The Life Sciences Law Review

Fifth Edition

Editor
Richard Kingham

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EDITOR'S PREFACE

The fifth edition of *The Life Sciences Law Review* covers a total of 37 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged to describe requirements throughout the life cycle of a regulated product, from discovery to clinical trials, the marketing authorisation process and post-approval controls. Certain other legal matters of special interest to manufacturers of medical products – including administrative remedies, pricing and reimbursement, competition law, special liability regimes and commercial transactions – are also covered. Finally, there is a special chapter on international harmonisation, which is of increasing importance in many of the regulatory systems that are described in the national chapters.

Now, more than ever, it is important for leaders in the pharmaceutical and medical device industries and their advisers to be knowledgeable about the laws and regulations in major jurisdictions around the world. In the past year, there have been significant developments in the regulation of drugs and medical devices, especially in the United States, where a new law – the 21st Century Cures Act – was passed at the end of 2016. There are prospects for further developments in the coming year. The new president and the Republican-controlled Congress will consider legislative measures affecting the pharmaceutical and medical device sectors, including proposed repeal of the Affordable Care Act, continuing inquiries into pricing of medical products and reauthorisation of user fee laws that fund a substantial part of the drug and device approval processes. The United Kingdom will initiate formal proceedings to begin the process of withdrawing from the European Union, with potential consequences for the medical products sectors. Other jurisdictions, including China and India, are considering reforms to their regulatory systems for medicinal products.

Each of the chapters has been written by leading experts within the relevant jurisdiction. They are an impressive group, and it is a pleasure to be associated with them in the preparation of this annual publication.

Richard Kingham
Covington & Burling LLP
Washington, DC
March 2017

Chapter 38

UNITED STATES

Richard Kingham and Krista Hessler Carver[1]

I INTRODUCTION

The United States accounts for about 35 per cent of the global pharmaceutical market and is the largest single investor in research and development of new products. The National Institutes of Health, the primary federal agency that funds biomedical research, will have a budget of more than $33 billion for 2017, and manufacturers based in the United States spend substantially more than that each year on research and development.

The principal federal regulatory authority for medicines and medical devices is the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services. The FDA, which has a staff of more than 15,000 and an annual budget in excess of $5 billion, regulates human drugs, human biological products, medical devices, foods, cosmetics, veterinary medicines, animal feeds, radiation-emitting products and tobacco. A substantial part of the agency's budget comes from 'user fees' imposed on certain of the industries it regulates (including drug and device manufacturers); these may include registration fees for marketing authorisation applications as well as annual fees for manufacturing facilities and marketed products.[2]

The FDA is headed by a Commissioner of Food and Drugs, who is appointed by the president with the approval of the senate. Only a handful of the Commissioner's subordinates are political appointees; the rest are career civil servants. Approximately half of the FDA's

1 Richard Kingham is a senior counsel and Krista Hessler Carver is a partner at Covington & Burling LLP. The authors would like to thank the following colleagues, who contributed to the preparation of this chapter: James Dean, Stefanie Doebler, John Hurvitz, Edward Dixon and Christina Kuhn.

2 The FDA budget request for fiscal year 2017 states that $2.3 billion of the total budget of $5.1 billion will come from user fees. An executive order issued by the President in January 2017 imposed a temporary hiring freeze for most government agencies. It is unclear how this will affect the FDA.

staff are located in the Washington, DC, metropolitan area, many serving in 'centres' that supervise the principal industry sectors that the agency regulates. Among these are the Center for Drug Evaluation and Research (CDER), which regulates small-molecule drugs and most therapeutic protein products; the Center for Biologics Evaluation and Research (CBER), which regulates vaccines, blood products, gene and tissue therapies and certain other biological products; and the Center for Devices and Radiological Health (CDRH), which regulates medical devices and radiation-emitting products. The CDER, CBER and CDRH all fall within the Office of Medical Products and Tobacco, which is headed by a Deputy Commissioner. The Office of Global Regulatory Operations and Policy, also headed by a Deputy Commissioner, manages the agency's inspectional and enforcement programmes, staffed by several thousand employees who are located in regional, district and field offices around the United States and in several foreign countries.[3]

The main statute administered by the FDA is the Federal Food, Drug and Cosmetic Act (FDCA), originally enacted in 1938, which governs foods (including dietary supplements), drugs, devices, cosmetics, veterinary drugs, radiation-emitting products and tobacco.[4] The statute prohibits 'adulteration' and 'misbranding' of regulated products and imposes numerous other requirements for specific types of products (e.g., pre-market approval or clearance procedures for certain drugs and medical devices). The FDA also administers portions of the Public Health Service Act (PHSA), including requirements for licensure of biological products, as well as numerous other regulatory statutes.[5]

The Drug Enforcement Administration (DEA), an agency within the Department of Justice, administers the Controlled Substances Act and other statutes relating to narcotics, psychotropics and other drugs with potential for abuse. Manufacturers of controlled substances are licensed and inspected by the DEA and may be required to obtain permits for specific activities (e.g., import and export licences and manufacturing and import quotas for certain products).

United States attorneys, located in every state, can bring cases to enforce the FDCA and other regulatory statutes governing drugs and devices. Federal prosecutors may act on referrals from FDA or on their own initiative.

The Federal Trade Commission (FTC) regulates the advertising of non-prescription drugs and medical devices (other than restricted devices) and also plays a major role in supervising compliance with the antitrust laws within the medical products industry.

The Office of Inspector General (OIG) in the Department of Health and Human Services investigates allegations of fraud, kickbacks and other abuses affecting federal healthcare programmes, including Medicare (for the elderly) and Medicaid (for indigent persons). It has the power to exclude companies or individuals from participation in those programmes if they are found to have committed specified offences.

3 The FDA website (www.fda.gov) contains information on the agency as well as links to relevant statutes, regulations, guidances and other documents.

4 The FDCA is codified at 21 USC, Section 301 et seq. It replaced the Food and Drugs Act, originally passed in 1906.

5 The relevant provisions of the PHSA are set out in 42 USC, Section 262. Requirements for federal licensing of establishments that manufacture biologics were originally enacted in 1902.

The state governments also have the power to regulate drug and device manufacturers. Many states have enacted 'mini' food and drug acts, as well as statutes prohibiting healthcare and consumer fraud. The states also maintain Medicaid fraud control units to investigate abuses by manufacturers, providers and beneficiaries under that programme.

II THE REGULATORY REGIME

i Classification

The FDCA defines foods, drugs, devices, cosmetics, dietary supplements and certain other types of products, and the PHSA defines biologics.[6] The same product may, however, be covered by two or more definitions and thus be subject to multiple regulatory requirements. Many of the classifications depend on the 'intended use' of an article, which is ordinarily determined by statements made in advertising, labelling or other materials issued by the seller. Thus, a fluoride toothpaste for which anti-cavity claims are made is regulated as a drug because it is intended to prevent tooth decay and a cosmetic because it is intended to clean the teeth and improve their appearance.

For certain borderline products that may be subject to more than one regulatory review process or for which the product category is unclear or in dispute, the FDA has issued regulations and guidelines to determine which review centre will take the lead, and it has established an Office of Combination Products to assign products. These regulations and processes apply to drugs, devices, biological products and combinations thereof, known as 'combination products'.[7] They do not apply to combinations of two drugs, two devices or two biologics, or to other combinations of regulated products.

The FDA can initiate enforcement actions against borderline products that it believes are marketed without required prior approval. For many years, the FDA often initiated such actions against dietary supplements for which therapeutic claims were made, on the basis that those products were unapproved new drugs. Such actions have been less frequent since the Dietary Supplement Health and Education Act of 1994 created a separate legal framework to govern those products. The agency continues to monitor the advertising and labelling of cosmetics for which anti-ageing claims are made, and it has taken several enforcement actions in recent years.

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6 Under the FDCA, the term 'drug' includes articles recognised in official pharmacopoeias; articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; and articles (other than food) intended to affect the structure or any function of the body (21 USC, Section 321(g)). The term 'device' is defined in substantially similar terms, but applies to articles that do not achieve their primary intended purposes 'though chemical action within or on the body…' and which are not 'dependent upon being metabolised for the achievement of [their] primary intended purposes' (21 USC, Section 321(h)). Under the PHSA, the term 'biologic' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesised polypeptide) or analogous product or arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment or cure of a disease or condition in humans (42 USC, Section 262(i)(1)).

7 21 CFR, Part 3.

ii Non-clinical studies

Non-clinical safety studies that are intended to be submitted to the FDA in support of clinical research applications or marketing authorisation applications generally must be conducted in compliance with good laboratory practice (GLP) regulations.[8] These are fundamentally the same as the principles established by the Organisation for Economic Co-operation and Development, which were based on the FDA rules.

The Animal and Plant Health Inspection Service (APHIS) within the Department of Agriculture administers regulations under the Animal Welfare Act governing research facilities using covered species. Facilities must be registered and comply with applicable welfare requirements and are subject to inspection by APHIS.

iii Clinical trials

The FDA maintains separate regulatory systems for clinical trials of drugs and medical devices. Both are subject to requirements for the protection of human subjects, including rules on informed consent and independent ethical review, performed by organisations known as institutional review boards, or IRBs.[9] FDA regulations also establish requirements for financial disclosures by investigators who conduct clinical trials submitted to the FDA in support of applications for drugs or medical devices.[10] Disclosure must be made if an investigator has a substantial financial interest in the product under investigation or the company that sponsors a trial, subject to detailed criteria set out in the rules.

Drugs

Clinical trials of unapproved new drugs or biologics must be carried out under an investigational new drug application (IND).[11] The application contains information on the manufacturing process and formulation of the investigational product, non-clinical and existing clinical safety data, the protocol for the proposed trial, a copy of the investigator brochure and information on the investigators who will carry out the trial. The FDA accepts INDs in the common technical document (CTD) format established by the International Conference on Harmonisation (ICH). The IND submission must clearly identify any obligations that the sponsor intends to delegate to another person, including contract research organisations (CROs). If the sponsor does not reside in or have a place of business in the United States, the application must be countersigned by an agent or attorney in the United States.

Review of an IND is supervised by a division within the CDER or CBER that specialises in the therapeutic area or product type to which the proposed study relates. That division will have lead responsibility for reviewing a marketing authorisation application if one is submitted and will retain supervisory control over the product after approval. As a result, there is considerable continuity in the review process from the earliest stages of clinical development.

Assuming that approval is granted by the relevant IRB, the sponsor may commence a clinical trial 30 days after the agency accepts the application for filing, unless the FDA informs the sponsor that it may commence the trial earlier or imposes a clinical hold. The

8 21 CFR, Part 58.

9 21 CFR, Parts 50, 56.

10 21 CFR, Part 54.

11 See generally, 21 CFR, Part 312.

rules establish several grounds for a clinical hold, but the main focus is on the safety of human subjects. The sponsor has the right to receive a prompt written statement of the reasons for a clinical hold and to take an appeal, which must be acted upon within 30 days. Once an IND is in effect, new protocols and substantial protocol amendments must be submitted to the FDA before they are initiated, but studies can commence as soon as IRB approval is received. Throughout the process, however, the FDA has the right to impose a clinical hold on studies under the IND if it believes that there is a risk to the safety of human subjects or if certain other criteria apply, subject to an appeal by the applicant.

A sponsor may seek informal, non-binding advice from the FDA at any time during the pendency of the IND. It may also seek advice through an 'end-of-Phase II' meeting, which is held to agree the design of the protocols for the pivotal clinical trials, or, for certain studies, a special protocol assessment. In either case, barring a significant scientific development, studies conducted in accordance with the agreement will be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

Sponsors and investigators are required to comply with provisions of good clinical practice (GCP), including requirements for informed consent, IRB review, monitoring, record-keeping, and reporting. Studies conducted in accordance with ICH GCP guidance will normally be acceptable to the FDA. There is no requirement for sponsors to maintain insurance or compensate subjects for injuries in clinical trials, but informed consent documents must make clear whether such arrangements have been made. There are requirements for annual reports and expedited reports of serious, unexpected adverse events that may be drug-related and certain significant findings in non-clinical studies.

