that 'a comprehensive compliance programme provides a mechanism that addresses the public and private sectors' mutual goals of reducing fraud and abuse; enhancing health care provider operational functions; improving the quality of health care services; and reducing the cost of health care'. According to the OIG, while recognising differences among companies in size, resources, priorities, risk areas and the like, a compliance programme should include at least the following seven elements:

- development and distribution of compliance written policies and procedures;
- a designated compliance officer and compliance committee;
- regular, effective training and education;
- creation and use of effective lines of communication;
- use of internal monitoring and auditing processes;
- published and enforced disciplinary guidelines; and
- development and enforcement of corrective action policies and procedures.

Industry codes

The PhRMA 'Code on Interactions with Health Care Professionals' (the PhRMA Code), is a voluntary code recognised by the federal government as a good-faith effort to comply with applicable federal health-care laws. The PhRMA Code emphasises that any interaction between the pharmaceutical industry and health-care professionals should focus on providing scientific and educational information and supporting scientific and medical research to maximise patient benefits. The PhRMA Code addresses general interactions between pharmaceutical companies and health-care professionals, including guidelines for consulting arrangements, scientific meetings and the provision of educational and practice-related items. PhRMA member companies have voluntarily agreed to comply with the PhRMA Code's principles. California, Connecticut and Nevada have enacted statutes mandating compliance with the PhRMA Code principles.

The PhRMA Code covers many interactions among the pharmaceutical industry and health-care professionals. Some of its principles include:

- meals provided by sales representatives or their immediate mangers must be in office or hospital settings and restaurant meals are prohibited;
- permitted meals are appropriate as long as they are modest in value as judged by local standards, not part of an entertainment or recreational event and provided in a manner conducive to informational communication;
- gifts and other items that do not advance disease or treatment education may not be provided to health-care professionals or their staff (examples of permitted items include medical texts, journal subscriptions, anatomical models for patient exam rooms);
- entertainment and recreation activities provided to health-care professionals are prohibited;
- consultants should be chosen based on defined criteria such as medical expertise and reputation or knowledge and experience in a particular therapeutic area; and
- companies should identify and comply with an internal cap

on the total amount of annual compensation to be paid to any health-care professional for speaking on behalf of the company.

The AdvaMed 'Code of Ethics on Interactions with Health Care Professionals' (the AdvaMed Code) is a code of conduct provided for the medical device industry. It is similarly a voluntary code, adopted by AdvaMed member companies, and includes many of the same principles as the PhRMA Code. The AdvaMed Code aims to:

facilitate ethical interactions between [member companies] and those individuals or entities involved in the provision of health-care services or items to patients, or both, which purchase, lease, recommend, use, arrange for the purchase or lease of, or prescribe [member companies' products] in the United States.

10 What are the most common infringements committed by manufacturers with regard to collaboration with health-care professionals?

In recent years, the number of actions taken by government agencies against pharmaceutical manufacturers has risen, as there have been investigations by the DOJ, OIG, US Attorney General's Office and state prosecutors' offices. These actions have resulted in civil and criminal lawsuits, indictments, deferred prosecution agreements, corporate integrity agreements, significant monetary fines, exclusion from federal and state health-care programmes, unwanted media attention and ongoing increased costs of compliance. Common violations include off-label promotion activities, kickbacks for making improper payments to health-care professionals and submission of false claims.

11 What are the main rules and principles applying to the collaboration of the pharmaceutical industry with patient organisations?

The United States does not restrict or otherwise govern interactions among members of the pharmaceutical industry and patient organisations. Grants and other payments to patient organisations, however, may be subject to the state compliance disclosure laws discussed above.

12 Are manufacturers' infringements of competition law pursued by national authorities?

Yes, both criminally and civilly by the Antitrust Division of the DOJ and civilly by the FTC. The primary statutes under which enforcement is conducted are the Sherman Antitrust Act, 15 USC subsection 1-7; the Clayton Act, 15 USC subsection 12-27; and the FTC Act, 15 USC subsection 41-58. Injunctive relief is also authorised.

