

THE LIFE SCIENCES
LAW REVIEW

NINTH EDITION

Editor
Richard Kingham

THE LAWREVIEWS

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PREFACE

The ninth edition of *The Life Sciences Law Review* covers a total of 28 jurisdictions, providing an overview of legal requirements of interest to pharmaceutical, biotechnology and medical device companies. The chapters are arranged so as 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.

The past year has been dominated by the covid-19 pandemic, and this will undoubtedly be true of 2021 as well. Manufacturers of healthcare products have expedited the development and testing of drugs, biologics, diagnostics and personal protective equipment. Vaccines, many making use of novel technologies, have moved from the laboratory to the clinic and then to patients in record times; a matter of months rather than years or decades. Regulatory agencies have reviewed marketing applications with unprecedented speed and efficiency and international organizations have taken measures in an effort to ensure equitable access to medicines and vaccines in all countries.

In times such as these, it is vitally important that lawyers who advise companies in the life sciences sector and the business executives whom they serve have a working knowledge of the regulations and policies that govern drugs, biologics and medical devices. It is equally important to keep up to date with developments in the regulatory systems that govern access to the market, pricing and reimbursement, advertising and promotion, and numerous other matters that are essential to success. It is our hope that this year's publication will be especially helpful in this respect.

All of the chapters have 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 publication.

Richard Kingham

Covington & Burling LLP

Washington, DC

February 2021

UNITED STATES

Krista Hessler Carver and Richard Kingham¹

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 US\$35 billion for FY2021, 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 17,000 and an annual budget in excess of US\$6 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 some 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 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. Many of FDA's staff are located in the Washington, DC, metropolitan area and serve 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 Office of Regulatory Affairs, headed by an associate

1 Krista Hessler Carver is a partner and Richard Kingham is a senior counsel 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, Kristie Gurley, Christina Kuhn, Mingham Ji, Julie Dohm, Jessica O'Connell, Christopher Hanson, Amy Leiser and Carrie Ansell.

2 The FDA budget request for fiscal year 2021 states that US\$2.9 billion of the total budget of US\$6.2 billion will come from user fees.

commissioner, manages the agency's inspection and enforcement programmes, staffed by several thousand employees who are located in regional, district and field offices around the United States.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 parts of the Public Health Service Act (PHSA), including requirements for licensing 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 the FDA or on their own initiative.

The Federal Trade Commission (FTC) regulates the advertising of non-prescription drugs and non-restricted medical devices and 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 (HHS) investigates allegations of fraud, kickbacks and other abuses affecting federal healthcare programmes, including Medicare (for the elderly and disabled) 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.

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.

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

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 biological products.⁶ However, the same product may 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 as a cosmetic, because it is intended to clean 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 enforcement actions against dietary supplements for which therapeutic claims were made, on the basis that those products were unapproved new drugs. These 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.

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.

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 ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein 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 human beings (42 USC, Section 262(i)(1)).

7 21 CFR, Part 3.

8 21 CFR, Part 58.

The Animal and Plant Health Inspection Service (APHIS) within the Department of Agriculture administers regulations under the Animal Welfare Act that govern 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 (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 generally must be carried out under an investigational new drug application (IND).¹¹ The application contains information about 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 about the investigators who will carry out the trial. The FDA ordinarily requires INDs to be submitted in the electronic common technical document (eCTD) 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 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 make 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

9 21 CFR, Parts 50, 56.

10 21 CFR, Part 54.

11 See generally, 21 CFR, Part 312.

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 ICH¹² GCP guidance will normally be acceptable to the FDA. There is no requirement for sponsors to maintain insurance or compensate subjects for injuries during 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 when there is a reasonable possibility that they are drug-related and of 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 the trials 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.¹³

Devices

Sponsors of device clinical trials conducted in the United States 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).¹⁴ 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). The FDA may disapprove an IDE if the risks to subjects are not outweighed by the anticipated benefits to the subjects and the importance of knowledge to be gained, among other bases for disapproval. The FDA may not disapprove an IDE because the study may not support clearance or approval of the device. The FDA has the authority to put a device investigation on clinical hold. Sponsors of SR investigations must also comply with the requirements of the IDE regulations, including requirements relating to IRB approval, informed consent, selection of investigators, monitoring, record-keeping and reporting.

12 The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

13 See 21 CFR, Section 312.120.

14 21 CFR Section 812.3(m); see also FDA, Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies (January 2006).

‘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 May 2019, the FDA issued a revised final guidance on the pre-submission programme.¹⁵

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.¹⁶ In 2012, Congress codified the FDA’s approach in Section 569B of the FDCA. In February 2018, the FDA issued a final rule amending the criteria for acceptance of foreign data in device submissions (including data to support an IDE, PMA, premarket notifications, humanitarian device exemption, and *de novo* classification) that are collected in accordance with GCP and subject to the FDA’s ability to validate the data through an inspection.¹⁷ The FDA has also issued final 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.¹⁸

iv Named-patient and compassionate use procedures, compounding, and similar frameworks

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

Pharmacists and physicians may prepare ‘compounded’ products without obtaining FDA approval. In 1997, Congress enacted a detailed statutory regime to govern traditional

15 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 (May 2019).

16 21 CFR, Section 814.15(b).

17 83 Fed Reg 7366 (21 February 2018).

18 FDA, Guidance for Industry and Food and Drug Administration Staff: Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions (February 2018).

pharmacy and physician compounding of drugs pursuant to prescriptions for specific patients.¹⁹ But in 2002, 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.²⁰ 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 that FDA's authority over traditional compounding remained intact. The Compounding Quality Act, signed by the president in November 2013, also established a new category of compounder, known as an 'outsourcing facility,' which prepares compounded products that are not necessarily intended for specific patients. Traditional compounders are regulated primarily by state boards of pharmacy, while outsourcing facilities are regulated primarily by the FDA. If a compounder voluntarily registers with the agency as an outsourcing facility and complies with certain conditions, its drugs will not be subject to pre-market approval. The compounding provisions of the FDCA apply only to drugs and do not contain any exemption from requirements for pre-market licensure of biologics.²¹ The FDA has indicated in guidance, however, that the agency does not intend to take action against the mixing, diluting or repackaging of licensed biological products as a violation of the PHSA's licensure requirement, provided certain conditions are satisfied.²²

In May 2018, the President signed the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act.²³ The law permits 'eligible patients' to receive wholly unapproved 'eligible investigational drugs' outside of a clinical trial and expanded access setting without violating federal law, subject to specified conditions. Eligible patients must have, among other things, been diagnosed with a life-threatening disease or condition. The law remains in the early stages of implementation, but to date, drug sponsors generally have continued to use the expanded access framework to provide access to drugs outside of clinical trials.

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 the FDA objects. As with treatment

19 21 USC, Section 353a.

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

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

22 FDA, Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2018).

23 Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176 (2018).

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. Emergency use authorisations (EUAs) are also available for devices.