The FDA will accept data from foreign clinical trials not conducted under a US IND in support of a marketing authorisation application, provided they are performed in accordance with GCP and the FDA is able to validate the data through an on-site inspection, if necessary. It is possible to obtain approval for a drug entirely on the basis of foreign clinical data, but in practice it is ordinarily desirable to carry out at least some part of the pivotal trials in the United States.[12]

Devices

Sponsors of device clinical trials must comply with the FDA's investigational device exemption (IDE) regulations. The regulatory requirements for a trial differ depending on whether the device is 'significant risk' (SR). SR devices are defined as those that present a potential for serious risks to the health, safety, or welfare of subjects (e.g., implants and life-supporting and life-sustaining devices).[13] Before beginning an investigation of an SR device, the sponsor must obtain FDA approval of an IDE application. The application has some similarities to an IND (e.g., it must contain the investigational plan and report prior studies of the device). Moreover, following enactment of the FDA Safety and Innovation Act (FDASIA) in 2012, the FDA now has express authority to put a device investigation on clinical hold. The FDASIA also provided that the FDA may not disapprove an IDE because the study may not support clearance or approval of the device.[14] In August 2014, the FDA issued guidance on

12 See 21 CFR, Section 312.120.

13 21 CFR Section 812.3(m).

14 Pub. L. No. 112-144, Section 601, 126 Stat. 193 (2012) (creating Section 520(g)(4)(C) of the FDCA).

its considerations for decision-making regarding IDEs and its plan to provide sponsors with feedback on study limitations that could preclude clearance or approval even though they would not preclude study initiation.[15]

'Abbreviated' IDE requirements apply to investigations of non-significant risk devices (i.e., those that do not meet the regulatory definition of SR). The sponsor must obtain IRB approval and informed consent and comply with record keeping and reporting requirements, but need not submit or obtain FDA approval of an IDE before commencing the study. Further, some device investigations are exempt from the IDE and abbreviated IDE requirements, including investigations of certain non-invasive diagnostic devices.

Device sponsors may obtain informal advice from the FDA on study design and other issues through a 'pre-submission' process (formerly the 'pre-IDE' process). In February 2014, the FDA issued a final guidance on the pre-submission programme.[16]

The FDA will accept foreign studies not conducted under an IDE to support a device pre-market approval application (PMA) if the data are valid and the investigators conducted the studies in accordance with the Declaration of Helsinki (1983 version) or the laws of the country where the research is conducted, whichever provides greater protection of trial subjects.[17] In 2012, Congress codified the FDA's approach in Section 569B of the FDCA. In February 2013, the FDA proposed to amend its regulations to permit supportive use of foreign data that are collected in accordance with GCP and subject to validation.[18] The amended regulation would apply to data in other device submissions, not just PMAs. The FDA also has issued draft guidance providing proposed recommendations on how to develop foreign data that are adequate to support approval or clearance of the device in the United States.[19]

iv Named-patient and compassionate use procedures

There are several procedures under which drugs or devices can be made available to treat patients even though they have not been cleared for commercial distribution.

Drugs

The FDA has established rules for 'expanded access' to investigational drug products that are intended to treat serious or life-threatening diseases. These include provisions for emergency INDs that permit physicians to treat individual patients following relatively simple applications to the FDA and treatment INDs, which provide for larger-scale use of investigational products. In certain cases, the FDA can authorise sponsors to charge for

15 FDA, Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff: FDA Decisions for Investigational Device Exemption Clinical Investigations (August 2014).

16 FDA, Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance (February 2014).

17 21 CFR, Section 814.15(b).

18 78 Fed Reg 12664 (25 February 2013).

19 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States (April 2015).

investigational drug products under treatment INDs; prices are limited to recovery of direct costs of manufacture and distribution. Treatment INDs require prior approval from the FDA, and sponsors must comply with requirements for informed consent, IRB review and reporting of adverse events.

Pharmacists may prepare 'compounded' products as part of the practice of the profession of pharmacy. In 1997, Congress enacted a detailed statutory regime to govern pharmacy compounding,[20] but the Supreme Court held that a provision of that regime that forbade compounders from advertising their services violated the First Amendment to the US Constitution, which guarantees freedom of speech.[21] The lower courts disagreed on the question of whether the Supreme Court's ruling invalidated the entire statute or only the prohibition on advertising. Reports of severe injuries associated with the use of injectable compounded products that were contaminated with infectious organisms led to enactment of legislation to clarify the FDA's authority. The Compounding Quality Act, signed by the president in November 2013, establishes two regulated entities: traditional compounders, which prepare products at the request of physicians for specific patients, and 'outsourcing facilities', which prepare compounded products in larger quantities. Traditional compounders will be regulated primarily by state boards of pharmacy, while outsourcing facilities will be regulated by the FDA. If they register with the agency, submit to inspections and comply with other requirements, their products will not be subject to requirements for pre-market approval. The new provisions apply only to drugs and do not contain any exemption from requirements for pre-market approval of biologics.[22]

Certain products for the prevention or treatment of pandemic diseases or to protect against bioterror agents can be sold under an emergency use authorisation (EUA). EUAs can only be approved if the Secretary of Health and Human Services declares that a pandemic is imminent, and authorisations remain valid only while the declaration is in effect.

Devices

Similar procedures apply to investigational devices intended for serious and immediately life-threatening diseases and conditions. The compassionate use framework permits access for individuals and small groups of patients who do not meet trial inclusion criteria. Prior FDA approval and certain patient protection measures (e.g., informed consent, IRB chair concurrence and institutional clearance) are required. The treatment IDE provisions permit wider use of an investigational device, although treatment use may not begin until completion of clinical trials if the disease is serious but not immediately life-threatening. The sponsor must submit an application for treatment use, and treatment use may begin 30 days after the FDA receives the application unless FDA objects. As with treatment INDs, sponsors of treatment IDEs must comply with requirements for informed consent, IRB review and reporting of adverse events. Sponsors generally may not charge for the device any more than necessary to recover the costs of manufacturing, research, development and handling. EUAs also are available for devices.

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20 21 USC, Section 353a.

21 *Thompson v. Western States Medical Center*, 535 US 357 (2002).

22 The FDA has issued guidance implementing the new legislation, which appears on the agency's website at www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm.

'Custom devices' are exempt from the requirements for an approved PMA and compliance with performance standards under Section 520(b) of the FDCA.[23] Traditionally, the FDA interpreted this exemption narrowly. In 2012, Congress enacted clarifying changes to Section 520(b), including a provision that states that production of custom devices 'is limited to no more than 5 units per year of a particular device type'. The FDA recently issued final guidance implementing the amended custom device provision.[24]

Laboratory-developed tests (LDTs) present special regulatory issues. LDTs are diagnostic tests that are developed, validated and performed by individual laboratories but not commercially distributed. Clinical laboratories performing LDTs are subject to the requirements of the Clinical Laboratory Improvements Amendments of 1988, including the requirements to validate the LDTs and obtain certifications to perform testing. Historically, the FDA asserted that LDTs are devices subject to regulation under the FDCA but exercised enforcement discretion and did not require pre-market approval or clearance for LDTs. In June 2010, the FDA announced that it intended to exercise authority over LDTs.[25] In the FDASIA, Congress required the FDA to notify Congress 60 days before issuing a draft or final guidance document regarding the regulation of LDTs. The FDA provided this notice on 31 July 2014, indicating its intent to publish two draft guidances describing a proposed regulatory framework for LDTs, and providing anticipated details of those draft guidances.[26] Thereafter, on 3 October 2014, the FDA formally announced the publication of the draft guidances in the Federal Register and opened a 120-day comment period ending on 2 February 2015.[27] Congress also began considering several different potential legislative approaches to address LDTs. The FDA stated that it intended to publish final guidance on the issue in 2016;[28] however, in November 2016, following the presidential election, the FDA announced that it would not move forward with efforts to finalise the draft guidances. Congress is expected to continue to consider potential legislation addressing LDTs.

The FDA also does not require *in vitro* diagnostic products labelled for research use only (RUO) and certain *in vitro* diagnostic products labelled for investigational use only (IUO)[29]

23 21 USC, Section 360j(b).

24 FDA, Guidance for Industry and Food and Drug Administration Staff: Custom Device Exemption (September 2014).

25 75 Fed. Reg. 34463 (17 June 2010).

26 Sally Howard, Deputy Commissioner for Policy, Planning, and Legislation, Notification to Congress (31 July 2014), www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.

27 79 Fed. Reg. 59776 (3 October 2014); 79 Fed. Reg. 59779 (3 October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) (October 2014).

28 CDRH Fiscal Year 2016 (FY 2016) Proposed Guidance Development and Focused Retrospective Review of Final Guidance, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm467223.htm.

29 21 CFR, Section 809.10(c)(2).

to comply with most regulatory controls, including pre-market clearance requirements. In November 2013, the agency issued final guidance describing its current thinking on when products are properly labelled and distributed as RUO and IUO.[30]

v Pre-market clearance

Drugs other than biologics

'New drugs', which are defined to mean drugs that are not generally recognised as safe and effective for their labelled conditions of use or that are so recognised but have not been used to a material extent or for a material time, may not be introduced into interstate commerce unless they are subject to a new drug application (NDA) or abbreviated new drug application (ANDA) approved by the FDA. Drugs that are not new may be marketed without pre-market approval.

In practice, the great majority of non-prescription drug products, which contain old, well-established active ingredients, are marketed in accordance with 'monographs' issued under the Over-the-Counter (OTC) Drug Review.[31] Monographs, which govern therapeutic categories (e.g., antacids, topical antimicrobials or ophthalmic drug products), specify permitted active ingredients, dosages and instructions for use. Products in compliance with monographs can be marketed without any prior submission to the FDA.[32] Many therapeutic categories are subject to proposed rather than final OTC monographs, and there are complex procedures for determining which products can be marketed while rulemaking procedures are under way.[33] Newer OTC drug products and virtually all prescription drug products are marketed under approved NDAs or ANDAs.[34]

An NDA for an innovator product must contain information on the manufacturing process and formulation of the product, full reports of non-clinical studies and clinical trials

30 FDA, 'Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Guidance for Industry and Food and Drug Administration Staff' (November 2013).

31 21 CFR, Parts 330-361.

32 General provisions of the FDCA require that all drug establishments register with the FDA and submit periodic product listings, but the system does not entail FDA review or approval. The registration and listing requirements apply to foreign establishments that export drug products to the United States.

33 Although the FDA has established procedures for inclusion of new active ingredients in the OTC drug monograph process based on history of use in other countries ('time and extent applications', or TEAs), those procedures have proved ineffective in practice. In 2014, Congress enacted the Sunscreen Innovation Act, Pub. L. 113-195, which requires the FDA to establish an expedited procedure for inclusion of new active ingredients in OTC sunscreen products, based in part on approval and safe use in other countries, and to consider methods for expediting inclusion of new active ingredients for other OTC drug products.

34 A handful of older prescription drug products remain on the market pending completion of a review of effectiveness of marketed drug products that was initiated in the 1960s (the Drug Efficacy Study Implementation, or DESI). Eventually, the FDA intends to subject these products to NDAs or remove them from the market. In the meantime, the products are marketed subject to the FDA's enforcement discretion.

demonstrating the safety and effectiveness of the product and proposed labelling.[35] Although the FDA has not amended its regulations to require use of the common technical document (CTD), in practice the agency expects submissions to be made in that format, and the FDA is in the process of requiring that all submissions be made electronically (in the eCTD format). The FDA also requires submission of tabulations of all patient data from the principal clinical trials, as well as copies of case report forms (CRFs) for patients who died during clinical trials or withdrew because of adverse events, and it can demand CRFs for all patients in pivotal clinical trials. An applicant that does not maintain a place of business in the United States must appoint a US agent, who signs the application and receives official communications from the agency.[36]

Legislation originally enacted in 1992 and known as the Prescription Drug User Fee Act (PDUFA),[37] requires sponsors of originator products to pay fees upon the submission and filing of NDAs and supplemental NDAs (proposing changes in approved NDAs), as well as annual fees for manufacturing establishments and products that are subject to the user fee requirement. The fees are adjusted each year according to a formula set out in the law.[38] As part of the process leading to enactment of each version of the PDUFA, the FDA has made commitments to Congress in the form of performance goals for the NDA review process, including (among many other things) requirements to hold prompt meetings with applicants prior to and during the NDA review process, timelines for the completion of reviews and procedures for appeals of negative decisions. Under current PDUFA commitments, the FDA aims to review non-priority applications within 12 months of submission and priority applications within eight months.[39] In practice, the actual time from submission to approval of most NDAs is more than a year. The review process is carried out by an interdisciplinary team under the direction of the relevant therapeutic review division within the CDER. The FDA may consult with one or more independent expert advisory committees. At the end

35 An NDA may rely on information contained in another NDA, an IND or a drug master file, subject to a right of reference from the submitter of that information. FDA regulations provide for submission of DMFs for active substances, inactive ingredients and drug packaging materials, as well as other types of information by prior agreement with the agency (21 CFR, Section 314.420).