13 Is follow-on private antitrust litigation against manufacturers possible?

Yes. Whether or not the DOJ or FTC acts, private lawsuits can be brought on behalf of a particular plaintiff or plaintiffs claiming to have been injured or on behalf of very broad classes of individuals or entities. The authorising statute is the FTC Act. Three times actual damages may be awarded as can injunctive relief.

Compliance – medical device manufacturers

14 Is the advertising of medical devices and the collaboration of manufacturers of medical devices with health-care professionals and patient organisations regulated as rigorously as advertising and collaboration in the pharmaceuticals sector?

The FDA regulates advertising for restricted medical devices. Medical devices are deemed restricted either by regulation or by order approving a pre-market approval. A prescription medical device may or may not be a restricted medical device. Restricted medical devices are deemed misbranded if their advertisements are 'false or misleading in any particular'. As with drugs, off-label promotion is prohibited.

Advertisements for restricted devices must include a true statement of the device's established name, printed prominently in type at least half as large as the brand name and a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications. Unlike drugs, device advertisements are not required to be submitted to the FDA at the time of initial publication or dissemination.

The FDA regulates labelling for all medical devices, but advertising for unrestricted medical devices is regulated by the FTC. The FTC Act prohibits medical device companies from using 'unfair or deceptive acts or practices in or affecting commerce' and specifically includes false advertising.

Advertising of medical devices is not regulated as rigorously as advertising in the pharmaceutical sector. This is in part because the requirements for device advertising are not as onerous as pharmaceutical advertising, and there are fewer regulations providing an enforcement framework for such requirements. Also, regulatory enforcement activities are divided between the FDA and FTC. Further, on the FDA side, the Center for Devices and Radiological Health (CRDH), responsible for medical devices, does not have an office or division specifically dedicated to monitoring medical device advertising, as the Center for Drug Evaluation and Research (CDER) does with OPDP. Although the CDRH issues letters for violations, without a specific office to focus on advertising, its enforcement actions are less frequent. Many device companies look to prescription drug promotion violations for guidance on interpretation of statutory requirements.

Unlike advertising specifically, the collaboration of medical device companies with health-care professionals and patients has been under a great deal of scrutiny in recent years. For example, in 2010 four medical device companies received considerable attention for their settlements with the DOJ for alleged violations of the federal anti-kickback law and FDCA. Wright Medical paid over US$7 million and agreed to execute a corporate integrity agreement and deferred prosecution agreement for allegedly violating the federal anti-kickback law.

According to the complaint, Wright entered into consultant agreements with orthopaedic surgeons to induce the surgeons to use Wright's hip and knee reconstruction and replacement products. Exactech, a company that manufactures orthopaedic implant devices and supplies, paid almost US$3 million and signed a corporate integrity agreement and deferred prosecution agreement for similar violations. Norian Corporation and its parent company, Synthes, also agreed to sign a corporate integrity agreement and to pay over US$22 million and over US$600,000, respectively, for allegedly promoting products for off-label uses. Specifically, Norian and Synthes allegedly promoted the products Norian XR and Norian SRS for vertebral compression fractures without receiving pre-market approval or clearance. According to the complaint, they also organised and sponsored meetings at which physicians were instructed on off-label uses and conducted an unauthorised clinical trial through an illegal 'test market' by selling the product to spinal surgeons and gathering safety and efficacy information from those surgeons. This upsurge in enforcement activities has caused device companies to more carefully examine their product promotion practices, although advertising in the device industry is not as rigorously regulated as in the drug industry.

Pharmaceuticals regulation

15 Which legislation sets out the regulatory framework for granting marketing authorisations and placing medicines on the market?

Section 505 of the FDCA, along with its implementing regulations found in Code of Federal Regulations, especially section 21, part

314, establishes the process by which a manufacturer or drug sponsor seeks approval to market and sell a new pharmaceutical in the United States.

16 Which authorities may grant marketing authorisation in your jurisdiction?

Only the FDA may grant approval to market and sell a new pharmaceutical in the United States. Specifically, the CDER reviews new drug applications and ensures that prescription and over-the-counter drugs are safe and effective.

17 What are the relevant procedures?

A drug manufacturer or sponsor formally requests approval to market and sell a new pharmaceutical by submitting a new drug application (NDA). The NDA includes both clinical and non-clinical data and analyses, drug information and details about the proposed manufacturing process. In the NDA, the sponsor must provide data and information that support a finding that the drug is safe and effective for its proposed use and that the benefits of the drug outweigh its risks. The FDA reviewer also evaluates the proposed labelling and the manufacturing methods provided in the NDA.