‘Custom devices’ that meet certain criteria are exempt from the requirements for an approved PMA and compliance with performance standards under Section 520(b) of the FDCA.²⁴ Traditionally, the FDA interpreted this exemption narrowly and many patient-matched devices are not exempt ‘custom devices’. 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 has issued final guidance implementing the amended custom device provision.²⁵

Laboratory-developed tests (LDTs) present special regulatory issues. The FDA has traditionally defined LDTs as diagnostic tests that are developed, validated and performed within a single laboratory but not commercially distributed. Clinical laboratories performing LDTs are subject to the requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 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. Over the last decade, however, the Agency has attempted to increase its oversight of LDTs. In June 2010, the FDA announced that it intended to exercise regulatory authority over LDTs.²⁶ In 2014, the FDA published two draft guidances describing a proposed regulatory framework for LDTs. Following the presidential election in 2016, however, the FDA announced that it would not move forward with efforts to finalise the draft guidances. In January 2017, the FDA published a discussion paper summarising comments on the guidance and a proposed revised approach for regulation of LDTs, but the discussion paper restated that the FDA would not issue final guidance on LDT regulation. Nonetheless, the FDA increased its oversight of what it perceived as especially high-risk LDTs, and in October 2018 the FDA issued a safety communication warning against the use of unapproved LDTs that describe relationships between gene variants and particular drugs (pharmacogenomic tests).²⁷ Beginning in February 2020, the FDA also has regulated LDTs for covid-19.²⁸ In August 2020, the Department of Health and Human Services issued a policy stating that the FDA would not require premarket review of any LDTs absent notice-and-comment rulemaking, but that the FDA could review applications for LDTs that are submitted voluntarily.²⁹ The incoming Biden administration is expected to revert to the pre-covid-19 status quo, where the

24 21 USC, Section 360j(b).

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

26 75 Fed. Reg. 34463 (17 June 2010).

27 FDA, The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication (31 October 2018), <https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific>.

28 FDA, Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff: Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised) (May 11, 2020) (originally issued 29 February 2020).

29 US Dep’t of Health & Hum Serv, Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests (Aug. 2020), www.hhs.gov/coronavirus/testing/

FDA asserts authority over LDTs while generally exercising enforcement discretion, except in circumstances where the FDA determines that an LDT presents an especially high risk (e.g., pharmacogenomic tests). Over the past several years, Congress also began considering potential legislative reforms to address LDTs and other diagnostics, culminating with the introduction of the Verifying Accuracy and Leading-edge IVCT Development Act of 2020 (VALID).³⁰ Given the spotlight on the regulation of LDTs during the covid-19 public health emergency, some version of diagnostic reform legislation could pass in the coming years.

The FDA 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)³¹ 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 for RUO or IUO.³²

v Emergency use authorisation

Drugs, biologics and medical devices for the prevention, treatment or diagnosis of pandemic diseases or to protect against bioterror agents can be sold under an EUA. EUAs can only be approved if the Secretary of Health and Human Services declares an emergency or material threat, and authorisations remain valid only while the declaration is in effect. An EUA can be granted if the FDA determines that a product ‘may be effective’ for a serious or life-threatening disease or condition, that the benefit-risk is favourable and that there are no satisfactory approved alternatives.³³

vi Pre-market clearance

Drugs other than biologics

‘New drugs’, which are defined as 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’ that were originally issued under the Over-the-Counter (OTC) Drug Review.³⁴ 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

recission-guidances-informal-issuances-premarket-review-lab-tests/index.html; see also US Dep’t of Health & Hum Serv, FAQs on Laboratory Developed Tests (LDT), www.hhs.gov/sites/default/files/laboratory-developed-tests-faqs.pdf.

30 S.3404 – VALID Act of 2020, www.congress.gov/bill/116th-congress/senate-bill/3404/text.

31 21 CFR, Section 809.10(c)(2).

32 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).

33 See Section 564A of the FDCA, Title 21 USC Section 360bbb-3; FDA Guidance on Emergency Use Authorization of Medical Products and Other Authorities (January 2017), www.fda.gov/media/97321/download.

34 21 CFR, Parts 330–361.

compliance with monographs can be marketed without any prior submission to the FDA.³⁵ Until recently, many therapeutic categories were subject to proposed rather than final OTC monographs, and there were complex procedures for determining which products could be marketed while rule-making procedures were still under way.³⁶ In March 2020, Congress enacted legislation that amended the FDCA to establish new procedures governing the marketing of monograph OTC drugs.³⁷ Monographs will now be established and amended using simplified procedures for administrative orders, with procedures for immediately effective changes in warnings and other safety labelling, expedited introduction of new dosage forms, and other measures designed to enhance the safety and effectiveness of monograph drugs. Manufacturers of monograph drugs will pay user fees that will provide additional funding to FDA. Newer OTC drug products and virtually all prescription drug products are marketed under approved NDAs or ANDAs.³⁸

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 demonstrating the safety and effectiveness of the product and proposed labelling.³⁹ The FDA now requires that most submissions be made electronically (in the eCTD format); this requirement became effective for drug marketing applications on 5 May 2017. 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.⁴⁰

35 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.

36 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 (SSIA), 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. Under legislation enacted in March 2020, the provisions of the SSIA will be phased out, and new applications for approval of sunscreens will be submitted under general procedures for OTC drug products.

37 The new provisions were contained in the Coronavirus Aid, Relief, and Security (CARES) Act, Pub. L. No. 116-136 and are codified in Section 505G of the FDCA, Title 21 USC Section 355g.

38 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). An FDA compliance policy guide governing such products was recently withdrawn, and a notice accompanying the withdrawal requested comment on the possibility of permitting certain prescription drug products that are off-patent and off-exclusivity to be marketed without approved NDAs or ANDAs on the theory that they are generally recognised as safe and effective. 85 Fed. Reg. 75331 (25 November 2020).

39 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 drug master files (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).

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

Legislation originally enacted in 1992 and known as the Prescription Drug User Fee Act (PDUFA)⁴¹ requires sponsors of original products to pay fees upon the submission of NDAs, as well as annual fees for products that are subject to the user fee requirement. The fees are adjusted each year according to a formula set out in the law.⁴² 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 for new molecular entities within 12 months of submission and priority applications for such entities within eight months.⁴³ 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 of a review cycle, the FDA issues either an approval or a ‘complete response’, informing the applicant why approval was not granted and identifying additional information required for approval.⁴⁴

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 the current good manufacturing practice (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.⁴⁵

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,⁴⁶ which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2),⁴⁷ which rely

41 The PDUFA sunsets every five years unless re-enacted by Congress. The most recent enactment, passed in August 2017 as part of the FDA Reauthorization Act (FDARA), is commonly referred to as ‘PDUFA VI’.

42 For fiscal year 2021, the fees are as follows: for an application containing clinical data, US\$2,875,842; for an application that does not contain clinical data, US\$1,437,921; and the programme fee, US\$336,432.

43 Priority designation is granted if the 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, a material threat medical countermeasure, 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.

44 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 because the process is time-consuming and seldom leads to a change in the outcome.

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

46 21 USC, Section 355(j).

47 21 USC, Section 355(b)(2).

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, 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).⁴⁸

A generic product for which an ANDA is submitted must (1) ordinarily be the same as the reference product in terms of active ingredients, dosage form, route of administration and strength; (2) contain safe and suitable inactive ingredients; (3) bear the same labelling as the reference product except for changes owing to differences in manufacturer (e.g., in inactive ingredients or composition of the product); and (4) 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 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 reauthorisation of the Generic Drug User Fee Act enacted in 2017, the FDA will collect fees for original applications and drug master file submissions, annual programme fees for sponsors with approved ANDAs, and annual fees for certain facilities.⁴⁹ There is a 10-month target for standard review of new applications, and priority review is now also available for certain generic applications.