36 Regulations governing the content and review of NDAs are set out in 21 CFR, Part 314.

37 The PDUFA sunsets every five years unless re-enacted by Congress. The most recent enactment, passed in July 2012 as part of the FDA Safety and Innovation Act (FDASIA), is commonly referred to as 'PDUFA V'.

38 For fiscal year 2017, the fees are as follows: for an application containing clinical data, $2,038,100; for an application that does not contain clinical data, $1,019,050; for an establishment, $512,000; and for a product, $97,750.

39 Priority designation is granted if FDA determines that a drug would represent a significant improvement in the treatment, diagnosis or prevention of a disease as compared with existing therapies. There are provisions under which the sponsor of an NDA for a rare paediatric disease or a drug for a designated tropical disease may obtain a transferable priority review voucher, which can be sold to another company to enable it to obtain priority review of a product that would not otherwise be eligible for priority review.

of a review 'cycle', the FDA either issues an approval or a 'complete response' informing the applicant why approval was not granted and identifying additional information required for approval.[40]

To approve an NDA, the FDA must determine that the product will be safe and effective for the conditions of use recommended in its labelling, that the manufacturing process and facilities are adequate and in compliance with requirements for current GMP, and that the labelling is not false or misleading. Proof of effectiveness must be based on 'substantial evidence' consisting of reports of adequate and well-controlled clinical investigations. Legislation enacted in 2012 requires the FDA to establish a 'structured risk-benefit assessment framework' for the new drug approval process.[41]

As interpreted by the FDA, the Drug Price Competition and Patent Term Restoration Act of 1984 (often called the Hatch-Waxman Act) establishes two pathways for less-than-full applications that refer to prior approvals: ANDAs, submitted under Section 505(j) of the FDCA,[42] which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2),[43] which rely on the finding of safety and effectiveness for a reference product but contain clinical data or other information in support of a change (e.g., a new indication or dosage form, a new combination of active substances or a different salt or ester of an active moiety). The starting point for such submissions is an FDA publication known as the Orange Book, which lists all products subject to approved NDAs with information on relevant patents and regulatory exclusivity periods (described in more detail below).[44]

A generic product for which an ANDA is submitted must ordinarily be the same as the reference product in terms of active ingredients, dosage form, route of administration and strength; contain safe and suitable inactive ingredients; bear the same labelling as the reference product except for changes owing to differences in the manufacturer (e.g., differences in inactive ingredients or in the composition of the product); and be bioequivalent to the reference product. ANDAs must contain full information on the composition, manufacturing process and manufacturing facilities for the generic product.

The FDA permits labelling for generic products to 'carve out' indications or other statements in labelling when necessary to comply with regulatory protection periods or patents for the reference product. Minor changes in dosage form (e.g., a capsule instead

40 If the sponsor elects to resubmit the NDA with additional studies or other information to correct the deficiencies identified in the complete response, the FDA is ordinarily obligated to act on the resubmission within two or six months, depending on the complexity of the submission. In lieu of resubmitting the NDA, the sponsor may invoke its right to a formal evidentiary hearing, which will eventually lead to a decision by the Commissioner of Food and Drugs that can be appealed to a federal court of appeals. Sponsors rarely invoke this right, however, because the process is time-consuming and seldom leads to a change in the outcome.

41 NDAs must contain data on paediatric use, unless the FDA grants a waiver or deferral of the requirement or the application is exempt (orphan drugs).

42 21 USC, Section 355(j).

43 21 USC, Section 355(b)(2).

44 The official name of the publication is Approved Drug Products with Therapeutic Equivalence Determinations.

of a tablet) and certain other product characteristics may be accepted if their safety and effectiveness can be demonstrated solely on the basis of bioequivalence studies and they are first determined to be acceptable by means of a 'suitability petition' approved by the FDA.

Responding to staff shortages and major delays in the FDA review process for ANDAs, in 2012, Congress enacted user fee legislation for generic drugs. Under the Generic Drug User Fee Act, the FDA will aim to clear the backlog of pending applications by the end of 2017 and set a 10-month target for review of new applications. Part of the new revenue will fund increased FDA manufacturing inspection programmes in the United States and abroad.[45]

Biologics

Biological products are subject to a separate statutory approval system under Section 351 of the PHSA. Sponsors of originator products submit biologic license applications (BLAs) that contain essentially the same information as NDAs, in the CTD format. The review process is substantially the same as for NDAs and is subject to the same user fees and performance goals under the PDUFA. To be approved, products must be 'safe, pure and potent' and be produced in manufacturing facilities that meet standards designed to assure that they continue to comply with these standards. The statute does not expressly require 'substantial evidence' of effectiveness (i.e., reports of adequate and well-controlled clinical investigations), and the FDA to an extent, therefore, has more discretion in determining whether efficacy has been demonstrated. In practice, however, the agency has ordinarily demanded the same evidence of efficacy for biologics as it expects for ordinary drugs.

In 2010, Congress enacted legislation[46] establishing an approval process for follow-on versions of biological products, or 'biosimilars'. Such a product must be 'highly similar' to a reference product 'notwithstanding minor differences in clinically inactive components'; have no clinically meaningful differences from a reference product in safety, purity or potency; be labelled for a condition of use for which the reference product is approved; have the same route of administration, dosage form and strength as the reference product; and be manufactured in facilities designed to assure safety, purity and potency. The legislation contemplates that the showing of biosimilarity will ordinarily be based on analytical tests, non-clinical studies and clinical trials, but the FDA has discretion to waive any of these requirements if it finds that the data are unnecessary. Additional showings are required for the FDA to make a determination that a biosimilar product is 'interchangeable' with a reference product.[47]

45 Application fees for 2017 are $70,480 for new ANDAs; $35,240 for supplements requiring prior approval; $51,140 for DMFs; $44,234 for domestic facilities that manufacturer active substances; $59,234 for foreign facilities that manufacture active substances; $258,646 for domestic facilities that manufacture finished products; and $273,647 for foreign facilities that manufacture finished products.

46 The Biologics Price Competition and Innovation Act (BPCIA), Pub. L. No. 111-148, Title VII, Subtitle A, 124 Stat. 119, 804–821 (2010).

47 A small number of biological products, including recombinant insulin and somatropin, were originally approved under the FDCA rather than the PHSA and were therefore eligible for submission of follow-on applications under Sections 505(b)(2) and 505(j) before the BPCIA was enacted. The FDA approved an application under Section 505(b)(2) for a follow-on

User fees for biosimilar applications are currently the same as those for originator products. To provide immediate funding for the review programme, however, portions of that fee must be prepaid. A portion of the application fee is due when a sponsor seeks development advice from the FDA, and thereafter, another 10 per cent is due annually as a biosimilar development fee. The initial and annual fees are subtracted from the user fee due when the sponsor submits its application. The FDA has issued final and draft guidance covering a number of issues relating to the implementation of the BPCIA and, in March 2015, approved its first biosimilar. Nevertheless, the programme is still at an early stage and many important issues remain undecided – for instance, how the FDA will interpret the statutory standard for interchangeability.

Expedited programmes

The FDCA and FDA regulations establish special procedures for the approval of drugs and biologics for serious or life-threatening diseases that provide meaningful benefits over existing therapies. For instance, pursuant to accelerated approval, effectiveness may be demonstrated on the basis of surrogate or intermediate clinical endpoints, with a commitment to carry out post-marketing studies to confirm the validity of those endpoints as predictors of clinical outcomes. The FDA may impose special restrictions on such drugs (e.g., pre-submission of promotional materials or restrictions on distribution). If post-marketing studies fail to confirm clinical benefit, approval may be withdrawn through an expedited procedure.

Medical devices

The pre-market clearance requirements for a device depend on the device's class, which in turn depends on the level of risk that the device presents. Class I devices present the least risk, and they generally are exempt from pre-market review. Class II devices present moderate risk, and most require clearance of a pre-market notification under Section 510(k) of the FDCA prior to marketing. Class III devices – the highest-risk category – typically require approval of a PMA before marketing. A special classification rule applies to 'post-amendments' devices (i.e., those that were not in commercial distribution before 28 May 1976, when Congress enacted the Medical Device Amendments to the FDCA). These devices are automatically in Class III. If, however, the manufacturer obtains clearance of a pre-market notification or the agency grants a *de novo* petition (discussed below), the FDA will place the device in Class I or II and allow the manufacturer to distribute the device.

To obtain clearance of a 510(k), the submitter must show that its device is 'substantially equivalent' to a legally marketed 'predicate' device. A predicate device may be a pre-amendments device, a device already cleared through the 510(k) process, or a device reclassified into Class I or II. To demonstrate substantial equivalence, the submitter must show its device has the same 'intended use' as the predicate device, and either has the same technological characteristics as the predicate device, or has different technological characteristics, but is as safe and effective as, and does not raise different questions of safety and effectiveness than, the predicate device. The 510(k) must contain, among other things,

version of recombinant somatropin in 2006, based on a substantial package of non-clinical and clinical data. In 2015, the FDA approved an application under Section 505(b)(2) for a follow-on insulin. In 2020, the proteins regulated under the FDCA will transfer to the PHSA. Id. Section 7002(e).

proposed labelling, a device description, and the submitter's rationale for concluding the device is substantially equivalent to the predicate device. In some cases, it may need to contain clinical data. The submitter also must pay a small user fee for the submission. By statute, the FDA must act on 510(k) notifications within 90 days, and the FDA has agreed to performance goals for acting on them. In August 2015, the FDA issued a final guidance describing its refuse to accept policy for 510(k) notifications, and the situations in which the agency will refuse to accept 510(k)s as incomplete.[48] The submitter may not market the device until the FDA has 'cleared' the 510(k) notification, even if the FDA misses the applicable deadline.

If the FDA determines that it cannot clear the device, it will issue a 'not substantially equivalent' determination, indicating that the device is Class III and cannot be marketed without a PMA. The submitter then has 30 days to request *de novo* classification of the device, if desired. This procedure is intended to permit clearance of low or moderate-risk devices that have no predicate device. In addition, under amendments made in the FDASIA, a manufacturer also may submit a *de novo* request in lieu of submitting a 510(k). The statute calls for the FDA to rule on a *de novo* request within 120 days, although no performance goals apply to review of *de novo* requests. In August 2014, FDA issued a draft guidance on the submission and review of *de novo* requests.[49]

The PMA pathway has some similarities to the NDA pathway for drugs. The PMA must contain manufacturing information, information regarding the device components and principles of operation, proposed labelling, and full reports of all information regarding investigations conducted to assess the device's safety and effectiveness. The PMA must contain clinical data, and the applicant must pay a substantial user fee. To be approved, the application must show that there is a reasonable assurance that the device is safe and effective for the proposed conditions of use. The FDA generally refers PMAs to an advisory panel for review and input. As with NDAs, the FDA agrees to performance goals for acting on PMAs. Action may take the form of an approval or a deficiency letter.

In April 2015, the FDA published a final guidance proposing a voluntary programme to expedite access to devices that 'demonstrate the potential to address unmet medical needs for life-threatening or irreversibly debilitating diseases or conditions' and are subject either to PMAs or *de novo* classification requests.[50] The 21st Century Cures Act, enacted in December 2016, amended the FDCA to establish a new priority review programme for 'breakthrough' devices, formally codifying and expanding the programme described in the agency's final guidance. A device subject to a PMA, *de novo* classification or 510(k) may qualify as a breakthrough device if the device represents a breakthrough technology or the device offers the potential to, compared to existing alternatives, reduce or eliminate the need for hospitalisation, improve patient quality of life, facilitate patients' ability to manage their

48 FDA, Refuse to Accept Policy for 510(k)s: Guidance for Industry and Food and Drug Administration Staff (August 2015).

49 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (August 2014).

50 FDA, Guidance for Industry and Food and Drug Administration Staff: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions (April 2015).

own care, or establish long-term clinical efficiencies. The programme, which was modelled partly on the expedited programmes for medicines, features more interactive communications with the agency during device development.