Before the drug manufacturer or sponsor can institute the large-scale studies that will serve as the backbone of the NDA, the sponsor must first perform pre-clinical research and submit data to the FDA demonstrating that the drug is reasonably safe for use in initial, small-scale clinical studies. The pre-clinical data often consists of an evaluation of the drug's pharmacologic effects and toxicity as determined through in vitro and laboratory animal testing. Pharmacokinetic and pharmacologic data include information about the drug and its metabolites' absorption, metabolism and excretion. The FDA generally will require the sponsor to provide a pharmacologic profile, data as to the acute toxicity in at least two animal species and short-term toxicity studies. Assuming that the results of pre-clinical testing are favourable, the sponsor will then file the data as part of an investigational new drug (IND) application pursuant to the regulations set forth in 21 CFR part 312. Obtaining IND approval of a drug exempts that drug from the FDA's pre-marketing approval requirements and permits the drug to be lawfully shipped for the purposes of conducting clinical investigations.

The general principles of the IND submission are set forth in 21 CFR section 312.22. The quantity and type of information supplied is dependent upon numerous factors including the novelty of the drug, the extent to which the drug has been previously studied, the severity of the known or suspected risks and the developmental phase of the drug.

Once the sponsor has obtained the IND, it may begin clinical trials. Clinical trials are categorised into three phases. The first use of a potential new drug in humans is done via Phase 1 clinical trials. These trials are generally on a very small scale and often utilise healthy volunteers. Phase 1 studies are designed to obtain data on the pharmacologic and metabolic properties as well as the side effects of increasing dosages in humans. Phase 1 studies are primarily designed to obtain sufficient pharmacologic and pharmacokinetic data for well-controlled, scientifically valid Phase 2 studies. CDER has the regulatory authority to stop or hold a Phase 1 study for safety reasons.

Preliminary data on the effectiveness of a proposed new drug product is obtained during Phase 2 clinical trials. Phase 2 studies are well-controlled, closely monitored studies on people with disease. The patient population is generally small and includes a few hundred test subjects. Phase 2 studies are also important in assessing the safety of the drug by providing data on short-term side effects and risks in the target population.

Phase 3 clinical studies are greatly expanded and include controlled and uncontrolled studies. Phase 3 studies are only performed where Phase 2 studies have produced evidence of effectiveness. Phase 3 studies involve larger populations, up to several thousand, and are designed to obtain statistically significant data supporting the drug's safety and effectiveness as well as the overall risk. CDER has the ability to impose clinical holds on Phase 2 and 3 studies if it determines that the study is unsafe or if the design of the protocol is insufficient to meet the study objectives.

The submission of an NDA is a collaborative process between the FDA and the sponsor. A pre-NDA meeting is held for the purpose of discussing the data in support of the application. The sponsor provides the FDA with a summary of the clinical studies and the organisation and format of the NDA and included data. This permits the FDA and the sponsor to address any unresolved issues or obvious deficiencies in the proposed NDA.

Because a typical NDA for a new compound can be in excess of 100,000 pages of documents, the review process is lengthy. The NDA is required to contain several technical sections that must contain data and information in sufficient detail to enable the agency to evaluate the drug. Federal regulations require an NDA to have several sections including the application form, index, summary, technical sections, samples and labelling, case report forms and tabulations and patent information. The requisite technical sections are chemistry, manufacturing and controls; non-clinical pharmacology and toxicology; human pharmacokinetics and bioavailability; microbiology; clinical data; statistical data; and paediatric use. The sponsor cannot be selective in presenting data, as the federal regulations require the sponsor to include in an NDA all other data and information relevant to an evaluation of safety and effectiveness obtained or received from any source, foreign or domestic, including any published or unpublished scientific literature. Likewise, the applicant is required to periodically update safety data during the pendency of the application. In some instances, including those where the drug has been placed on a fast track or is indicated for long-term usage to treat chronic conditions, the FDA may require post-marketing safety studies.