Biologics

Biological products are subject to a separate statutory approval system under Section 351 of the PHSA. Sponsors of original products submit biologics licence applications (BLAs) that contain essentially the same information as NDAs in the eCTD 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 ensure 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.

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

49 Application fees for fiscal year 2021 are US\$196,868 for new ANDAs; US\$69,921 for DMFs; US\$41,671 for domestic facilities that manufacturer active substances; US\$56,671 for foreign facilities that manufacture active substances; US\$184,022 for domestic facilities that manufacture finished products; and US\$199,022 for foreign facilities that manufacture finished products.

In 2010, Congress enacted legislation establishing an approval process for follow-on versions of biological products, or ‘biosimilars’.⁵⁰ Such a product must:

- a* be ‘highly similar’ to a reference product ‘notwithstanding minor differences in clinically inactive components’;
- b* have no clinically meaningful differences from a reference product in safety, purity or potency;
- c* be labelled for a condition of use for which the reference product is approved;
- d* have the same route of administration, dosage form and strength as the reference product; and
- e* be manufactured in facilities designed to ensure 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.⁵¹ In 2019, the FDA released final guidance describing its expectations for data and information, including from switching studies, needed to support interchangeability.⁵²

Although user fees for biosimilar applications were previously the same as those for original products, they are now subject to their own user fee framework. The FDA sets the amount of each type of biosimilar user fee via publication in the Federal Register. In addition to fees for original applications and product fees now called a ‘programme’ fee, a biosimilar developer also must pay a fee when it seeks development advice from the FDA and, thereafter, an annual fee as a biosimilar development fee.⁵³ Unlike under the previous law, the initial and annual fees are no longer 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 FDA has not approved any biosimilars as interchangeable with their reference products.

50 The Biologics Price Competition and Innovation Act (BPCIA), Pub. L. No. 111-148, Title VII, Subtitle A, 124 Stat. 119, 804–821 (2010). This legislation is part of the Affordable Care Act. The Supreme Court is currently considering a constitutional challenge to provisions of this Act, as discussed further below. See *California v. Texas*, No. 19-10011 (2020).

51 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 version of recombinant somatropin in 2006, based on a substantial package of non-clinical and clinical data. Subsequently, the FDA has approved applications under Section 505(b)(2) for follow-on insulin analogues. Effective 23 March 2020, the proteins approved under the FDCA were deemed licensed in BLAs under Section 351(a) of the PHSA. *Id.* Section 7002(e).

52 FDA, Guidance, Considerations in Demonstrating Interchangeability with a Reference Product (May 2019).

53 21 USC 379j-52; 85 Fed. Reg. 47,220 (4 August 2020).

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, generally, they are exempt from pre-market review. Class II devices present moderate risk, and most require FDA clearance of a pre-market notification under Section 510(k) of the FDCA (510(k)) prior to marketing. Class III devices – the highest-risk category – typically require approval of a PMA before marketing. Devices that have not yet been classified are automatically in Class III. For such devices that present a low or moderate risk, the manufacturer can request classification into Class I or II through the *de novo* classification process.

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, proposed labelling, a device description, performance data, and the submitter's rationale for concluding that the device is substantially equivalent to the predicate device. In some cases, it may need to contain clinical data. In addition to a traditional 510(k), the FDA also permits two other types of 510(k) submissions: Special 510(k) and Abbreviated 510(k).⁵⁴ A Special 510(k) can be used when a manufacturer makes certain modifications to its own device. An Abbreviated 510(k) relies on adherence to guidance documents, special controls, and/or FDA-recognised consensus standards to demonstrate substantial equivalence and facilitate 510(k) review. The Abbreviated 510(k) and Special 510(k) programmes were originally developed in 1998, and in 2019, the FDA issued updated guidances clarifying these programmes.⁵⁵ Also, in 2019, the FDA issued a guidance describing the Safety and Performance Based Pathway, an expansion of the concept of the Abbreviated 510(k) pathway for certain well understood device types.⁵⁶ The FDA has

54 FDA, Guidance: The New 510(k) Paradigm: Alternative Approaches to Demonstrating Substantial Equivalence in Premarket Notifications (March 1998).

55 FDA, Draft Guidance for Industry and Food and Drug Administration Staff: Abbreviated 510(k) Program (September 2019); FDA, Draft Guidance for Industry and Food and Drug Administration Staff: The Special 510(k) Program (September 2019).

56 FDA, Guidance for Industry and Food and Drug Administration Staff: Safety and Performance Based Pathway (September 2019).

issued guidances describing proposed performance criteria to support use of the Safety and Performance Based Pathway for spinal plating systems, cutaneous electrodes for recording purposes, conventional Foley catheters, orthopaedic non-spinal metallic bone screws and washers and magnetic resonance coils.⁵⁷ The submitter of a 510(k) must pay a modest 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. The submitter may not market the device until the FDA has 'cleared' the 510(k) notification, even if the FDA misses the applicable deadline.

For low and moderate risk devices that lack an appropriate predicate or where the FDA determines that a 510(k) submission has not demonstrated the device is substantially equivalent to the predicate device, the submitter may submit a *de novo* classification request. If the FDA grants the request, the agency will classify the device into Class I or Class II and authorise the marketing of the device (which then also serves as a predicate device for subsequent 510(k) submissions). The statute calls for the FDA to rule on a *de novo* request within 120 days, although historically the time to FDA action was often up to a year. FDARA added a user fee for *de novo* requests, and the FDA agreed to corresponding performance goals for the agency's review. In December 2018, the FDA issued a proposed rule to implement the *de novo* classification process.⁵⁸ The proposed rule largely aligns with the agency's existing guidance on the submission and review of *de novo* requests.⁵⁹

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 valid scientific evidence, which typically requires clinical trial data, demonstrating the safety and effectiveness of the device, 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 for novel devices 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.⁶⁰ 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 it represents a breakthrough technology or offers the potential, compared to existing alternatives, to reduce or eliminate the need for hospitalisation, improve

57 FDA, Framework for the Safety and Performance Based Pathway, www.fda.gov/medical-devices/premarket-notification-510k/framework-safety-and-performance-based-pathway.

58 83 Fed. Reg. 63127 (7 December 2018).

59 FDA, Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (October 2017).

60 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).

patients' quality of life, facilitate patients' ability to manage their 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 published final guidance on the breakthrough devices programme in December 2018.⁶¹

The FDA also may reclassify devices under a procedure that was streamlined in the Food and Drug Administration Safety and Innovation Act (FDASIA). Prior to the FDASIA, the FDA use notice-and-comment rule-making to reclassify devices, and this proved burdensome. As amended by the FDASIA, the statute permits the 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'.⁶² 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'.⁶³

vii 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 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). In 2019, the FDA revoked one of the few orphan-drug designations granted on the economic basis many years after its initial grant and based on a conclusion that it erred in granting the designation.⁶⁴ 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).⁶⁵ As part of FDARA, Congress codified the FDA's practice of requiring an applicant seeking orphan-drug exclusivity for a drug that is the 'same' as a previously approved drug to show clinical superiority to that prior drug, even if the prior drug never had orphan-drug exclusivity or it expired.⁶⁶ Litigation raised the issue of whether the FDA can apply the clinical superiority

61 FDA, Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program (December 2018).

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

63 79 Fed. Reg. 16252, 16254 (25 March 2014).