The FDA also may reclassify devices under a procedure that was streamlined in the FDASIA. Prior to the FDASIA, the FDA use notice-and-comment rulemaking to reclassify devices, and this proved burdensome. As amended by the FDASIA, the statute permits FDA to reclassify a device by administrative order '[b]ased on new information respecting [the] device' and 'following publication of a proposed reclassification order in the Federal Register, a meeting of a device classification panel […] and consideration of comments to a public docket'.[51] Although this language suggests the three activities must occur in chronological order, in a proposed rule to amend the governing regulations to conform to the FDASIA, among other things, the agency stated: 'The panel meeting must occur before the final order is published, and may occur either before or after the proposed order is published.'[52]

vi Regulatory incentives

Drugs

The United States has established a complex series of regulatory incentives to encourage the development of innovative medicines and follow-on products. These may be best explained in their chronological order of enactment.

The Orphan Drug Amendments to the FDCA, originally passed in 1983, establish incentives for development of drugs and biologics to treat rare diseases, including a seven-year period of market exclusivity (i.e., protection against the approval of the same drug for the same indication). Orphan drug designations may be granted on the basis of prevalence (i.e., that the drug is intended for a disease that affects fewer than 200,000 persons in the United States) or an economic criterion (which has rarely been applied in practice). FDA regulations establish detailed criteria for determining when competitive products may be approved during the orphan exclusivity period, including rules for determining when subsequent products are not the 'same' as first entrants (e.g., because of differences in the composition of their active substances or because they are clinically superior).[53]

The Hatch-Waxman Act establishes several incentives for development of originator products, as well as a significant incentive for development of certain follow-ons. First, the statute provides for patent term extensions to restore a portion of the patent life that is lost during clinical development and FDA review of new drugs and biological products. Credit is given for half the time spent in the IND process and all of the time spent in the NDA or

51 FDASIA, Section 608 (amending FDCA, Section 513(e)).

52 79 Fed. Reg. 16252, 16254 (25 March 2014).

53 See 21 USC, Sections 360n-360ff; 21 CFR, Part 316. The FDA also demands a showing of clinical superiority when an applicant seeks an orphan designation for a drug containing the same active ingredient for the same indication as one previously granted orphan status. In *Depomed, Inc. v. Department of Health and Human Services*, Case No. 1:12-cv-01592 (D.D.C. 2014), a federal court rejected this policy as inconsistent with the language of the statute, but the FDA subsequently issued a notice reaffirming its position and stating that the decision in the Depomed case was limited to its facts. 79 Fed. Reg. 76,888 (23 December 2014).

BLA review process (subject to a reduction for any period during which the applicant was not pursuing development with due diligence), with a maximum extension of five years and a maximum effective patent life, following FDA approval, of 14 years.[54]

Second, the statute provides for periods of data exclusivity (i.e., protection against approval of ANDAs and Section 505(b)(2) applications) for originator products approved under the FDCA. New chemical entities (NCEs) receive a five-year protection period, while changes in approved products (e.g., new indications or dosage forms) receive three years if they are required to be supported by clinical investigations other than bioequivalence studies. Except as noted below, follow-on applications for NCEs may not be filed until the expiry of the five-year period, so that the effective period of protection includes the time required for review and approval of a follow-on product. Follow-on applications relating to changes in approved products can be submitted during the three-year period but approvals cannot be made effective until the period expires.[55]

Third, the statute contains complex provisions linking the approval of follow-on products to patents for reference drugs. Sponsors of originator products are required to submit patent information for their products, including expiry dates, which the FDA includes in the Orange Book. Sponsors of follow-on products are required to make one of four patent certifications:

a that no patents are listed for the reference product;
b that all listed patents have expired;
c that patents are listed and have not expired, but the applicant wishes that approval of its product be made effective upon expiry; or
d that the listed patents are invalid or unenforceable or will not be infringed by the applicant's product.

Submission of a certification under the last provision (a 'Paragraph IV' certification) has two consequences: if the reference product is an NCE with an unexpired period of data exclusivity, the follow-on application may be submitted at the end of the fourth year following approval of the originator product, instead of the fifth year; and the follow-on applicant must submit a notification to the patent holder (and NDA sponsor) for the reference product, including a statement of reasons why the patent is invalid or unenforceable or will not be infringed. Submission of a follow-on application with a Paragraph IV certification is deemed an act of infringement under the patent laws, and if the patent holder initiates an infringement action within 45 days of receiving the notification, approval of the follow-on product is stayed for 30 months or until the court rules that the patent is invalid, unenforceable or not infringed.[56]

Finally, the Hatch-Waxman Act provides for a 180-day period of generic marketing exclusivity for the first ANDA applicant that files a successful Paragraph IV certification (e.g., if the patent for the reference product is held to be invalid, unenforceable or not infringed, or in certain other circumstances, including situations in which the generic applicant launches

54 35 USC, Section 156.

55 21 USC, Section 355(j).

56 If the Paragraph IV notification is submitted before the end of the fifth year following approval of the reference product, the period of the stay is adjusted so that the follow-on product may not be approved until seven-and-a-half years after the approval of the reference product.

'at risk' when patent litigation extends beyond the period of the administrative stay on approval of an ANDA). The provision, which was intended to create an incentive to challenge patents for reference products and clear the way for early entry of generic products, has been complicated to administer in practice, and the rules have been modified to reduce the potential for abuse or other unintended results.

Legislation originally enacted in 1997, as part of the FDA Modernization Act, provided regulatory incentives for paediatric studies of drugs. An applicant that carries out such testing in compliance with a written request from FDA can receive a six-month extension of every form of regulatory exclusivity pertaining to its product, including five and three-year exclusivity under Hatch-Waxman, seven-year orphan drug exclusivity and protection against approval of ANDAs or Section 505(b)(2) applications after patent expiry.[57]

Most recently, the Generating Antibiotic Incentives Now Act, which was included in the FDASIA, established procedures under which certain new antibacterial or antifungal drugs intended for serious infections caused by 'qualifying pathogens' (drug-resistant organisms designated by FDA) can receive five-year extensions of the four-, five- and three-year exclusivity under the Hatch-Waxman Act and seven-year orphan drug exclusivity.[58]

Biologics

Under the BPCIA, applications for biosimilar products may not be filed until four years, and may not be approved until 12 years, after the approval of the reference product. Those periods can be extended by six months if the sponsor of the reference product licence carries out paediatric studies in compliance with an FDA request. A 'first licensure' provision limits availability of new exclusivity periods for modified versions of previously authorised reference products. In general, it allows for a new exclusivity period when the licence application for the subsequent product is submitted by an entity that is not related to the sponsor of the earlier product, or when the subsequent product differs from the earlier product in structure and in safety, purity or potency. The BPCIA does not provide for patent linkage of the type established by the Hatch-Waxman Act, but it does contain provisions for exchange of information between sponsors of biosimilar and reference products and early resolution of some patent issues. In July 2015, the Federal Circuit held that these procedures are optional, but also concluded that a provision of the BPCIA requiring the biosimilar applicant to give the reference product sponsor 180 days' notice of its planned commercial launch is triggered on the day the FDA licenses the biosimilar.[59]

Devices

A six-year regulatory exclusivity period applies to devices approved pursuant to PMAs. After that exclusivity period expires, the FDA may use safety and effectiveness data in a PMA, but not trade secrets, to approve another device, establish special controls for a class of devices, or classify or reclassify other devices, *inter alia*. Patent term extension is also available for PMA-approved devices.

57 21 USC, Section 355a.

58 21 USC, Section 355f.

59 *Amgen v. Sandoz*, 794 F.3d 1347 (Fed. Cir. 2015). An appeal is pending in the US Supreme Court.

The humanitarian device exemption (HDE), rather than regulatory exclusivity, is available for sponsors of devices for rare disease or conditions. It exempts the device from compliance with the effectiveness requirements of Section 515, relating to PMA approval, and Section 514, relating to performance standards. To qualify, the sponsor must show that the device: (1) is intended for diagnosis or treatment of a disease or condition affecting fewer than 8,000 individuals in the United States; (2) it will not be available to these patients without the exemption, and no comparable device (other than another humanitarian use device (HUD)) is available for them; and (3) it will not expose patients to an 'unreasonable or significant risk of illness or injury', and the probable benefit from using the HUD outweighs its risks. IRB approval is required before use of HUDs. Sponsors may charge a commercial, rather than cost-recovery, price for an HUD intended for use in a paediatric population or subpopulation, or a disease or condition that is very rare or non-existent in children, if certain conditions are met. For example, the number of devices distributed annually cannot exceed the 'annual distribution number' (i.e., the number of devices reasonably needed to treat, diagnose, or cure 8,000 people in the United States).

vii Post-approval controls

Drugs

FDA regulations establish requirements for the reporting of adverse events associated with approved drugs and biologics, including expedited (15-day) reports of serious, unexpected events as well as periodic adverse drug experience reports (PADERs). In lieu of PADERs, the FDA will grant waivers to permit submission of periodic safety update reports (PSURs) in the CIOMS format as well as the more recent ICH format for periodic benefit risk evaluation reports. Special rules apply to reports of adverse events associated with non-prescription products that are marketed under OTC drug monographs rather than NDAs.

Holders of approved NDAs and BLAs must also submit reports when they discover defects in products released for commercial distribution. The criteria for making such reports and the deadlines and procedures for their submission are different for drugs and biologics.[60] Manufacturers of approved drugs and biologics are also required to notify the FDA of discontinuance or interruption in production of life-supporting and life-sustaining drugs, as well as drugs 'intended for use in the prevention or treatment of a debilitating disease or condition'.[61]

As part of the approval process, the FDA can impose requirements for risk evaluation and mitigation strategies (REMS), which may include special labelling or 'elements to assure safe use', such as patient testing and restricted distribution. The effectiveness of the REMS must be periodically evaluated after approval. The FDA can also impose requirements for post-marketing tests and changes in safety labelling of approved drug products. Sponsors may invoke informal dispute resolution procedures to challenge imposition of these requirements, but there is no provision for formal hearings.

BLAs may impose requirements for testing and certification of each batch of a biologic by the FDA before it can be released for commercial use. Such requirements are imposed on many vaccines and certain other products regulated by the CBER.

60 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).

61 21 USC, Section 356c.

FDA regulations establish detailed rules for changes in products that are subject to approved NDAs or BLAs.[62] Major changes (e.g., addition of new indications, new manufacturing facilities or significant changes in the manufacturing process) require submission and approval of a supplemental NDA or BLA (a prior approval supplement, or PAS). Less significant changes can be made after submission of a changes-being-effected supplement; in some cases, the applicant is required to wait 30 days before implementing a change, but certain changes can be made immediately upon submission.[63] Minor changes (e.g., minor editorial changes in labelling) can be notified in annual reports to the NDA or BLA file. For drugs, the FDA has issued detailed guidance on classification of changes in the quality aspects of products (manufacturing facilities, manufacturing processes, components, containers, etc.); the guidance for biologics is less detailed.

Ownership of NDAs can be transferred by submission of a letter to the FDA, although related changes may require supplemental applications, including prior approval supplements for new manufacturing facilities. Transfer of ownership of BLAs is somewhat more complex and, depending on the circumstances, may require prior consultation with the FDA, as well as supplemental applications for related changes.

Under the provisions of the FDCA, the FDA cannot ordinarily withdraw approval of an NDA without first affording the sponsor notice and an opportunity for an administrative hearing, a process that can last several years. The Secretary of Health and Human Services can, however, suspend approval of a drug pending completion of the required administrative hearing, if it is determined that the drug presents an imminent hazard to public health.[64] Although the PHSA does not contain provisions governing revocation of BLAs, FDA regulations establish a system that is similar to the one for NDAs: the sponsor is ordinarily entitled to notice and an opportunity for a hearing, but the licence may be suspended if there is a danger to health. In practice, when significant safety issues arise, sponsors often withdraw products from the market voluntarily in response to a request from FDA.

Special procedures apply to drugs and biologics authorised under the accelerated approval procedure (e.g., on the basis of surrogate endpoints). If required post-marketing studies fail to confirm the safety or effectiveness of such a product, the FDA can withdraw approval after an informal hearing before a specially constituted advisory committee.

62 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).

63 The regulations permit sponsors to add or strengthen a contraindication, warning, precaution or adverse reaction to the prescribing information without prior approval from FDA, provided there is a causal relationship to the drug (21 CFR, Section 314.70). The FDA traditionally advised that this regulation did not apply to generic drugs, because their labelling must be the same as that of reference products. In 2013, however, the agency proposed amendments to its regulations that would establish a procedure for generic manufacturers to add new safety information to the labelling for their products (78 Fed. Reg. 67985 (13 November 2013)).