Moreover, a manufacturer may submit an abbreviated new drug application (ANDA), instead of an NDA, when the manufacturer wants to commercialise a generic drug product. Unlike an NDA, an ANDA does not require pre-clinical and clinical data to establish safety and effectiveness. On the contrary, the applicant must prove that the product is a bioequivalent.

18 Will licences become invalid if medicinal products are not marketed within a certain time? Are there any exceptions?

No.

However, a drug's patent or exclusivity may continue to run even if a product is not actively marketed. A drug patent from the Patent and Trademark Office generally expires 20 years from the date of filing, although a number of factors may affect its duration. In contrast, marketing exclusivity, which is granted by the FDA when certain requirements are met at the time of approval, is generally much shorter. For example, orphan drug exclusivity lasts for seven years, while paediatric exclusivity only adds six months to an existing patent or exclusivity.

19 Which medicines may be marketed without authorisation?

According to the FDA website, 'every new drug has been the subject of an approved NDA before US commercialisation' since 1938. The FDA recognises, however, that a prescription drug lacking FDA approval may be marketed legally under the law if it is grandfathered or is otherwise not a new drug. Although the existence of such drugs is theoretically possible, the FDA commented in its 19 September 2011 guidance that the existence of such a drug is unlikely. In addition, a company can manufacture and market an over-the-counter product without FDA pre-approval once a final monograph has been

implemented. A product that conforms to the final monograph may be marketed without further review.

20 Are any kinds of named patient programmes in place? If so, what are the requirements for pre-launch access?

Under certain circumstances, the FDA grants individuals access to unapproved, investigational drugs or devices for serious diseases under a 'single patient investigational new drug application,' also commonly referred to as a 'single patient IND' or the 'compassionate use' exception. To obtain access for a particular patient to a drug that is in clinical trials, the treating physician must obtain permission from the drug manufacturer and submit an application for approval by the FDA. The FDA will grant individual access to the investigational drug if the following criteria are satisfied:

- the patient's physician determines that there is 'no comparable or satisfactory alternative therapy available' to treat the patient's disease or condition and the risk from the investigational drug or device is no greater than the risk posed by the disease or condition;
- the FDA determines that there is 'sufficient evidence of safety and effectiveness to support the use' of the investigational drug or device;
- the FDA concludes that providing access to the drug or device will not interfere with the ongoing clinical trial; and
- the clinical investigator or sponsor submits to the FDA a clinical protocol for the patient's use of the investigational drug or device (21 USC section 360bbb(b)).

The FDA follows similar procedures for consideration of requests for access to small groups of patients.

Pricing and reimbursement of medicinal products

21 To what extent is the market price of a medicinal product governed by law or regulation?

The market price of pharmaceutical products is not controlled by law or regulation. Generally, pharmaceutical manufacturers are free to set the market price for their products. In this regard, the United States is almost unique. This issue has been the subject of much discussion, but the argument that has held the most weight is that imposing price controls on manufacturers would effectively restrict a manufacturer's ability to determine appropriate market pricing for its drug products and could stifle innovation due to the significant expense associated with research and development activities.

While manufacturers in the United States may establish the market pricing for their drugs, a set of very complex laws and regulations governs the pricing and reimbursement of such products when purchased by or through federal and state government health-care programmes. As a result, manufacturers must consider the potential impact of government pricing rules when determining the market or commercial pricing for its products in the United States.

The following sections provide a high-level overview of some of the issues surrounding pricing and reimbursement of pharmaceutical products in the United States.

22 Must pharmaceutical manufacturers negotiate the prices of their products with the public health-care providers?

The United States health-care system operates differently from many other countries. Pharmaceutical manufacturers are free to negotiate the price of their products directly with health-care providers. However, the ability of pharmaceutical manufacturers to negotiate pricing with federal and state governments, significant purchasers of pharmaceutical products, is limited with respect to certain government programmes. The prices ultimately paid by the government to health-care providers and other entities for pharmaceutical products are subject to special pricing rules, and in some cases, based on statutorily imposed formulae for rebates and discounts.

23 In which circumstances will the national health insurance system reimburse the cost of medicines?

The United States health-care system consists of numerous commercial and government payer entities with distinct coverage and reimbursement rules. Whether a commercial-payer entity will reimburse for a particular drug depends upon its specific benefit plans and the coverage and reimbursement policies, as well as such factors as formulary placement.