64 FDA, Citizen Petition Response Letter to Lassman Law + Policy (7 November 2019), www.regulations.gov/document?D=FDA-2019-P-1679-0079.

65 See 21 USC, Sections 360n-360ff; 21 CFR, Part 316.

66 Pub. L. No. 115-52, Section 607 (2017).

requirement to a product designated and approved before enactment of FDARA; both the DC Circuit and the district court ruled that the FDA must recognise orphan-drug exclusivity without proof of clinical superiority in this case.⁶⁷

The Hatch-Waxman Act establishes several incentives for development of original 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 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.⁶⁸

Second, the statute provides for periods of data exclusivity (i.e., protection against submission or approval of ANDAs and Section 505(b)(2) applications) for original 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) and approvals of non-NCE drugs receive three years if they are required to be supported by clinical investigations other than bioequivalence studies that are essential to approval and conducted or sponsored by the applicant. Except as noted below, follow-on applications for NCEs may not be submitted until 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 or non-NCE drugs can be submitted during the three-year period but approvals cannot be made effective for the innovator drug's conditions of approval until the period expires.⁶⁹ The FDA was recently involved in litigation addressing the meaning of 'conditions of approval'.⁷⁰ In a decision on remand, the FDA construed this phrase to mean the innovative change for which the new clinical investigations were essential for approval of the active moiety, which the FDA determines principally by asking what unique clinical question or questions about the moiety's safety or effectiveness did the clinical investigations answer for the first time.⁷¹

Third, the statute contains complex provisions linking the approval of follow-on products to patents for reference drugs approved under the FDCA. Sponsors of original 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 a patent is listed and has not expired, but the applicant wishes that approval of its product be made effective upon expiry; or
- d* that the listed patent is invalid or unenforceable or will not be infringed by the applicant's product.

67 *Eagle Pharmaceuticals, Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020); *Eagle Pharmaceuticals, Inc. v. Azar*, 2018 WL 3838265 (D.D.C. 2018).

68 35 USC, Section 156.

69 21 USC, Section 355(j).

70 *Braeburn, Inc. v. U.S. Food & Drug Administration*, 289 F.Supp.3d 1 (D.D.C. 2019).

71 FDA Letter to Braeburn, Inc., at 4, *Braeburn v. FDA*, No. 19-00982 (D.D.C. 7 November 2019).

In 2020, the FDA opened a docket to receive comment on several issues regarding its implementation of the patent listing provisions.⁷²

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 original 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.⁷³

Finally, the Hatch-Waxman Act provides for a 180-day period of generic marketing exclusivity for a first ANDA applicant that submits a substantially complete application that contains and lawfully maintains a Paragraph IV certification. 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-year 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, assuming the statutory requirements are met.⁷⁴

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 or life-threatening infections can receive five-year extensions of the four-year, five-year and three-year exclusivity under the Hatch-Waxman Act and seven-year orphan-drug exclusivity.⁷⁵

Biologics

Under the BPCIA, applications for biosimilar products may not be filed until four years, and may not be approved until 12 years, after first licensure 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

72 85 Fed. Reg. 33,169 (1 June 2020).

73 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.

74 21 USC, Section 355a.

75 21 USC, Section 355f.

earlier product, or when the subsequent product differs from the earlier product in structure and in safety, purity or potency. In July 2018, the FDA sought public comment on whether it should adopt an ‘umbrella’ exclusivity policy for biologics as it has for drugs.⁷⁶ Under such a policy, new uses, dosage forms and other modifications to exclusivity-protected products that do not independently qualify for reference product exclusivity will benefit from the balance of reference product exclusivity on the first-licensed product.

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 a June 2017 opinion, the United States Supreme Court interpreted the BPCIA’s information-sharing provision as not enforceable by injunction under federal law and remanded to the Federal Circuit to determine whether a state law injunction was available. The Supreme Court also held that a biosimilar applicant may give notice of commercial marketing contemplated by the BPCIA before the FDA licenses the biosimilar.⁷⁷ In December 2017, the Federal Circuit held that the BPCIA pre-empts state law remedies for a biosimilar applicant’s failure to comply with the BPCIA’s information sharing provision.⁷⁸

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. However, in practice, given the nature of innovation for devices, device manufacturers very rarely seek to rely on data in another approved PMA and this exclusivity period typically does not have a significant impact on the submission of subsequent PMAs for similar technologies. Patent term extension is also available for PMA-approved devices.

The humanitarian device exemption (HDE), rather than regulatory exclusivity, is available for sponsors of devices for rare diseases or conditions. It exempts the device from compliance with the effectiveness requirements of Section 515 of the FDCA, 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) will not be available to these patients without the exemption, and no comparable device (other than another a humanitarian use device (HUD)) is available for them; and (3) 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).

76 Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments, 83 Fed. Reg. 35,154 (25 July 2018).

77 *Sandoz Inc v. Amgen Inc*, No. 15-1039 (S. Ct. 12 June 2017).

78 *Amgen Inc v. Sandoz Inc*, No. 15-1499 (Fed. Cir. 14 December 2017).

viii 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 CIOMS⁷⁹ 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.⁸⁰ Manufacturers of approved drugs and biologics are also required to notify the FDA of discontinuance or certain interruptions 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,’ and NDA and ANDA holders are subject to an additional notification requirement for product withdrawals and products not available for sale.⁸¹

As part of the approval process, the FDA can impose requirements for risk evaluation and mitigation strategies (REMS), which may include special labelling, packaging and disposal technology, 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 certain 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. These requirements are imposed on many vaccines and certain other products regulated by the CBER.

FDA regulations establish detailed rules for changes in products that are subject to approved NDAs or BLAs.⁸² 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 (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.⁸³ Minor changes (e.g., minor editorial changes in labelling) can be notified in annual reports to the NDA or

79 Council for International Organizations of Medical Sciences.

80 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).

81 21 USC, Section 356c, 356i; 21 CFR Section 600.82.

82 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).

83 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 reasonable evidence of a causal relationship to the drug (21 CFR, Sections 314.70; 601.12(f)(2)). 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)). The FDA subsequently withdrew the proposal. 83 Fed. Reg. 64299 (14 December 2018).

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.), and in 2017 released draft guidance that addresses this topic for certain biologics.⁸⁴

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 typically requires 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.⁸⁵ 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 the 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.

Devices

The FDCA's 'general controls' apply to all devices, including Class I devices exempt from pre-market review.⁸⁶ The general controls include prohibitions on adulteration and misbranding, as well as requirements for device labelling, 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 must file a report 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.⁸⁷ 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 only

84 FDA, Draft Guidance for Industry, Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (December 2017), www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Chemistry--Manufacturing--and-Controls-Changes-to-an-Approved-Application--Certain-Biological-Products--Draft-Guidance-for-Industry.pdf.

85 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).

86 Some Class I devices are exempt from certain elements of the quality system regulation.

87 21 CFR, Section 803.50(a).

serious injuries to the manufacturer. Manufacturers must 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 public health.⁸⁸ Importers must complete their reports within 30 days; for user facilities, the deadline is 10 days.⁸⁹ 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.⁹⁰ Also, in December 2016, the FDA issued a final guidance describing when and how the agency will provide public notice of emerging post-market safety signals for devices.⁹¹

The FDA also requires manufacturers and importers to report certain corrections and removals of devices in the field 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 from its point of use to some other location for remediation or destruction.⁹² These actions are 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'.⁹³ In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.⁹⁴

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.⁹⁵ 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 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.⁹⁶

Different frameworks apply to post-approval changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.⁹⁷ 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); certain modifications

88 21 CFR, Section 803.40.