64 This power has been exercised only once, in relation to the oral hypoglycaemic drug phenformin in 1977. See *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977), appeal denied as moot, CCH Food Drug Cosm. L. Rpts. Paragraph 38,241 (D.C. Cir. 1979).

Devices

The FDCA's 'general controls' apply to all devices, including Class I devices exempt from pre-market review. The general controls include prohibitions on adulteration and misbranding, as well as requirements for establishment registration and device listing and for compliance with the FDA's medical device reporting (MDR) regulations and the quality system regulation (QSR).

Under the MDR regulations, a manufacturer generally must file reports if it becomes aware of information that reasonably suggests that its marketed device: may have caused or contributed to a death or serious injury; or malfunctioned, and recurrence of this malfunction in the device (or any similar device marketed by the manufacturer) would be likely to cause or contribute to a death or serious injury.[65] Importers must report deaths and serious injuries to the FDA and the manufacturer, and they must report malfunctions to the manufacturer. User facilities must report deaths to the FDA and the manufacturer, but need to report serious injuries only to the manufacturer. Manufacturers must usually make their reports within 30 days of becoming aware of the information, although this is shortened to five days for events that require remedial action to prevent an unreasonable risk of substantial harm to the public health.[66] Importers must complete their reports within 30 days, and for user facilities, the deadline is 10 days.[67] In November 2016, the FDA issued a final guidance document on MDR reporting for manufacturers, which generally takes a broad view of the situations in which reporting is appropriate.[68] Also, in December 2016, the FDA issued a final guidance describing when and how the agency will provide public notice of emerging postmarket safety signals for devices.[69]

The FDA also requires manufacturers and importers to report certain device corrections and removals within 10 working days of initiating the action. Corrections include actions taken to repair, relabel, destroy or remediate a device at its point of use, whereas removals involve the physical removal of the device to some other location for remediation or destruction.[70] These actions are generally reportable if taken 'to reduce a risk to health posed by the device' or 'to remedy a violation of the act that may present a risk to health'.[71] In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.[72]

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.[73] The agency may also establish a performance standard for a Class II or Class III device, under Section 514 of the FDCA, if the agency determines that such a standard

65 21 CFR, Section 803.50(a).

66 21 CFR, Section 803.40.

67 21 CFR, Section 803.10.

68 FDA, Guidance for Industry and Food and Drug Administration Staff: Medical Device Reporting for Manufacturers (November 2016).

69 FDA, Guidance for Industry and Food and Drug Administration Staff: Public Notification of Emerging Postmarket Medical Device Signals (December 2016).

70 21 CFR, Section 806.2(d) and (i).

71 21 CFR, Section 806.10(a).

72 FDA, Distinguishing Medical Device Recalls from Medical Device Enhancements: Guidance for Industry and Food and Drug Administration Staff (October 2014).

73 FDCA, Sections 519(e), 522.

is appropriate and necessary to provide reasonable assurance of the safety and effectiveness of the device. The FDA also may impose 'special controls' for Class II devices, which may include performance standards, patient registries and guidelines for the submission of clinical data in 510(k)s. The FDA also finalised regulations generally requiring the labels of devices to bear a unique device identifier.[74]

Different frameworks apply to post-approval changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.[75] Major changes (i.e., those affecting safety or effectiveness) require approval of a PMA supplement. Certain other changes, including some labelling changes and some manufacturing changes, may be implemented with prior notice to the FDA. Other changes may be reported in periodic reports that are required as a condition of device approval. A different approach applies to 510(k)-cleared devices. Some modifications to these devices may be made without submitting a new 510(k), provided that the manufacturer documents the changes in a 'letter to file'. Others require a new pre-market notification (not a supplement). These changes are those that 'could significantly affect the safety or effectiveness of the device' (such as a major modification to the device's design) or that involve a major change to the device's intended use.[76] In August 2016, the FDA issued two draft guidances describing how manufacturers should determine whether a new 510(k) should be submitted for change to an existing device.[77] These draft guidances, when final, will replace the agency's existing final guidance on the topic, which was issued in 1997.[78]

As with drugs, ownership of PMAs may be transferred upon letter notification to the FDA. If the changes affect device safety or effectiveness or the conditions of approval, the new owner must obtain approval of a PMA supplement before marketing. In December 2014, the FDA published draft guidance regarding the procedures for notifying the FDA of a 510(k) transfer via compliance with the device-listing requirements.[79]

The FDA has statutory authority to withdraw approval of PMAs, IDEs and HDEs and to suspend an HDE approval after providing notice and an opportunity for a hearing.[80] The FDA also may temporarily suspend approval of a PMA and IDE pending completion of withdrawal proceedings in certain situations where there are serious risks to public health. The FDA has taken the position that it can rescind a 510(k) notification, although there is no specific statutory or regulatory basis for this position. In 2011, a device manufacturer challenged the FDA's claimed authority in court. The district court found that the FDA has inherent authority to rescind a 510(k) clearance in 'rare situation[s]', if the agency acts within

74 78 Fed. Reg. 58,786 (24 September 2013).

75 See 21 CFR, Section 814.39.

76 21 CFR, Section 807.81(a)(3).

77 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (August 2016); FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Software Change to an Existing Device (August 2016.

78 FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (January 1997).

79 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Transfer of a Premarket Notification (510(k)) Clearance – Questions and Answers (December 2014).

80 21 USC, Sections 360e(e), 360j(g)(5), 360j(m)(5).

a 'reasonable time' and upheld the FDA's rescission in that case, emphasising its conclusion that 'procedural irregularities' occurred throughout the clearance process for the device in question.[81] On appeal, however, the DC Circuit Court of Appeals reversed. The Court reasoned that, because rescission of the 510(k) clearance resulted in automatic reclassification of the device into Class III, the FDA had to follow the statutory reclassification procedure rather than revoking the 510(k) based on claimed inherent rescission authority.[82]

viii Manufacturing controls

Drugs

Facilities that manufacture drugs or biologics for distribution in the United States, including foreign facilities, must be registered with the FDA, but the procedure is ministerial and there is no requirement for a manufacturing authorisation. NDAs and BLAs contain detailed information on manufacturing facilities, which are normally inspected by the FDA before marketing authorisations are granted. All facilities that manufacture drugs or biologics (including 'old' drugs, such as monograph OTCs, for which prior approval is not required) must comply with regulations governing current GMP,[83] which are supplemented by detailed guidances. Transfer of ownership of drug manufacturing facilities does not normally require prior approval from the FDA, but changes must be made in establishment registrations, and other changes resulting from a transfer of ownership may require supplemental applications for products made in an establishment.

Devices

The FDA also requires establishment registration for device facilities through a ministerial procedure. Devices must be manufactured in accordance with the FDA's QSR, which includes provisions governing design control and validation, and GMP.[84] PMAs must contain a detailed description of methods, facilities, and controls used in manufacturing the device.[85] The FDA may also conduct a pre-approval inspection of the manufacturing facility. In contrast, 510(k)s need not contain detailed manufacturing information, and their submitters typically do not undergo pre-market inspections. For PMAs, transfer of ownership of the manufacturing facility may require a PMA supplement.[86] For 510(k)-cleared devices, the manufacturer must assess whether a facility change requires a new 510(k) (i.e., whether the change could significantly affect the device's safety or effectiveness).

ix Advertising and promotion

Drugs

The FDA regulates advertising and promotional labelling for prescription drugs. Detailed rules govern the content of advertisements, including requirements for fair balance, adequate substantiation of claims, consistency with the approved prescribing information, inclusion of a 'brief summary' of the prescribing information and prominent disclosure of

81 *Ivy Sports Medicine v. Sebelius et al.*, 938 F. Supp.2d 47, 58, 59, 61 (D.D.C. 2013).

82 *Ivy Sports Medicine, LLC v. Burwell*, 767 F.3d 81, 87 (D.C. Cir. 2014).

83 21 CFR, Parts 210, 211.

84 21 CFR, Part 820.

85 21 CFR, Section 814.20(b)(4)(v).

86 21 CFR, Section 814.39(a)(3).

the non-proprietary name of the drug product. There is an exemption from some of these requirements for 'reminder' advertisements, which do not make claims; drugs with serious side effects for which 'boxed warnings' are required may not take advantage of this exemption.[87]

Promotional labelling (e.g., brochures and similar materials used by sales representatives) is subject to similar requirements, except that the full prescribing information (in lieu of the brief summary) must accompany all such labelling (except for reminder labelling).

Direct-to-consumer (DTC) advertising of prescription drugs is permitted in the United States. Print advertisements must fully comply with the general rules on prescription drug advertising, using language that is understandable to the ordinary person. Broadcast advertisements, including television advertisements, must maintain fair balance, provide important safety information and incorporate mechanisms by which listeners or viewers can obtain complete information (e.g., websites, print advertisements or other measures). Although FDA pre-clearance of DTC advertisements is not ordinarily required, companies often submit television advertisements for FDA review prior to use.

Oral statements by sales representatives and other agents of drug manufacturers may be taken as evidence of the intended uses of a drug product. If those statements recommend uses that are not included in the approved prescribing information, the FDA will take the position that the drug product is misbranded (and therefore in violation of the FDCA) because its labelling does not include adequate directions for such uses.[88]

The FDA maintains a number of policies that are intended to permit 'free exchange' of scientific information relating to unapproved drug products or new uses for approved products (e.g., drug company support for continuing medical education programmes for healthcare professionals, as well as responses to unsolicited requests from healthcare professionals for information on unapproved uses of drug products), and it also permits disease awareness communications that do not promote specific drugs. In recent years, there has been growing concern that the agency's policies prohibit drug companies from communicating truthful, non-misleading information concerning research on new uses for approved drug products, and that this prohibition infringes the right of freedom of speech guaranteed by the First Amendment to the US Constitution. Under pressure from the federal courts, the FDA has adopted guidance that permits drug companies to distribute reprints of articles from peer-reviewed medical journals and independent medical texts that contain information on unapproved uses of approved drug products.[89] Decisions by the US Supreme

87 See 21 CFR, Part 202.

88 See 21 USC, Section 352(f)(1) (requiring that drugs bear adequate directions for use); 21 CFR, Section 201.100 (requiring that the labelling for prescription drugs contain adequate directions for all purposes for which they are 'intended'); and 21 CFR, Section 201.128 (defining the meaning of 'intended uses' to include all expressions of the objective intent of the seller, including oral or written statements).

89 See *Washington Legal Foundation v. Henney*, 202 F. 3d 331 (D.C. Cir. 2000).

Court in 2011,[90] an influential federal court of appeals in 2012,[91] and most recently, a federal district court in 2015,[92] suggest the need for the FDA to consider further changes to its existing rules, but as yet the FDA has not done so.[93]

The FDA regulates the labelling of non-prescription drug products, including brochures and point-of-purchase materials. These must be consistent with the terms of approved NDAs or applicable OTC drug monographs, and they must not contain false or misleading information. The Federal Trade Commission regulates the advertising of non-prescription drugs under general provisions of the Federal Trade Commission Act that prohibit unfair or deceptive practices in commerce and special provisions that govern false advertising of drugs. The FTC requires prior substantiation for claims as to the safety or effectiveness of non-prescription drugs.

Devices

The FDA and FTC also share responsibility for regulating advertising and promotion of non-restricted devices. The FTC regulates their advertising, and the FDA regulates their labelling (including promotional labelling). With respect to restricted devices, the FDA regulates both labelling and advertising.

The FTC's approach to regulation of device advertising is parallel to its approach to regulating OTC drug advertising. The FTC focuses its efforts on ensuring that advertising claims are not deceptive and are substantiated by competent and reliable evidence.[94] Similarly, the principles for FDA's regulation of device promotion and restricted device advertising are generally consistent with those for regulation of drug promotional labelling and advertising.[95] For example, device promotional materials must be consistent with the device labelling and cannot promote the product for an unapproved or uncleared intended use. Important

90 *Sorrell v. IMS Health Inc*, No. 10-779, 131 S. Ct. 2653 (2011). The decision invalidated a state law that prohibited pharmaceutical marketing research companies, but not other persons, from collecting information from pharmacists on physician prescribing practices.

91 *United States v. Caronia*, 703 F. 3d 149 (2d Cir. 2012). The court reversed the conviction of a pharmaceutical sales representative for 'misbranding' an approved drug product by presenting information on unapproved uses in a conversation with a physician, where there was no allegation that the information was false or misleading.

92 *Amarin Pharma, Inc. v. FDA*, No. 15-3588, 2015 WL 4720039 (S.D.N.Y. 7 August 2015).

