THE LIFE SCIENCES LAW REVIEW

ELEVENTH EDITION

Editor
Peter Bogaert

THE LAWREVIEWS

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PREFACE

The eleventh edition of *The Life Sciences Law Review* covers a total of 24 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 showed a transition from the covid-19 pandemic to more normal health conditions, but also an enhanced awareness of new challenges. During the two preceding years, manufacturers of healthcare products, together with healthcare professionals and services, focused on the development and testing of vaccines, other drugs, biologics, diagnostics and personal protective equipment. This was done on an expedited basis, and regulatory agencies have reviewed marketing applications with unprecedented speed and efficiency. Manufacturers and international organisations have also worked closely together in an effort to ensure equitable access to vaccines and other important healthcare products in low- and middle-income countries, but much work remains to be done. Regulators are now making preparations for later emergencies and are also drawing lessons from the experience gained during the pandemic for the development and assessment of new health products in important therapeutic areas. Efforts to support effective and equitable access to key products at a more international level also continue.

Given the constant challenges and quick developments, 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.

Peter Bogaert
Covington & Burling LLP
Brussels
February 2023

Chapter 24

UNITED STATES

Krista Hessler Carver and Michelle Divelbiss[1]

I INTRODUCTION

The United States accounts for about 45 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, has a proposed budget of more than US$62 billion for FY2023 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 (HHS). The FDA, which has a staff of more than 18,000 and an annual budget in excess of US$8 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 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.

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1 Krista Hessler Carver is a partner and Michelle Divelbiss is an associate at Covington & Burling LLP. The authors would like to thank the following colleagues, who contributed to the preparation of this chapter: Richard Kingham, James Dean, Stefanie Doebler, Christina Kuhn, Julie Dohm, Jessica O'Connell, Kristie Gurley and Carrie Ansell.

2 The FDA budget request for fiscal year 2022 states that US$2.9 billion of the total budget of US$6.5 billion will come from user fees.

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.[3] 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.[4]

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 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.

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.[5] However, the same product may be covered by two or more definitions and thus be subject to multiple regulatory

3 The FDCA is codified at 21 USC, Section 301 et seq.

4 The relevant provisions of the PHSA are set out in 42 USC, Section 262.

5 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

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'.[6] They do not apply to combinations of two drugs, two devices or two biologics, or to other combinations of regulated products.

In April 2021, the DC Circuit appeals court decided a case addressing whether a barium sulfate contrast agent could be regulated as a drug when FDA concluded that it also met the statutory definition of a 'device'. The court held that FDA did not have discretion to classify as a drug any product that meets the statutory definition of device, and that, except for combination products, 'devices must be regulated as devices and drugs—if they do not also satisfy the device definition—must be regulated as drugs'.[7] As mentioned below, Congress partially overruled this decision as part of the year-end appropriations package in December 2022.

The FDA can initiate enforcement actions against borderline products that it believes are marketed without required prior approval. The agency continues to monitor the advertising and labelling of cosmetics for which anti-ageing or other claims that implicate the definition of a drug or device 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 regulations.[8] These are fundamentally the same as the principles established by the Organisation for Economic Co-operation and Development, which were based on the FDA rules.

The Animal and Plant Health Inspection Service (APHIS) within the Department of Agriculture administers regulations under the Animal Welfare Act 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

condition in human beings (42 USC, Section 262(i)(1)). The FDA promulgated a final rule that defines 'protein' as 'any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size' (21 CFR, Section 600.3(h)(6)).

6 21 CFR, Part 3.

7 *Genus Med Techs LLC v. FDA*, No. 19-cv-00533 (D.C. Cir. 16 April 2021).

8 21 CFR, Part 58.

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. In addition, sponsors must comply with National Institutes of Health (NIH) regulations related to registration of certain clinical trials in the public clinicaltrials.gov database.[11]

Drugs

Clinical trials of unapproved new drugs or biologics generally must be carried out under an investigational new drug application (IND).[12] 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 Council for Harmonisation (ICH). The IND submission must clearly identify any obligations that the sponsor intends to delegate to another person, including contract research organisations. 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 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 on the design of the protocols for the pivotal clinical trials, or, for certain studies,

9 21 CFR, Parts 50, 56.

10 21 CFR, Part 54.

11 42 CFR Part 11; *see* 42 U.S.C. § 282(j) (describing requirements for submission of clinical trial information for drugs and devices).

12 See generally, 21 CFR, Part 312.

a special protocol assessment. In either case, barring a significant scientific development, studies conducted in accordance with the agreement will be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

Sponsors and investigators are required to comply with provisions of good clinical practice (GCP), including requirements for informed consent, IRB review, monitoring, record-keeping and reporting. Studies conducted in accordance with ICH[13] 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.[14]

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).[15] 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.

'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 application 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.

13 The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

14 See 21 CFR, Section 312.120.

15 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).

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).[16] Device sponsors may also obtain informal advice from the FDA on whether a device is a SR device through a study risk determination process.[17]

The FDA will accept foreign studies not conducted under an IDE to support a device pre-market submission if the data is 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.[18] 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 pre-market submissions (including data to support an IDE, pre-market approval application (PMA), 510(k) pre-market notification, humanitarian device exemption and *de novo* classification request) that are collected in accordance with GCP and subject to the FDA's ability to validate the data through an inspection.[19] The FDA has also issued final guidance providing proposed recommendations on how to develop foreign data that is adequate to support approval or clearance of the device in the United States.[20]

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; costs that can be recovered generally are limited to 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.