89 21 CFR, Section 803.10.

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

91 FDA, Guidance for Industry and Food and Drug Administration Staff: Public Notification of Emerging Post-market Medical Device Signals (December 2016).

92 21 CFR, Section 806.2(d) and (i).

93 21 CFR, Section 806.10(a).

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

95 FDCA, Sections 519(e), 522.

96 78 Fed. Reg. 58,786 (24 September 2013).

97 See 21 CFR, Section 814.39.

may be submitted in a Special 510(k) rather than a traditional 510(k). Changes that require a new 510(k) 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.⁹⁸ In October 2017, the FDA issued two final guidances describing how manufacturers should determine whether a new 510(k) should be submitted for change to an existing device.⁹⁹

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,¹⁰⁰ but subsequently withdrew the guidance in March 2020 without clarifying the reason for doing so.

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.¹⁰¹ The FDA also may temporarily suspend approval of a PMA and an HDE 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 clearance of a 510(k) notification, although there is no specific statutory or regulatory basis for this position, and in 2001, the agency published a proposed rule describing when FDA may rescind a 510(k) clearance.¹⁰² 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 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.¹⁰³ 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.¹⁰⁴

ix 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

98 21 CFR, Section 807.81(a)(3).

99 FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Change to an Existing Device (October 2017); FDA, Guidance for Industry and Food and Drug Administration Staff: Deciding When to Submit a 510(k) for a Software Change to an Existing Device (October 2017).

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

101 21 USC, Sections 360e(e), 360j(g)(5), 360j(m)(5).

102 66 Fed. Reg. 3523 (16 April 2001).

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

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

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,¹⁰⁵ 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.¹⁰⁶ PMAs must contain a detailed description of methods, facilities and controls used in manufacturing the device.¹⁰⁷ The FDA frequently also conducts 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.¹⁰⁸ 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).

x 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 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.¹⁰⁹

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.

105 21 CFR, Parts 210, 211.

106 21 CFR, Part 820.

107 21 CFR, Section 814.20(b)(4)(v).

108 21 CFR, Section 814.39(a)(3).

109 See 21 CFR, Part 202.

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.¹¹⁰

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); 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.¹¹¹ Decisions by the US Supreme Court in 2011,¹¹² an influential federal court of appeals in 2012,¹¹³ and a federal district court in 2015,¹¹⁴ established the principle that communication of truthful, non-misleading information about unapproved uses of approved drugs and devices is protected by the First Amendment, and the FDA has issued guidance documents that are partly responsive to those decisions.¹¹⁵

110 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). In 2017, the FDA revised its regulations governing intended uses, but stayed the changed rules when comments contended that the revisions could be read to require a manufacturer to include adequate directions for an unapproved use solely because it was aware that such use was occurring in practice. In September 2020, the FDA issued new proposed rules which made clear that this interpretation would not apply. Nevertheless, the wording of the proposal still leaves the agency broad discretion to determine when a manufacturer 'intends' an unapproved use of an approved product. See 85 Fed. Reg. 59718 (23 September 2020).

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

112 *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.

113 *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.

114 *Amarin Pharma Inc v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

115 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). 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. In June 2018, FDA issued revised final versions of the guidance. FDA, Guidance for Industry and Review Staff, Drug and Device Manufacturer Communications with Payors, Formulary Committees, and

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 FTC 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 the 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.¹¹⁶ Similarly, the principles for the FDA's regulation of device promotion and restricted device advertising are generally consistent with those for regulation of drug promotional labelling and advertising.¹¹⁷ 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 differences include a 'valid scientific evidence' standard for substantiation (rather than 'substantial evidence') and the lack of an express requirement for 'fair balance' in the regulations.¹¹⁸ Device promotion remains subject to the statutory prohibitions on false and misleading representations, however (including misleading omissions of material risk information).¹¹⁹ The new guidances mentioned above also apply to device promotion.

xi 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 the licensing of pharmaceutical distributors and distribution facilities, and the FDA has issued guidelines for those states.¹²⁰

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

Similar Entities – Questions and Answers (June 2018); FDA, Guidance for Industry, Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers (June 2018).

116 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*.

117 *id.*

118 *id.*

119 21 USC, Sections 502(a) and (q).

120 21 CFR, Part 205.

lists of authorised distributors.¹²¹ 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.

xii 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.¹²² For prescription drugs, elements to ensure safe use, established as part of FDA-imposed REMS, can limit use of a product to certain medical specialities or settings (e.g., hospitals).

Devices, like drugs, may be limited to prescription status. The FDA may also classify a device as restricted and thus limit access and distribution of the device, if 'there cannot otherwise be reasonable assurance of its safety and effectiveness'.¹²³ 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.

xiii Imports and exports

The FDCA includes a limited exemption under which certain drugs, biologics and devices 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 generally 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.

As part of the Trump Administration's efforts to reduce prescription drug prices, the HHS and FDA effectuated Section 804 of the FD&C Act to allow commercial importation of drugs from Canada without the manufacturer's permission.¹²⁴ HHS Secretary Azar certified to Congress that Section 804 implementation will pose no additional risk to the public's health and safety and will result in a significant reduction in the cost of covered products to

121 21 CFR, Part 203.

122 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.

123 21 USC, Section 360j(e).

124 85 Fed. Reg. 62094 (Oct. 1, 2020).

the US consumer.¹²⁵ The FDA promulgated a final rule implementing Section 804 through time-limited Section 804 Importation Programs (SIPs) to be authorised by FDA and managed by states and Indian Tribes.¹²⁶ To be eligible for importation under the final rule, a drug must be approved by Health Canada and meet the conditions of an FDA-approved NDA or ANDA but for the Canadian labelling, subject to certain exclusions. The final rule went into effect on 30 November 2020, and is the subject of a pending legal challenge.¹²⁷

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.¹²⁸ 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.¹²⁹

xiv Controlled substances

Narcotics, psychotropics and other drugs that are liable to abuse are regulated under the Controlled Substances Act,¹³⁰ which is administered by the DEA 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, the 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

125 www.safemedicines.org/2020/09/hhs-secretary-sent-congress-the-certification-to-allow-canadian-drug-importation.html.

126 www.regulations.gov/document?D=FDA-2019-N-5711-1252.

127 *Pharmaceutical Research and Manufacturers of America v. U.S. Dep't of Health and Human Services*, No. 1:20-cv-03402 (D.D.C. filed 23 November 2020).

128 21 USC, Section 381(e).

129 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 United States 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.

130 21 USC, Section 801 et seq.

recommendation to the DEA for the appropriate scheduling of the product, although the actual rule-making to include a new substance in a schedule under the statute is conducted by the DEA.¹³¹

In recent years, there have been significant developments relating to the legal status of cannabidiol (CBD) products in the United States, which now depends on the product's intended use, the product source and where the product is sold.¹³²

xv 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

131 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 statutory 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).