93 The FDA held a two-day hearing in December 2016 to receive information from industry and the general public on regulation of off-label claims for approved drugs and devices. See 81 Fed. Reg. 60299 (1 September 2016). The docket for written submissions remains open until April 2017. In January 2017, the FDA issued draft guidance documents on communications that are consistent with approved labelling for drugs and devices, and communications with payers.

94 Michael S Labson, 'Regulation of Advertising, Promotion, and Distribution of Drugs, Medical Devices, and Biologics', Section 6.1.3, in *Fundamentals of Life Sciences Law*.

95 Id.

differences include the lack of a 'substantial evidence' standard for substantiation and the lack of an express requirement for 'fair balance' in the regulations.[96] Device promotion remains subject to the statutory prohibitions on false and misleading representations, however.[97]

x Distributors and wholesalers

The FDA does not license distributors or wholesalers, but warehouses and distribution facilities used for drug products may be inspected for compliance with applicable requirements of GMP. Many states impose requirements for licensing of pharmaceutical distributors and distribution facilities, and the FDA has issued guidelines for the states.[98]

The FDA regulations implementing the Prescription Drug Marketing Act establish a number of requirements that apply to manufacturers, wholesalers and distributors, including provisions governing distribution of samples and drugs supplied to charitable institutions, documentation of the chain of distribution and requirements for manufacturers to maintain lists of authorised distributors.[99] The Drug Supply Chain Security Act, signed in November 2013, provides for an electronic system to track and trace prescription drug products, to be implemented by the FDA over a 10-year period.

xi Classification of products

The FDCA establishes two legal classifications of drug products: prescription drugs, which can be dispensed or administered only on the prescription of or under the supervision of a physician or other licensed practitioner, and non-prescription (or OTC) drugs. There is no federal 'third class' of pharmacy-only non-prescription drugs. Some FDA officials have suggested that the process for switching drugs from prescription to OTC status might be facilitated if the agency had the authority to impose additional conditions on newly switched products, perhaps including a transition period during which they were available only after consultation with a pharmacist, but no concrete measures have been proposed.[100] For prescription drugs, elements to ensure safe use, established as part of FDA-imposed REMS, can limit use of a product to certain medical specialties or settings (e.g., hospitals).

Devices, like drugs, may be limited to prescription status. The FDA may also classify a device as restricted and limit access and distribution of the device this way, if 'there cannot otherwise be reasonable assurance of its safety and effectiveness'.[101] Possible restrictions include training requirements for users, limiting use to certain facilities, and labelling requirements. The FDA may impose these restrictions by regulation or through a PMA approval order. Special controls for Class II devices may also limit sale, distribution or use of the device.

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96 Id.

97 21 USC, Sections 502(a) and (q).

98 21 CFR, Part 205.

99 21 CFR, Part 203.

100 The FDA has approved one product (Plan B, an emergency contraceptive) for OTC use by women 17 years of age or older and as a prescription product for younger patients; in practice, both versions of the product are sold only in pharmacies. In 1985, Florida enacted a law that established a list of prescription drugs that could be dispensed by pharmacists without a physician's prescription; but the procedure was seldom used, and the law was later repealed.

101 21 USC, Section 360j(e).

xii Imports and exports

The FDCA includes a limited exemption under which certain drugs and biologics that do not fully comply with requirements for sale in the United States may be imported for the purpose of further processing and re-export. Otherwise, imported drugs and devices must fully comply with requirements for shipment in domestic commerce. If they are deemed adulterated or misbranded, or if they fail to comply with a requirement for pre-market clearance, they may be detained at the point of entry, and the FDA can issue import alerts that effectively block entry of a product to the United States. The importer of a detained product has the right to an informal hearing before local FDA officials, but in practice, the agency has great discretion in the use of the import detention power.

The FDCA includes complex provisions governing the export of drugs and devices that do not comply with requirements for shipment in domestic commerce. If such products are 'adulterated' or 'misbranded', they may be exported provided that they comply with the specifications of the foreign purchaser, do not conflict with the law of the country to which they are exported, are labelled for export and are not reintroduced into domestic commerce.[102] The FDA has interpreted these provisions to impose requirements for record-keeping and other forms of documentation.

Exports of products that do not comply with requirements for FDA pre-clearance (e.g., NDAs and PMAs) are subject to much more elaborate rules.[103]

xiii Controlled substances

Narcotics, psychotropics and other drugs that are liable to abuse are regulated under the Controlled Substances Act,[104] which is administered by the Drug Enforcement Administration in the Department of Justice. Substances are assigned to one of five schedules under the statute, which determines the level of controls to be imposed. Schedule I comprises substances (e.g., heroin) that have a high potential for abuse and no currently accepted medical use in the United States, while Schedules II to V include substances with accepted medical uses and decreasing potential for abuse. The DEA issues licences for the manufacture, import, export, distribution, prescribing and dispensing of controlled substances and imposes requirements for security and record-keeping measures to protect against diversion of controlled substances. For certain controlled substances, DEA issues import and manufacturing quotas based on estimates of legitimate medical needs. DEA agents inspect licensed facilities, and the statute includes multiple enforcement measures, including provisions for seizures of unlawful products and criminal prosecutions.

Companies that are developing new chemical entities with a potential for abuse inform the FDA at the time of submission of an IND or NDA. The FDA then makes a

102 21 USC, Section 381(e).

103 21 USC, Section 382. See FDA Guidance for Industry: Exports under the FDA Export Reform and Enhancement Act of 1996 (23 July 2007). The FDA takes the position that foreign trade zones, which are exempt from customs requirements, are within the territory of the US for purposes of the FDCA. Thus, goods that are produced within a foreign trade zone can only be exported in compliance with the provisions of the FDCA. See *United States v. Yaron Laboratories*, 365 F. Supp. 917 (N.D. Calif. 1972); FDA Compliance Policy Guide Sec. 110.200.

104 21 USC, Section 801 et seq.

recommendation to the DEA for the appropriate scheduling of the product, although the actual rulemaking to include a new substance in a schedule under the statute is conducted by the DEA.[105]

xiv Enforcement

The principal formal enforcement measures under the FDCA are seizures of non-complying goods, injunction actions to restrain future violations and criminal prosecutions. The FDA lacks authority to initiate these actions on its own, but must refer them to the Department of Justice. The statute has been interpreted to impose strict criminal liability for misdemeanour (i.e., charges can be lodged against any person who stands in a responsible relationship to the enterprise that causes the violation, with no requirement for proof of intent, negligence or other form of *mens rea*).[106] Felony penalties may be imposed upon proof that a violation was committed with intent to defraud or mislead, or upon a second conviction for a strict liability offence.[107] The FDA also has authority to impose civil monetary penalties for certain violations of the FDCA and the PHSA, subject to judicial review in the federal courts. In practice, the FDA relies heavily on voluntary enforcement measures, including regulatory correspondence ('warning' and 'untitled' letters). The agency also issues public health alerts and other announcements to the news media that can have significant commercial effects on the products and companies to which they relate.

Recent investigations of pharmaceutical and medical device companies by the Department of Justice, often prompted by whistle-blower actions under the federal False Claims Act, have led to major civil and criminal penalties, in many cases based in whole or in part on alleged violations of the FDCA. Offences have included improper distribution of free samples, off-label promotion, manufacturing deficiencies and failure to comply with

105 The FDA has required applicants to agree not to market new drugs containing controlled substances until the DEA issues a final scheduling regulation. In recent years, the DEA process has often not been completed until months after FDA approval, thus delaying access to the new drug and effectively depriving the applicant of the value of a portion of any period of market exclusivity. This led one manufacturer to sue the FDA, demanding a proportionate extension of its market exclusivity period, but the court ruled in the FDA's favour. *Eisai, Inc. v. FDA*, Case No. 1:14-cv-01346-RCL, 2015 WL 5728882, at *12 (D.D.C. 30 September 2015). On 25 November 2015, however, Congress enacted legislation providing that approval of the NDA will not take effect until the DEA issues an interim final rule scheduling the drug. The legislation also imposes a 90-day deadline for the DEA's scheduling action running from the later of: (1) the date when the DEA receives the FDA's scheduling recommendation; or (2) the date when the DEA receives notification that the FDA has approved the drug. Pub. Law No. 114-89 (2015).

106 *United States v. Park*, 421 US 658 (1975); *United States v. Dotterweich*, 320 US 277 (1943).

107 The FDCA imposes penalties of $1,000 and imprisonment for one year per violation for misdemeanours and $10,000 or imprisonment for three years for felonies. General federal criminal legislation provides for significantly greater fines than those imposed under the FDCA.

rules on safety reporting and clinical investigations.[108] Convictions for certain offences under the FDCA may form the basis for mandatory or permissive exclusion of individuals and companies from participation in federal healthcare programmes.

III PRICING AND REIMBURSEMENT

Reimbursement for prescription drugs in the United States is provided through a mixed system of private and public coverage. More than 60 per cent of all patients have private insurance, often provided through their employer, which covers prescription drugs,[109] although private insurance plans vary greatly as to the number and types of drugs that are covered and the share of costs for which the patient is responsible. Patients who are enrolled in government-sponsored health programmes, including Medicare, which provides healthcare for the elderly and disabled, and Medicaid, which provides healthcare for low-income individuals, receive coverage through these programmes. Beyond Medicare and Medicaid, a range of federal and state programmes offer drug benefits to individuals who meet certain eligibility criteria (e.g., TRICARE is a federal healthcare programme for military personnel and their dependents, and many states offer AIDS drug assistance programmes). These private and public programmes are known as 'payers' and generally do not purchase or dispense drugs directly but instead pay for the products patients receive from their physicians, retail or specialty pharmacies, hospitals and other distribution channels.

Both public and private payers use a variety of mechanisms to control drug prices and utilisation. Private payers typically contract with pharmacy benefits managers (PBMs) to manage their prescription drug benefits. PBMs negotiate prices and rebates with drug manufacturers, develop drug formularies (lists of drugs that a health plan will cover), and impose utilisation management techniques, such as prior authorisation and quantity limits. The manner in which public programmes will reimburse prescription drugs is often dictated by statute. For example, states may establish maximum allowable costs to cap payments for brand or generic versions of the same drug.[110]

Public programmes also use mechanisms to control costs similar to those used by private plans. Medicare Part D, which covers outpatient prescriptions, imposes significant beneficiary cost sharing in a coverage gap known as the 'donut hole' (although recent legislation will close the donut hole by 2020). Drug manufacturers whose products are covered by Medicaid are required to pay rebates to states for their drugs to ensure that the Medicaid programme receives the manufacturer's most favourable pricing. Likewise, states often negotiate supplemental rebates with manufacturers in exchange for placement of the manufacturer's drugs on a preferred drug list.

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108 It is estimated that total judgments in such cases over the past decade have exceeded $20 billion. The largest settlement to date related to GlaxoSmithKline, which agreed to pay a total of $3 billion in civil and criminal penalties to resolve allegations under the FDCA and the False Claims Act relating to multiple drug products in July 2012.

109 United States Census Bureau, Health Insurance Coverage in the United States: 2014 (2015), www.census.gov/content/dam/Census/library/publications/2015/demo/p60-253.pdf.

110 Most states have adopted rules under which pharmacists are permitted or required to dispense a lower-cost generic equivalent on a prescription for a brand-name product. These rules often rely on therapeutic equivalence evaluations made by FDA and published in the Orange Book.

Access to coverage is likely to expand as a result of the health insurance mandate set forth in the Affordable Care Act (ACA) enacted in 2010, which is intended to provide health coverage for those individuals (by some estimates, as least 30 million) who are not covered by other programmes. Although the ACA is not fully effective until 2018, provisions already in effect establish minimum requirements for health insurance programmes, require most individuals to purchase insurance and subsidise premiums for low-income individuals. In particular, prescription drug coverage is an 'essential health benefit' that must be included in health plans offered by state health insurance exchanges and in the benchmark benefit packages for newly eligible adults under Medicaid.[111]

IV ADMINISTRATIVE AND JUDICIAL REMEDIES

The FDCA and FDA regulations and policies provide several mechanisms for internal administrative review of agency decisions. Certain decisions (e.g., to refuse or withdraw approval of an NDA) may be contested under statutory procedures that include formal evidentiary hearings before an administrative law judge.[112] The majority of disputes are, however, resolved through less formal mechanisms. The FDA regulations establish a general right to informal review of any decision within the agency hierarchy.[113] Certain FDA commitments made under the PDUFA (e.g., to decide appeals of clinical holds of INDs and complete responses to NDA and BLA submissions) include dispute resolution procedures with deadlines for completion. Statutory provisions authorising the FDA to require REMS, post-approval safety studies and safety labelling changes afford sponsors a right to an informal dispute resolution procedure.[114] Similarly, the FDCA provides for supervisory review of 'significant decisions' regarding medical devices and imposes a 30-day deadline for the sponsor to file its appeal.[115] In guidance, the FDA describes its interpretation of 'significant decision' and strictly interprets the 30-day deadline for filing an appeal, noting that '[t]here is no provision in the statute for extensions or waivers, or for partial submissions or "placeholders"'.[116]

Judicial review of final agency action by the FDA is ordinarily subject to review in the federal courts under provisions of the FDCA and the Administrative Procedure Act

111 The incoming Administration and Republican leaders in Congress have announced plans to repeal the Affordable Care Act, but it remains unclear when or how this will be accomplished. In the meantime, there is continued focus on prices charged for innovative medicines in the US, and there is a possibility that measures will be introduced in response to that issue.