Although similar in some ways, reimbursement by government-payer entities is more complicated. For funding to be available for a manufacturer's products through major federal and state health-care programmes, a manufacturer must enter into agreements with and provide statutorily required discounts or rebates to the federal and state agencies that administer health-care programmes. In accordance with these agreements and pursuant to applicable law, pharmaceutical manufacturers must provide pricing information – including information on discounts and rebates (or other reductions in price) that it may offer to other non-government health-care payers and providers – so that the government agency can determine the appropriate reimbursement for a product. An array of pricing, coverage and reimbursement rules dictate how and when health-care providers will receive payment.

24 If applicable, what is the competent body for decisions regarding the pricing and reimbursability of medicinal products?

Pricing and reimbursement of pharmaceutical products is determined by many different entities, including private payers and federal and state agencies that are responsible for paying for prescription drugs. Pharmaceutical manufacturers are free to establish and negotiate pricing, discounting and reimbursement for drug products with the many different health-care payers and providers in the United States. Discount and rebate agreements with private payers or providers will generally govern pricing and reimbursement, or both, and applicable coverage rules for the various payer entities will dictate when and how reimbursement will occur. These rules vary from private payers to government payers. For drugs provided to federal or state health-care programme beneficiaries, the applicable federal or state agencies tasked with administering a particular health-care programme will generally act as the 'competent body' for making decisions regarding pricing and reimbursement subject, however, to the varied and complex laws, rules and regulations applicable to such decisions.

25 Are manufacturers or distributors of medicinal products statutorily obliged to give a discount?

Although drug manufacturers and distributors in the United States are not statutorily obliged to provide discounts on their products to private payers (and even some government entities), certain government entities are entitled by law to receive the lowest available price of a drug. Pursuant to applicable law, payment by these entities for prescription medications is conditioned on a number of factors. Pharmaceutical manufacturers must enter into special agreements with the entities that administer these government programmes, to report specific pricing information and to provide discounts or rebates in accordance with statutory formulae.

The layers of pricing and reimbursement laws and regulations in the United States are complex and ever-changing. The recent passage of the ACA and the Health Care and Education Reconciliation Act of 2010, which have additional pricing implications for pharmaceutical manufacturers, adds yet another layer regarding discounts, rebates

Update and trends

Almost immediately after its passage in March 2010, the ACA was challenged in dozens of federal courts. Plaintiffs alleged that the ACA represents an unconstitutional exercise of Congressional power and violates various sections of the United States Constitution, ranging from the commerce clause to the due process clause.

Numerous federal district courts have ruled on the matter, which resulted in various judgments. District courts throughout the country have upheld the law in its entirety, invalidated the law in its entirety, and carved out portions that are valid and invalid. Many of the federal district court decisions were appealed to federal courts of appeals. Again, the rulings represented split decisions, leaving the law in limbo. In November 2011, the United States Supreme Court announced that it would review the constitutionality of various parts of the ACA. The Supreme Court's decision, whatever it is in terms of upholding or striking down various parts of the ACA, will have an enormous impact in this field and is expected to be released in the summer of 2012.

and pricing of pharmaceutical products. Due to the numerous obligations imposed on pharmaceutical manufacturers related to government pricing and the many risks associated with non-compliance, companies should fully explore the applicable laws and regulations with specialised guidance from legal counsel.

Medicine quality and access to information

26 What rules are in place to counter the counterfeiting and illegal distribution of medicines?

While no specific anti-counterfeiting statute has been passed, a variety of laws address counterfeiting, illegal distribution of medicines and supply chain integrity. Those laws include pedigree requirements, which have been enacted by a majority of states and at the federal level through the PDMA (see 21 CFR section 203.50).The federal pedigree requirements were stayed for some time by ongoing litigation. Although they are no longer stayed, the FDA recently released a notice of its intent to remove much of the federal requirements. Still, companies should take care to comply with the full landscape of pedigree laws, particularly each state's laws because they tend to be unique. In essence, pedigree laws require distributors to provide a document tracking each wholesale distribution of a prescription drug as it travels from the manufacturer to the end-user. Thus, the pedigree document is intended to show the product's chain of distribution step-by-step. This should establish the product's integrity as it moves through the stream of commerce. Recently, states and the federal government have begun proposing and enacting laws requiring the passage of pedigrees electronically (eg, via RFID or bar code) rather than hard-copy paper pedigrees.