132 There is one cannabidiol product approved for sale as a drug in the United States, and it remains a Schedule V controlled substance unless and until the DEA takes administrative action to reschedule the substance. Whether a person may sell a CBD product as a food, dietary supplement, cosmetic, or consumer product depends on federal and state law. Some CBD products are schedule I controlled substances and are prohibited from general commercial sale. On 20 December 2018, the Agricultural Improvement Act of 2018 (the Farm Bill) effectively descheduled CBD products derived from cannabis sativa containing no more than 0.3 per cent THC (typically referred to as industrial hemp), but CBD derived from cannabis with more than 0.3 per cent THC remains a schedule I controlled substance. Pub. L. No. 115-334 (2018). Separately, the FDA currently has not authorised the sale of CBD products as food or dietary supplement for humans and animals in the United States. The FDA takes the position that CBD was not used in dietary supplements or foods before the start of substantial drug clinical investigations on CBD and thus, is excluded from use in dietary supplements and foods under particular provisions of the FDCA. The FDA has indicated that it is considering whether it should issue a regulation allowing the use of CBD in a food or dietary supplement, but has not yet taken any such action. See the FDA, FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD), www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. Federal enforcement against CBD products, to date, has largely consisted of the FDA and FTC issuing warning letters to manufacturers marketing CBD products with medical claims for serious diseases. Aside from federal restrictions, CBD products must also comply with state law. Each state has controlled substance laws, which are not pre-empted by the CSA. Many states have descheduled CBD that contains no more than 0.3 per cent THC, but a few remaining states regulate CBD in any form as a Schedule I controlled substance and, other than in the approved drug, prohibit CBD for sale. Other states have established specific requirements for CBD products for certain uses, such as CBD intended for use as a dietary supplement or for consumption as a food, including frameworks that expressly authorise the manufacture or sale of such products at a state level. To date, most states have not systematically enforced against CBD products, and in many states, enforcement has been local where it occurred. Most states are assessing their regulatory frameworks in an effort to harmonise their existing regulatory schemes, particularly for the growth and sale of industrial hemp, with the Farm Bill's hemp provisions.

Justice. The statute has been interpreted to impose strict criminal liability for a 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*).¹³³ Felony penalties may be imposed subject to proof that a violation was committed with the intent to defraud or mislead or upon a second conviction for a strict liability offence.¹³⁴ 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 informal 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.

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 rules on safety reporting and clinical investigations.¹³⁵ 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. Approximately 68 per cent of all patients have private insurance, often provided through their employer,¹³⁶ which covers prescription drugs, 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 drug 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 dependants, 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 speciality pharmacies, hospitals and other distribution channels.

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

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

135 It is estimated that total judgments in such cases over the past decade have exceeded US\$20 billion. The largest settlement to date related to GlaxoSmithKline, which agreed to pay a total of US\$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.

136 United States Census Bureau, Health Insurance Coverage in the United States: 2019 (2020), www.census.gov/content/dam/Census/library/publications/2020/demo/p60-271.pdf.

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.¹³⁷

Public programmes also use mechanisms to control costs similar to those used by private plans. Medicare Part D, which covers outpatient prescription drugs, imposes significant beneficiary cost sharing in a coverage gap known as the ‘donut hole’ (although subsequent legislation closed the donut hole in 2020). Drug manufacturers whose outpatient 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. The federal government is not currently permitted to negotiate drug prices under Medicare Part D.¹³⁸

Despite the availability of public and private insurance, many people (approximately 26.1 million by one estimate) lack coverage in the United States.¹³⁹ The Affordable Care Act (ACA) was enacted in 2010 to provide health coverage for those individuals who were not covered by other programmes. The ACA established minimum requirements for health insurance programmes, required most individuals to purchase insurance (although the individual mandate has since been repealed) and subsidised premiums for low-income individuals. In particular, the ACA established prescription drug coverage as 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. The Trump administration and many members of Congress have undertaken significant efforts to repeal the ACA, and its future is uncertain. A Texas district court struck down the entire ACA as unconstitutional;¹⁴⁰ the Supreme Court agreed to hear the case and heard oral arguments on it in November 2020.

There are also significant efforts aimed at reducing drug prices in the United States. At the federal level, the Trump administration set forth¹⁴¹ and ultimately issued a number

137 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. Similar laws exist for substitution of interchangeable biosimilars; however, the FDA has not yet approved any such products.

138 42 USC Section 1395w-111(i)(1) (Social Security Act Section 1860D-11(i)(1)) (providing that the HHS Secretary ‘may not interfere with the negotiations between drug manufacturers and pharmacies and PDP sponsors’ and ‘may not require a particular formulary or institute a price structure for the reimbursement of covered part D drugs’).

139 United States Census Bureau, Health Insurance Coverage in the United States: 2019 (2020), www.census.gov/content/dam/Census/library/publications/2020/demo/p60-271.pdf.

140 *Texas v. United States*, 340 F.Supp.3d 579 (N.D. Tex. 2018).

141 See Trump Admin., American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs (May 2018), available at www.hhs.gov/sites/default/files/AmericanPatientsFirst.pdf; see also U.S. Dep’t of Health & Hum. Serv., HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, 83 Fed. Reg. 22692, 22695 (16 May 2018).

of reform proposals aimed at lowering drug prices, including on commercial importation of drugs from Canada, as discussed above. In addition, President Trump signed executive orders to provide for: (1) eliminating Anti-Kickback Statute safe harbour protection for rebates to Part D plans and PBMs operating on their behalf, for which a final rule was published on 30 November 2020;¹⁴² (2) providing for 340B programme discounts on insulin and epinephrine to pass through to patients;¹⁴³ and (3) proposing to link payments for certain Medicare Part B drugs (with potential for expansion into Medicare Part D) to the lowest price paid in identified foreign countries, for which an interim final rule was issued with respect to Part B on 27 November 2020.¹⁴⁴ These proposals are subject to ongoing litigation. President-elect Joe Biden also has set forth a number of potential drug pricing reform proposals, including an 'independent review board' that would assess the value of certain new specialty drugs and recommend a price for Medicare reimbursement.¹⁴⁵ Additionally, Congress is considering reform measures that could include international price indexing and other reforms such as federal government drug price negotiation and caps on price increases or rebates for increases greater than inflation.¹⁴⁶

At the state level, numerous states have adopted measures aimed at increasing transparency regarding drug pricing activities. For example, Oregon requires manufacturers to submit annual reports and advance notice of price increases above a certain threshold, as well as notice upon the introduction of certain new high price drug products.¹⁴⁷ A smaller number of states have enacted laws aimed at limiting manufacturers' ability to increase drug prices. For example, in 2017, Maryland enacted a law that would have allowed the state's Attorney General to sue manufacturers for significantly high price increases;¹⁴⁸ while this law was struck down in federal court, the state has adopted a new measure creating a board to set upper payment limits for certain prescription drugs.¹⁴⁹ Additional drug pricing reform efforts are ongoing.

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.¹⁵⁰ However, the majority of disputes are resolved through less formal mechanisms. The FDA regulations establish a general right to

142 See OIG, Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Service Fees, 85 Fed. Reg. 76666 (30 November 2020).

143 See Access to Affordable Life-Saving Medications, E.O. 13937 of Jul 24, 2020, 85 Fed. Reg. 45755 (29 July 2020).

144 See CMS, Most Favored Nation (MFN) Model, 85 Fed. Reg. 76180 (27 November 2020).

145 Joe Biden, Healthcare, <https://joebiden.com/healthcare/> (last visited 13 December 2020).

146 See, e.g., Prescription Drug Pricing Reduction Act (PDPRA), S. 33542, 116th Cong. (2019); Lower Drug Costs Now Act of 2019, H.R. 3, 116th Cong. (2019).