112 21 USC, Section 355(d), (e).

113 21 CFR, Section 10.75. If a request for review is denied, the requestor may appeal to the agency's Chief Mediator and Ombudsman. In certain circumstances, the person seeking review may request that a scientific controversy be submitted to an FDA advisory committee, although FDA is not required to grant such a request.

114 21 USC, Sections 355(o), 355-1.

115 FDCA Section 517A(b).

116 FDA, Guidance for Industry and Food and Drug Administration Staff: Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A (July 2014); FDA, Guidance for Industry and Food and Drug Administration Staff: Center for Devices and Radiological Health Appeals Processes (May 2013).

(APA).[117] Certain agency decisions (e.g., the refusal or withdrawal of approval of an NDA following a formal evidentiary hearing) are subject to review in a federal court of appeals; the FDA's findings as to facts are deemed conclusive if supported by substantial evidence in the administrative record. In most cases, however, judicial review is available in a federal district court under general provisions of the APA. The court may set aside agency action if it is arbitrary, capricious or otherwise contrary to law, contrary to constitutional right, in excess of statutory power or without observance of required procedure.[118]

The APA also permits judicial review of agency action unlawfully withheld or unreasonably delayed, but the courts will normally hear such cases only if the applicant has exhausted its administrative remedies and the matter is otherwise ripe for a decision. This can make it difficult to challenge general FDA policies that have not been set out in final regulations or guidances, although it is sometimes possible to obtain judicial review following the submission of a 'citizen petition' under the FDA's procedural regulations.[119] The courts have generally held that warning letters and other informal communications used by the FDA to secure voluntary compliance do not constitute final agency action and are not reviewable under the APA.[120]

A person seeking judicial review of FDA action must demonstrate the requisite legal interest (standing). In practice, the rules on standing followed by the federal courts are relatively liberal, and, depending on the facts, challenges to FDA actions may be permitted by competitors, trade associations, professional groups and consumer organisations that are directly affected by FDA decisions.[121]

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117 5 USC, Section 501 et seq.

118 5 USC, Section 706. Subject to somewhat complex rules enunciated by the Supreme Court and the US Court of Appeals for the District of Columbia Circuit, the federal courts often defer to FDA's interpretation of the statutes and regulations it administers, and in practice they also tend to give great weight to the agency's findings on matters of science and medicine within its special areas of expertise.

119 21 CFR, Section 10.30. The regulation requires the FDA to respond to a petition within 180 days of receipt, but permits the agency to provide a 'tentative response' stating that it has been unable to deal with the matter; in practice, the agency sometimes takes several years to provide a final response. However, for certain citizen petitions – those that may delay approval of a pending follow-on or biosimilar application – the FDA must respond within 150 days of the petition's filing under Section 505(q)(1)(F) of the FDCA. Pre-enforcement review is available as to final regulations issued by the FDA. *Abbott Laboratories v. Gardner*, 387 US 136 (1967).

120 See, e.g., *Biotics Research Corp v. Heckler*, 710 F.2d 1375 (9th Cir. 1985); but see *Den-Mat Corp v. United States*, CCH Food Drug Cosm. L. Rpts. Paragraph 38,272 (D. Md. 1992).

121 See, e.g., *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982) (competitor alleging unlawful use by FDA of confidential information in its NDA); *Pharmaceutical Manufacturers Association v. FDA*, 484 F. Supp. 1179 (D. Del. 1980), aff'd *per curiam* 634 F.2d 106 (3d Cir. 1980) (trade association and physician organisations challenging patient labelling requirements for oestrogen drug products).

V FINANCIAL RELATIONSHIPS WITH PRESCRIBERS AND PAYERS

With limited exceptions, the FDA does not enforce federal laws governing financial relationships between pharmaceutical and medical device companies and prescribers or payers.[122] Instead, these are subject to provisions of law enforced by the Department of Justice and the OIG of the Department of Health and Human Services. The federal Anti-Kickback Statute[123] prohibits the provision of anything of value in an effort to induce or reward the referral of federal healthcare programme business. The law is enforced by criminal and civil penalties, coupled with the potential for exclusion from participation in federal healthcare programmes. There is no private right of action under the statute, but whistle-blowers (relators) may initiate *qui tam* lawsuits on behalf of the federal government under the False Claims Act.[124] Such suits may result in penalties equal to three times the cost of unlawful activities to federal healthcare programmes, a portion of which may be awarded to the whistle-blower.

The OIG has established a number of 'safe harbours' to protect specific business practices, such as discounting arrangements and fee-for-service engagements, from enforcement actions under the Anti-Kickback Statute.[125] In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers,[126] and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals.[127]

The states also maintain statutes governing improper payments and other forms of fraud affecting public healthcare programmes, and many impose similar controls on improper payments in connection with private healthcare programmes. These are typically enforced by state attorneys general and by state Medicaid fraud control units.

The federal Sunshine Act, passed as part of the ACA in 2010, requires pharmaceutical and medical devices companies to report payments to physicians to the Department of Health and Human Services for disclosure on a public website.[128] The federal requirement pre-empts some, but not all, such disclosure requirements that had previously been established in some states.

VI SPECIAL LIABILITY OR COMPENSATION SYSTEMS

The United States has established several systems governing liability and compensation for injuries associated with drugs and biologics. The most important is the Vaccine Injury Compensation Program (VICP), originally enacted as part of the National Childhood

122 FDA requires a person submitting a marketing authorisation application for a drug or medical device to disclose specified financial interests of investigators who conducted clinical trials relied on in the application (21 CFR, Part 54).

123 42 USC, Section 1320a-7b.

124 31 USC, Sections 3729-3733.

125 42 CFR, Section 1001.952.

126 68 Fed. Reg. 23731 (5 May 2003).

127 PhRMA Code on Interactions with Healthcare Professionals – www.phrma.org-guidelines/code-interactions-healthcare-professionals.

128 www.cms.gov/openpayments.

Vaccine Injury Act of 1986.[129] The VICP is a no-fault compensation system for injuries or death associated with vaccines listed in the vaccine injury table issued under the programme, funded by an excise tax on each dose of the listed vaccines. A vaccine is listed following a determination by the Department of Health and Human Services to recommend it for routine administration to children. Compensation claims are submitted to the US Court of Federal Claims and reviewed by special masters within what is popularly known as the 'Vaccine Court'. Compensation may include actual, non-reimbursable expenses for medical care, rehabilitation, custodial care and similar needs; lost earnings; pain and suffering (capped at $250,000); a $250,000 payment for a vaccine-related death; and reasonable attorneys' fees. Claimants may reject awards in the no-fault system and bring suits for damages under state tort law, but the statute imposes significant limitations on those suits, including defences based on compliance with FDA standards for product design and labelling, limits on punitive damages, and trial procedures designed to facilitate consideration of scientific evidence as to causation.

Section 304 of the Homeland Security Act of 2002[130] established a special programme to protect covered persons (including doctors and pharmaceutical companies) from liability for injuries caused by a smallpox vaccine during a period of public health emergency declared by the Secretary of Health and Human Services. The Public Readiness and Emergency Preparedness (PREP) Act of 2005[131] prohibits suits against specified persons (including pharmaceutical manufacturers) for injuries allegedly caused by covered countermeasures during the period of a pandemic declaration issued by the Secretary of Health and Human Services, except for suits alleging wilful misconduct, which may be brought only in the federal district court in Washington.[132]

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

One of the most contentious legal issues in the US drug approval system involves the interplay between the Hatch-Waxman Act and the US antitrust laws. To facilitate the marketing of generic products, the Hatch-Waxman Act incentivises generic applicants to challenge the patents of innovative companies at very little financial risk to themselves.[133] And under the Hatch-Waxman Act, patent holders that file an infringement suit within a specified period are provided with guaranteed protection of their intellectual property for a period of generally at least 30 months, during which the FDA cannot approve the alleged infringer's product. But

129 42 USC, Section 300aa-10 et seq.

130 42 USC, Section 233(p). Suits must instead be brought against the United States, which has a right to recover for gross misconduct or violations of contractual obligations on the part of covered persons.

131 42 USC, Section 247d-6d.

132 In December 2014, a PREP Act declaration was issued for designated vaccines under development for Ebola virus disease.

133 The number of lawsuits between pioneer and generic drug companies increased significantly after the enactment of the Hatch-Waxman Act. FTC, Generic Drug Entry Prior to Patent Expiration: An FTC Study (July 2002) (FTC Generic Drug Entry Report), available at www.ftc.gov/os/2002/07/genericdrugstudy.pdf.

once the companies are embroiled in the lengthy, unpredictable patent litigation encouraged under the structure of the Hatch-Waxman Act, the companies often wish to resolve the litigation.

These settlements take many forms, and may include a payment or other consideration that flows to the generic company, such as manufacturing assistance from the innovative company, and an agreement that the generic may enter the market on a certain date prior to the expiration of the innovative company's patent. Consideration does not usually flow the other way, aside from the value of settlement and the certainty that it brings, because the Hatch-Waxman Act results in infringement actions being filed before the generic company has entered the market (i.e., before infringing sales have been made). This is in contrast with other types of patent litigation, where the patent holder has a damages claim and where, as a result, consideration to settle a matter might be expected to flow from the alleged infringer to the patent holder.

The FTC has sought for over a decade to demonstrate that settlements that involve consideration flowing back to the generic company are anticompetitive. In particular, the FTC has argued that but for the consideration given by the innovative company to the generic company, the generic company would have entered the market earlier, resulting in lower-cost generic drugs for consumers.[134]

Notwithstanding the FTC's concerns, most courts that considered the issue recognised the importance of settlement of Hatch-Waxman patent infringement cases to maintaining the careful balance established by the Act. The Federal, Eleventh and Second Circuits consistently held that the antitrust laws allow patent settlements that include consideration flowing from an innovative manufacturer to a generic manufacturer along with an agreed entry date for the generic product, so long as the settlement does not exclude competition beyond the scope of the patent.[135] This conclusion flows from the courts' recognition that the patent grant provides the innovative company with the lawful right to exclude.

Thus, under the 'scope of the patent' standard, these settlements were lawful unless the patent was procured by fraud; the underlying infringement action was objectively baseless; or the settlement obtains more coverage than the patent grant, for example, by excluding products not covered by the patent from the market or by excluding products covered by the patent from the market until some point after the patent expires.[136]

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134 A 2010 analysis by the FTC asserts that reverse payment settlements cost consumers $3.5 billion annually. FTC, Pay-for-Delay: How Drug Company Pay-Offs Cost Consumers Billions, at 8 (2010), available at www.ftc.gov/os/2010/01/100112 payfordelayrpt.pdf. The FTC estimates that one year after a generic product enters the market the generic captures over 90 per cent of the pioneer drug's sales and sells for 15 per cent of the price of the pioneer. Id.

135 *FTC v. Watson Pharms. Inc*, 677 F.3d 1298 (11th Cir. 2012); *In re Ciprofloxacin Hydrochloride Antitrust Litig*, 544 F.3d 1323 (Fed. Cir. 2008), cert. denied, 557 US 920 (2009); *In re Tamoxifen Citrate Antitrust Litig*, 466 F.3d 187 (2d Cir. 2006), cert. denied, 551 US 1144 (2007); *Valley Drug Co v. Geneva Pharms Inc*, 344 F.3d 1294 (11th Cir. 2003), cert. denied, 543 US 939 (2004); *Schering-Plough Corp v. FTC*, 402 F.3d 1056 (11th Cir. 2005), cert. denied, 548 US 919 (2006).