To some extent, state licensing laws help ensure that product is not counterfeited or illegally distributed. Nearly every state has licensing requirements that companies must comply with to ship products from, to or through or manufacture products in, that state. These licences are typically granted on an annual basis and must be renewed regularly. To secure licences and subsequent renewals, companies must pay a fee, often undergo inspections or background checks, or both, and meet various other standards. Address changes, officer changes and other business model alterations can impact a company's licensure in a state.

While pedigree and licensing laws generally focus on the wholesale distribution of a trade product, the PDMA also governs the distribution of product samples. The PDMA helps protect against counterfeiting and illegal distribution of samples by requiring, among other actions, that samples be stored in secure facilities, tracked meticulously, documented and provided only to validly licensed prescribers who must sign for the samples.

27 What recent measures have been taken to facilitate the general public's access to information about prescription-only medicines?

In recent years, the FDA has undertaken a number of initiatives to provide the public, including health-care professionals and patients, with more comprehensible information about prescription drugs. As of 29 January 2010, the FDA began issuing one easy-to-read drug safety information communication, rather than a variety of different communications. In January 2006, the FDA also changed the format of a prescription drug's package insert. That new format is designed to ensure that the most important pieces of drug information are viewed by the patient before a drug is taken and the prescriber before it is prescribed. For instance, there are new graphic requirements, a new highlights section, a table of contents, a patient counselling information section, a toll-free number and internet reporting information for suspected adverse events. Current prescription information provided in the new format was made available online at no cost to consumers and health-care professionals and providers through DailyMed, a new inter agency online health information clearinghouse and a website called Facts@FDA.

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The Food and Drug Administration Amendments Act of 2007 also gave the FDA the authority to require a risk evaluation and mitigation strategy (REMS) from manufacturers to ensure that the benefits of a drug outweigh its risks. Potential REMS elements incorporate a patient package insert and a communication plan to health-care providers. Other REMS may require a paper handout known as a medication guide, if the FDA believes that adherence to directions is essential to its effectiveness or that patients need to be aware of particular side effects or adverse events. When these elements are insufficient to mitigate known serious risks, a REMS will also include elements to ensure safe use, which can include providing certain health-care providers who prescribe the drug and pharmacies, practitioners, or health-care settings that dispense the opportunity to obtain certification with respect to the drug.

28 Outline major developments to the regime relating to safety monitoring of medicines.

Traditionally, the FDA passively monitored the safety of drugs through case reports, post-approval clinical studies and reports from health-care professionals or patients who suffered adverse drug experiences. Under the federal regulations, NDA holders must report all adverse drug experiences, regardless of whether they are considered drug related. A serious and unexpected adverse event is classified as an 'alert report' and must be reported to the FDA within 15 days. Applicants must also submit 'periodic adverse drug experience reports' quarterly for three years following approval. Thereafter, reporting is effected on an annual basis. These adverse event reports, in conjunction with post-approval studies and case reports, have allowed the FDA to monitor drug safety.

In response to the Food and Drug Administration Amendments Act of 2007 (FDAAA), however, the FDA has sought to supplement traditional monitoring by creating and instituting a national, integrated, electronic system, which will allow more active medical product safety monitoring. Through this new electronic system, known as Sentinel, the FDA will be able to access the information in numerous existing data systems, including health record systems and medical claims databases. Using Sentinel, the FDA has the ability to search numerous systems and records for relevant product safety information. This will enable the FDA to monitor the performance of a drug throughout its life cycle.

The goal established by FDAAA was to monitor 25 million patients by 1 July 2010 and 100 million patients by 1 July 2012. In an attempt to meet this ambitious goal, the FDA already implemented the 'Mini-Sentinel' pilot programme, which includes the data of almost 100 million patients. The Mini-Sentinel programme's data analysis capabilities were presented at a conference this summer and are available at the Mini-Sentinel website http://mini-sentinel.org.

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