147 Or. H.B. 4005 (eff. 1 January 2019 and 15 January 2019); Or. H.B. 2658 (eff. 1 January 2020).

148 Md. H.B. 631 (eff. 1 October 2017).

149 Md. S.B. 759 (eff. 1 July 2019).

150 21 USC, Section 355(d), (e).

informal review of any decision within the agency hierarchy.¹⁵¹ Certain FDA commitments made under the PDUFA (e.g., to decide appeals of ‘procedural or scientific matters involving the review of human drug applications and supplements’)¹⁵² include performance goals for completion. Nevertheless, the FDA recently issued final guidance providing that only appeals of ‘regulatory action[s] taken by the FDA that . . . ha[ve] scientific and/or medical significance’ are major disputes subject to the PDUFA goals and the FDA’s formal dispute resolution process and expressly excluded FDA advice given in meeting minutes and other correspondence from that definition, even though such advice can have great developmental significance.¹⁵³ Statutory provisions authorising the FDA to require REMS, post-approval studies and labelling changes afford sponsors a right to an informal dispute resolution procedure.¹⁵⁴ 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.¹⁵⁵ 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”’.¹⁵⁶

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 (APA).¹⁵⁷ 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.¹⁵⁸

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

151 21 CFR, Section 10.75. 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.

152 FDA, PDUFA VI Commitment Letter, Section I.E.

153 FDA, Guidance for Industry and Review Staff, Formal Dispute Resolution: Sponsor Appeals Above the Division Level (Nov. 2017).

154 21 USC, Sections 355(o), 355-1.

155 FDCA Section 517A(b).

156 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).

157 5 USC, Section 501 et seq.

158 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.

following the submission of a ‘citizen petition’ under the FDA’s procedural regulations.¹⁵⁹ 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.¹⁶⁰

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.¹⁶¹

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.¹⁶² Instead, these are subject to provisions of law enforced by the Department of Justice and the OIG of the HHS. The federal Anti-Kickback Statute¹⁶³ prohibits the provision or acceptance 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.¹⁶⁴ Such suits may result in penalties equal to three times the cost of unlawful activities to federal healthcare programmes plus a penalty for each false claim, and a significant portion of the damages 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

159 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 being filed under Section 505(q)(1)(F) of the FDCA. In recent guidance, the FDA interprets this deadline to apply only in certain circumstances, including that a pending abbreviated application that could be delayed by the petition has a user fee goal date that is within 150 days of submission. FDA, Guidance for Industry, Citizens Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act (September 2019). Pre-enforcement review is available as to final regulations issued by the FDA. *Abbott Laboratories v. Gardner*, 387 US 136 (1967).

160 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).

161 See, e.g., *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982) (competitor alleging unlawful use by the 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).

162 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).

163 42 USC, Section 1320a-7b.

164 31 USC, Sections 3729-3733.

under the Anti-Kickback Statute.¹⁶⁵ In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers¹⁶⁶ and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals, which the OIG has endorsed.¹⁶⁷

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 and teaching hospitals to the Department of Health and Human Services for disclosure on a public website.¹⁶⁸ The federal requirement pre-empts some, but not all, similar 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 Vaccine Injury Act of 1986.¹⁶⁹ 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:

- a* actual, non-reimbursable expenses for medical care, rehabilitation, custodial care and similar needs;
- b* lost earnings;
- c* pain and suffering (capped at US\$250,000);
- d* a US\$250,000 payment for a vaccine-related death; and
- e* 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.

165 42 CFR, Section 1001.952.

166 68 Fed. Reg. 23731 (5 May 2003).

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

168 www.cms.gov/openpayments.

169 42 USC, Section 300aa-10 et seq.

Section 304 of the Homeland Security Act of 2002¹⁷⁰ 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 2005¹⁷¹ 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.¹⁷² The act also incorporates a no-fault compensation system. Persons alleging injury must make a submission to that system as a precondition to litigation, and if a compensation award is accepted, litigation is precluded.

VII TRANSACTIONAL AND COMPETITION ISSUES

i Competition law

The interplay between the statutory mechanisms providing for approval of generic/biosimilar products and the US antitrust laws has produced a constant stream of antitrust issues in recent years. Government enforcers, generic developers and customer groups routinely challenge conduct that they allege prevents the development of competitive products that the drug and biologics regulatory regimes are intended to encourage.

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.¹⁷³ And under the Hatch-Waxman Act, in the case of a patent challenge, 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 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 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 expiry 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 to 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.

170 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.

171 42 USC, Section 247d-6d.

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

173 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/reports/generic-drug-entry-prior-patent-expiration-ftc-study.

The FTC has taken the position 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.¹⁷⁴

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.¹⁷⁵ 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.¹⁷⁶

The Third Circuit rejected the 'scope of the patent' standard in a significant 2012 decision, *In re K-Dur Antitrust Litigation*.¹⁷⁷ 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.¹⁷⁸ 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'.¹⁷⁹ The Third Circuit's explicit rejection of the standard applied by the majority of other courts to consider the issue 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*.¹⁸⁰ The *Actavis* decision held that reverse payment settlements can in some circumstances violate the antitrust laws

174 A 2010 analysis by the FTC asserts that reverse payment settlements cost consumers US\$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/2010/01/100112payfordelayrpt.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.

175 *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).

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

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

178 *id.* at 219.

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

180 *Federal Trade Commission v. Actavis Inc*, 570 U. S. 136, 133 S.Ct. 2223 (2013).

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 pro-competitive benefits. The application of the *Actavis* ruling to particular cases is extremely fact-intensive. Significant uncertainty remains as the lower courts evaluate a number of settlements subject to renewed litigation following the Supreme Court ruling. One of the key issues that continues to be litigated is what constitutes a ‘large and unjustified’ reverse payment required by the *Actavis* decision to subject the settlement to antitrust scrutiny.¹⁸¹

In addition, California passed Assembly Bill 824, which generally presumes that agreements to settle patent infringement claims related to drugs have anticompetitive effect if the generic company ‘receives anything of value’, including an exclusive licence, and ‘agrees to limit or forego research, development, manufacturing, marketing, or sales of [its] product for any period of time’. This legislation is the subject of a pending constitutional challenge.¹⁸²

In addition to allegations based on settlement of infringement suits under the Hatch-Waxman Act, 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 there is a reason to protect public health.¹⁸³ Nevertheless, the FTC and private plaintiffs have continued to challenge alleged improper petitioning activity harming generic competition.¹⁸⁴

Finally, both regulators and generic and biosimilar manufacturers have been exploring whether certain commercial practices unduly restrict the ability of generic or biosimilar products to launch successfully. One practice that has received significant scrutiny is the refusal of brand companies to provide product samples for bioequivalence testing required to complete an ANDA. Such refusals to provide samples have most often been challenged by generics for products that have regulatory restrictions on their distribution and thus cannot be obtained from normal wholesale channels.¹⁸⁵ On 20 December 2019, Congress passed

181 See *In re Lipitor Antitrust Litig.* (Lipitor), 868 F.3d 231, 274 (3d Cir. 2017). *In re Solodyn (Minocycline Hydrochloride) Antitrust Litig.* (Solodyn), No. 14-md-02503, 2018 WL 563144, at *4–13 (D. Mass. 25 January 2018); *In re Novartis and Par Antitrust Litig.*, 18 Civ. 4361(AKH), 2019 WL 3841711, at *4–5 (S.D.N.Y. 15 August 2019) (finding that whether a no-AG agreement is unjustified under *Actavis* should be subject to rule of reason); *In re Zetia (Ezetimibe) Antitrust Litig.*, 400 F. Supp. 3d 418, 425 (E.D. Va. 2019) (holding that unreasonableness of no-AG agreement should be evaluated ‘in relation to the payor’s anticipated future litigation costs’).