136 See, e.g., *In re Tamoxifen Citrate Antitrust Litig*, 466 F. 3d at 213.

The Third Circuit rejected the 'scope of the patent' standard in a significant 2012 decision, *In re K-Dur Antitrust Litigation*.[137] The Third Circuit held that any payment from a patent holder to a generic patent challenger who agrees to delay entry into the market constitutes *prima facie* evidence of an unreasonable restraint of trade, and the patent holder then bears the burden of showing that the payment was for a purpose other than delayed entry or offers some pro-competitive benefit.[138] In adopting such a standard, the Third Circuit stated that the scope of the patent test 'improperly restricts the application of antitrust law and is contrary to the policies underlying the Hatch-Waxman Act'.[139] The Third Circuit's explicit rejection of the standard applied by the majority of other courts to consider the issue has generated considerable uncertainty as to how such settlements will be evaluated in future cases.

In June 2013, the Supreme Court rejected both the 'scope of the patent' standard and the more stringent approach taken by the Third Circuit in *FTC v. Actavis*.[140] The Actavis decision held that reverse payment settlements can in some circumstances violate the antitrust laws and that they should be evaluated under a traditional rule-of-reason analysis, which involves comparing the likely anticompetitive effects of the settlement versus any procompetitive benefits. The application of the *Actavis* ruling to particular cases is extremely fact-intensive. Significant uncertainty remains as the lower courts begin to evaluate a number of settlements now subject to renewed litigation following the Supreme Court ruling. One of the key issues that continues to be litigated is whether the reverse payment required by the *Actavis* decision must be a cash payment or whether other forms of consideration flowing from the innovative company to the generic can subject the settlement to antitrust scrutiny.[141]

Generic manufacturers have often brought antitrust suits against manufacturers of reference products that submitted citizen petitions to the FDA identifying scientific, medical or legal reasons why generic marketing authorisation applications should not be approved, or suggesting additional testing necessary to ensure the safety or effectiveness of generic products. Although petitions submitted to federal agencies are normally protected under the First Amendment to the US Constitution, which guarantees the right to petition the government for redress of grievances, generic manufacturers have argued that citizen petitions relating to their products are a sham intended solely to delay market entry. Amendments to the FDCA enacted in 2007 impose specific requirements for submission of petitions relating to the generic drug approval process and expressly prohibit the FDA from delaying action on a generic application unless necessary to protect public health.[142] In view of these provisions, courts may be reluctant to hear antitrust claims based on the allegation that citizen petitions delayed market entry of generics.[143]

137 See *In re K-Dur Antitrust Litig*, 686 F. 3d 197 (3d Cir. 2012).

138 Id. at 219.

139 *In re K-Dur Antitrust Litig*, 686 F.3d 197, 214 (3d Cir. 2012).

140 *Federal Trade Commission v. Actavis Inc*, 570 US __ , 133 S.Ct. 2223 (2013).

141 See *In re Loestrin 24 FE Antitrust Litig*, No. 13-md-2472 (D.R.I. Sept. 4, 2014) (dismissing antitrust challenge where no cash payment was made).

142 21 USC, Section 355(q).

143 See *Apotex Inc v. Acorda Therapeutics Inc*, No. 11 Civ. 8803 (LTS) (S.D.N.Y. 7 February 2013).

ii Transactional issues

Although licence agreements, collaborations and other transactions in the life sciences industry in the United States have many elements in common with transactions in Europe, there are certain aspects that are unique. Perhaps the most noticeable difference is in the transactional documents themselves – US documents tend to be more detailed than their European counterparts, and persons not familiar with US practice are often surprised by the length and complexity of US agreements. The goal is to provide a comprehensive and precise road map, anticipating where possible significant actions and decision points that might arise to eliminate ambiguities as to the parties' rights and obligations and reduce the likelihood of disputes. For this reason, drafting and negotiating these agreements requires input from a wide range of functional experts with knowledge of industry practice and legal requirements, including regulatory, intellectual property, tax, product liability, commercial and antitrust issues.

The IP and regulatory regimes also differ from those in Europe in ways that must be expressly addressed in agreements for the United States. For example, joint patent owners have an equal and undivided interest in the joint patent, and in the absence of contract language to the contrary each may exploit it freely without accounting to the other. Also, the royalty term under a patent licence typically may not extend beyond the life of the licensed patents. In addition, patent and regulatory regimes for drug products are linked, which requires special provisions dealing with patent listings, patent term restoration and the enforcement of patents against generic competitors. Similarly, the recently enacted, and evolving, biosimilar regime in the United States may require drafting attention depending on the interests of the parties.

Product liability is also a more significant consideration in the United States than elsewhere, which requires attention to indemnification and insurance provisions, as well as dispute resolution mechanisms.

US bankruptcy law also affords special protection to licensees of patents and certain other IP rights. Generally, a party that declares bankruptcy in the United States has the right to stop performing, or reject, its obligations under agreements to which it is a party. But the US bankruptcy statute provides that a licensee of IP rights under a licence agreement retains its licence in the event that the licensor rejects the agreement. The statutory provisions are, however, complex, and licensees must structure agreements carefully to take full advantage of them.

VIII CURRENT DEVELOPMENTS

In December 2016, President Obama signed the 21st Century Cures Act, which amends the FDCA and PHSA, among other laws, with the aim of accelerating the discovery, development and delivery of new medicines, and medical technologies.[144] The 21st Century Cures Act includes a number of provisions related to the discovery, development and delivery of drugs devices. Significant features of the legislation include provisions:

a reauthorising the priority review voucher programme for certain drugs intended to treat rare paediatric diseases;

b creating a new priority review voucher programme for drug applications determined to be material threat medical countermeasure applications;

144 Public Law No. 114-255.

c requiring the FDA to create a programme to evaluate the potential use of 'real world evidence' to help support approval of new indications for approved drugs and satisfy post-approval study requirements;

d providing a new 'limited population' approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections;

e creating a process for the FDA to designate a drug as a 'regenerative advanced therapy', which is eligible for the same actions to expedite the development and review of a marketing application as breakthrough-designated drugs, and may be eligible for priority review and accelerated approval (with certain modifications for drugs with the new designation);

f broadening the safe harbour created by Section 114 of the Food and Drug Administration Modernization Act for communication of healthcare economic information by drug sponsors to payer audiences;

g significantly revising the FDCA provisions on combination product regulation with the aim of streamlining review of combination product applications;

h establishing of a statutory 'breakthrough' designation and review pathway for medical devices;

i carving out of the FDA's jurisdiction certain health software, including certain clinical decision support functions that make patient-specific recommendations to providers; and

j expanding the size of the patient population that may be served by a 'Humanitarian Use Device'.

Additional changes to the laws regarding the regulation of drugs (including, in particular, non-prescription drugs), biosimilars and their reference products, or devices are also possible in connection with the reauthorisation of the corresponding user fee statutes, the Prescription Drug User Fee Act, the Biosimilars User Fee Act and the Medical Device User Fee Act, all three of which must be renewed in 2017.

Cybersecurity for medical devices is an area of increasing concern and activity for the FDA, as devices become increasingly networked and digital health technologies continue to develop. In October 2014, the FDA issued a final guidance describing cybersecurity issues that manufacturers should consider in the design and development of devices and in preparing premarket submissions.[145] And the agency issued a final guidance document addressing the post-market management of cybersecurity in medical devices in December 2016.[146] The FDA also issued its first safety communication related to cybersecurity vulnerabilities with a particular device, encouraging healthcare facilities to discontinue use of the device.[147] Both the guidance and the safety communication suggest that the FDA is treating cybersecurity vulnerabilities in a similar matter to more traditional product risks. The FDA, in

145 FDA, Guidance for Industry and Food and Drug Administration Staff: Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (October 2014).

146 FDA, Guidance for Industry and Food and Drug Administration Staff: Postmarket Management of Cybersecurity in Medical Devices (December 2016).

147 FDA, Cybersecurity Vulnerabilities of Hospira Symbig Infusion System: FDA Communication (31 July 2015), www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm456815.htm.

collaboration with HHS and the Department of Homeland Security, held public workshops in October 2014 and January 2016 to discuss models for evaluating cybersecurity status and unresolved challenges hampering process in advancing medical device cybersecurity.[148] Finally, as part of omnibus spending legislation, Congress passed the Cybersecurity Act of 2015, which requires HHS to establish a healthcare industry cybersecurity task force and to establish voluntary consensus guidelines that support adoption and implementation efforts to improve safeguards that address cybersecurity threats.[149]

The regulation of diagnostic tests, including LDTs, next-generation sequencing (NGS)-based tests, and companion diagnostics, continues to evolve in light of rapid technological advancements and increasing focus on precision medicine. In 2014, the FDA issued draft guidances describing a proposed regulatory framework for LDTs.[150] Although the agency recently announced, in November 2016, that it would not move forward with finalising those guidances, Congress, the agency and other stakeholders are considering the appropriate regulatory framework for LDTs and potential legislation. In addition, the agency held six public workshops in 2015 and 2016 to discuss its consideration of developing a new, more flexible approach to the regulation of NGS-based tests.[151] The agency also issued two draft guidance documents in July 2016 that address the use of public genetic variant databases to support a demonstration of clinical validity for NGS-based tests and the use of standards in the agency's oversight of NGS-based tests used for diagnosing germline diseases.[152] The FDA has stated that it intends to finalise both guidances in 2017.[153] Finally, also in July 2016, the FDA issued a draft guidance document providing recommendations on the co-development of a companion diagnostic with a therapeutic product.[154]

148 79 Fed Reg 56814 (23 September 2014); 80 Fed Reg 76022 (7 December 2015).

149 Consolidated Appropriations Act, 2016, H.R. 2029, Div. N.

150 FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (October 2014); FDA, Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) (October 2014).

151 79 Fed Reg 78092 (29 December 2014); 80 Fed Reg 54290 (9 September 2015); 80 Fed Reg 54292 (9 September 2015); 81 Fed Reg 1426 (12 January 2016); 81 Fed Reg 1955 (14 January 2016); 81 Fed Reg 56656 (22 August 2016).

152 FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (July 2016); FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used For Diagnosing Germline Diseases (July 2016).

153 CDRH Fiscal Year 2017 (FY 2017) Proposed Guidance Development and Focused Retrospective Review of Final Guidance, www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm529396.htm.

154 FDA, Draft Guidance for Industry, Food and Drug Administration Staff: Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product (July 2016).

Changes to the agency's regulation of electronic health technologies and software-based devices are also possible. The 21st Century Cures Act included a provision removing certain types of software functions from the statutory definition of a device. Many of the software functions that are the subject of this provision were subject to the agency's enforcement discretion and were not required to comply with the regulatory requirements for devices pursuant to final guidance documents addressing general wellness products and mobile medical apps.[155] But the new provision expands those software functions that will not be regulated as devices to include certain software that supports clinical decision-making by healthcare professionals. The scope and impact of the new legislative provision remain to be seen.

There is the potential for further court challenges to the FDA's regulations governing 'off-label' promotion of approved prescription drugs and devices, based on the argument that they prohibit truthful claims in violation of the First Amendment to the US Constitution. Even if these are successful, it is unlikely that enforcement actions by the FDA or the Department of Justice will abate significantly, since it will remain possible to pursue cases relating to fraudulent and misleading claims.

155 FDA, Guidance for Industry, Food and Drug Administration Staff: Mobile Medical Applications (February 2015); FDA, Guidance for Industry, Food and Drug Administration Staff: General Wellness: Policy for Low Risk Devices (July 2016).

Appendix 1

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Richard Kingham is a senior counsel in the firm of Covington & Burling LLP, where he serves as co-head of the life sciences industry group and the industry, regulatory and legislative practice group. He previously served as the managing partner of the firm's London office and as a member of the firm-wide management committee. Since joining the firm in 1973, he has concentrated on regulation of pharmaceuticals and related products. He has acted for most of the major pharmaceutical and biotechnology companies in the United States and Europe, as well as the principal trade associations of the pharmaceutical industry. He has served on committees of the World Health Organization, the Center for Global Development, the Institute of Medicine of the US National Academy of Sciences and the National Institutes of Health. He is currently an adjunct professor at the Georgetown University Law Center, and he has lectured at the University of Virginia School of Law and the graduate programme in pharmaceutical medicine at Cardiff University. He received his law degree in 1973 from the University of Virginia, where he served as articles editor of the law review and was elected to the Order of the Coif (the law school honour society).

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