182 See *As’n for Accessible Meds. v. Becerra*, No. 20-01708 (E.D. Cal. 25 August 2020).

183 21 USC, Section 355(q).

184 *In Re: Restasis (Cyclosporine Ophthalmic Emulsion) Antitrust Litigation*, 1:18-md-02819 (E.D.N.Y. 18 September 2018) (denying motion to dismiss); *FTC v. Shire ViroPharma Inc.*, case no. 18-1807 (3d Cir. 2018) (appeal of dismissal of FTC challenge).

185 See *In re Thalomid and Revlimid Antitrust Litig.*, No. 14-6997 (KSH), 2015 WL 9589217, at *16 (D.N.J. 29 October 2015) (declining to dismiss Section 2 claim based on refusal to provide

legislation providing eligible product developers a private right of action for the licence holder's failure to timely sell samples on commercially reasonable, market-based terms, with the potential for injunctive and monetary relief.¹⁸⁶ A second area that has resulted in recent lawsuits involves the use of contractual provisions that allegedly incentivise purchasers to forgo dealing with a generic or biosimilar product.¹⁸⁷ US antitrust laws normally favour discounting and other competitive responses to competitive entry.

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 intellectual property (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 evolving biosimilar regime in the United States may require drafting attention depending on the interests of the parties.

Product liability is 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.

samples for ANDA); Prepared Statement of Markus H Meier, Acting Director, U.S. Federal Trade Commission, Before the Subcommittee on Regulatory Reform, Commercial, and Antitrust Law (27 July 2017), at www.ftc.gov/system/files/documents/public_statements/1234663/p859900_commission_testimony_re_at_concerns_and_the_fda_approval_process_house_7-27-17.pdf.

186 Pub. L. No. 116-94, §610 (2019).

187 *In re Remicade Antitrust Litig.*, 345 F. Supp. 3d 566, 580 (E.D. Pa. 2018).

VIII CURRENT DEVELOPMENTS

By far the most important development in 2020 related to the response to the covid-19 pandemic. The Secretary of Health and Human Services issued a declaration of a public health emergency in January 2020,¹⁸⁸ which was later revised and extended. Coupled with subsidiary determinations, this action triggered provisions of the PREP Act that provide virtual immunity to manufacturers, distributors and other covered persons against personal injury suits relating to covered countermeasures (including drugs, biologics and medical devices used in accordance with the relevant determinations)¹⁸⁹ and granted authority to the FDA to issue EUAs for such products. As of the time of writing, EUAs had been granted for over 50 medical devices (including personal protective equipment, ventilators, and patient monitoring devices, among others), over 300 diagnostic tests for the SARS-CoV-2 virus, two vaccines, and eight therapeutic agents (not including withdrawals).¹⁹⁰ At least two early EUAs for therapeutic agents (for chloroquine and hydroxychloroquine and for convalescent plasma) were the subject of controversy, including allegations of undue political influence.¹⁹¹ The FDA subsequently took extraordinary measures to help ensure public confidence in covid-19 vaccines that were introduced under EUAs, publishing detailed guidance requirements for proof of safety and efficacy,¹⁹² issuing a public statement, signed by the FDA Commissioner and the Director of the CBER committing to an independent, science-based review process, publishing detailed information on the data supporting each vaccine and televising public hearings on each vaccine before a panel of independent scientific experts. The FDA also issued more than 60 immediately-in-effect final guidance documents addressing a variety of regulatory issues related to the pandemic, including enforcement policies and medical product development advice.¹⁹³ It is to be expected that covid-19 issues will also dominate the political landscape throughout 2021.

Another significant development in 2020 was the election of a new US President. Although the Biden administration will have its own health policy agenda, the outgoing administration is first taking steps to roll out its policy initiatives in the 'lame duck' session before the inauguration of President-Elect Biden. For example, the Department of HHS issued a proposed rule requiring its agencies to engage in retrospective re-evaluations of their

188 See pandemic emergency declaration dates 31 January 2020: www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx.

189 As part of the CARES Act passed in March 2020, Congress also appropriated funds for the no-fault compensation system that operates in conjunction with the PREP Act, thus requiring persons alleging injury due to covered countermeasures to pursue compensation under that system before initiating litigation.

190 FDA, Emergency Use Authorization, www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

191 The EUA for chloroquine and hydroxychloroquine was later withdrawn after reports from multicenter clinical trials suggested that it was ineffective for the treatment of covid-19 infections. See FDA press release: www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.

192 FDA Guidance Document on Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020) www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.

193 See FDA, COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders, www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

regulations and providing that regulations not subject to required reviews will sunset within specified time periods.¹⁹⁴ As another example, HHS issued a notice requesting comment on the possibility of permitting certain prescription drug products that are off-patent and off-exclusivity to be marketed without approved NDAs or ANDAs on the theory that they are generally recognised as safe and effective.¹⁹⁵ This proposal, if implemented, would fundamentally alter the FDA regulatory framework by reducing the number of drugs for which approval is needed. In the lame duck session, Congress has passed certain sections of prior legislation meant to work regulatory reforms that lower drug prices indirectly in the Lower Health Care Costs Act,¹⁹⁶ and President Trump has signed these bills before leaving office.

The incoming Biden administration likely will emphasise science-based decision-making and continue to focus on the covid-19 pandemic response. Other initiatives, including measures to reduce the cost of prescription drugs as well as broader efforts to increase the coverage and stability of the US healthcare system, are likely. With respect to drug pricing, it remains to be seen whether the Biden administration will take up some of the Trump administration's initiatives, such as the drug importation final rule, or revoke them. It is likely that the Biden administration will continue the FDA's increased focus on competition issues started by Commissioner Scott Gottlieb, including building upon the Drug Competition Action Plan and Biosimilars Action Plan, which were aimed at increasing access to generic and biosimilar drugs by streamlining and incentivising their development. On the other hand, the Biden administration will likely reverse some of the Trump administration's actions described in the preceding paragraph, including the proposal to sunset FDA regulations if not retrospectively reviewed at specified intervals.

Finally, the new administration is likely to focus on other key agency priorities from the past several years, including the regulation of regenerative medicine products and enforcement action against those such products that FDA views as improperly marketed; decentralised clinical trials; and digital health technologies and real-world evidence. The new administration can be expected to review both the progress of these initiatives to date and take its own approach to them going forward. These subject areas also can be expected to be important focal points for anticipated 2022 legislation to reauthorise the FDA's user fee programmes.

194 85 Fed. Reg. 70096, 70119 (4 November 2020).

195 85 Fed. Reg. 75331 (25 November 2020).

196 Pub. Law Nos. 116–260, Div. BB, Title III, Subtitle C; H.R. 1503 (116th Cong., signed 5 January 2021).

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