Traditional pharmacists and physicians may prepare 'compounded' products for identified patients without obtaining FDA approval and without complying with current good manufacturing practice (GMP) requirements if certain conditions are met.[21] In 2012, 753 patients in 20 states were diagnosed with fungal infections after receiving injections

16 FDA, Guidance for Industry and Food and Drug Administration Staff: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (January 2021).

17 Id.

18 21 CFR, Section 814.15(b).

19 83 Fed Reg 7366 (21 February 2018).

20 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).

21 FDCA, Section 503A.

of a steroid compounded by the New England Compounding Center.[22] In response to this outbreak, Congress enacted legislation in 2013 to establish a then-new, voluntary category of compounder, known as an 'outsourcing facility', whose products must comply with GMP requirements.[23] Unlike a traditional compounder, an outsourcing facility may prepare compounded products for unidentified patients without obtaining pre-market approval if certain conditions are met.[24] Traditional compounders are regulated primarily by state boards of pharmacy, while outsourcing facilities are regulated primarily by the FDA. The compounding provisions of the FDCA apply only to drugs and do not contain any exemption from requirements for pre-market licensure of biologics.[25] 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.[26]

In May 2018, the President signed the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act.[27] 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. 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 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.[28]

'Custom devices' that meet certain criteria are exempt from the requirements for an approved PMA and compliance with performance standards under Section 520(b)

22 See, CDC, Multistate Outbreak of Fungal Meningitis and Other Infections, https://www.cdc.gov/hai/outbreaks/meningitis.html.

23 Compounding Quality Act, Pub. L. 113-54, 127 Stat. 587 (2013).

24 FDCA, Section 503B.

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

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

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

28 See, FDA, Expanded Access for Medical Devices, https://www.fda.gov/medical-devices/investigational-device-exemption-ide/expanded-access-medical-devices.

of the FDCA.[29] 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.[30]

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.[31] 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).[32] Beginning in February 2020, the FDA also has regulated LDTs for covid-19.[33] In August 2020, the Department of Health and Human Services issued a policy revoking prior FDA guidances and informal statements regarding LDTs and stating that the FDA would not require pre-market review of any LDTs absent notice-and-comment rulemaking, but that the FDA could review applications for LDTs that are submitted voluntarily. As expected, in November 2021, the Biden administration announced it was withdrawing the August 2020 policy, stating that 'HHS no longer has a policy on LDTs that is separate from FDA's longstanding approach in this area'.[34] Thus, the regulation of LDTs has reverted to the pre-2020 approach, where the FDA asserts authority to regulate 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

29 21 USC, Section 360j(b).

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

31 75 Fed. Reg. 34463 (17 June 2010).

32 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).

33 FDA, Guidance for Developers and Food and Drug Administration Staff: Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised) (27 September 2022) (originally issued 29 February 2020).

34 US Dep't of Health & Hum Serv, Statement by HHS Secretary Xavier Becerra on Withdrawal of HHS Policy on Laboratory-Developed Tests (15 November 2021), https://www.hhs.gov/about/news/2021/11/15/statement-hhs-secretary-xavier-becerra-withdrawal-hhs-policy-laboratory-developed-tests.html.

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), which was reintroduced in 2021.[35] 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)[36] 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.[37]

v Emergency use authorisation (EUA)

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.[38] The FDA has granted numerous EUAs for treatment and prevention of covid-19.[39]

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.[40] 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

35 S.3404 – VALID Act of 2020, www.congress.gov/bill/116th-congress/senate-bill/3404/text; S.2209 – VALID Act of 2021, https://www.congress.gov/bill/117th-congress/senate-bill/2209/text.

36 21 CFR, Section 809.10(c)(2).

37 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).

38 See Section 564 of the FDCA; FDA Guidance on Emergency Use Authorization of Medical Products and Other Authorities (January 2017), www.fda.gov/media/97321/download.

39 FDA, Coronavirus Disease 2019 (COVID-19) EUA Information, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas.

40 21 CFR, Parts 330–361.

compliance with monographs can be marketed without any prior submission to the FDA.[41] 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.[42] In March 2020, Congress enacted legislation that amended the FDCA to establish new procedures governing the marketing of monograph OTC drugs.[43] 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.[44]

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.[45] The FDA now requires that most submissions be made electronically (in the eCTD format). The FDA also requires submission of tabulations of all patient data from the principal clinical trials, as well as copies of case report forms (CRFs) for patients who died during clinical trials or withdrew because of adverse events, and it can demand CRFs for all patients in pivotal clinical trials. An applicant that does not maintain a place of business in the United States must appoint a US agent, who signs the application and receives official communications from the agency.[46]

41 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.

42 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.

43 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.

44 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 withdrawn at the end of the Trump administration, 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). The Biden administration then withdrew the notice and indicated it planned to issue guidance on the topic. 86 Fed. Reg. 28605 (27 May 2021).

45 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).

46 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)[47] 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.[48] 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 application 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.[49] 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.[50]

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 GMPs, 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.[51]

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,[52] which typically contain no safety or effectiveness data other than reports of bioequivalence studies; and applications submitted under Section 505(b)(2),[53] which rely on the finding of safety and effectiveness for a reference product but contain clinical data

47 The PDUFA sunsets every five years unless re-enacted by Congress. The most recent enactment, passed in September 2022, is commonly referred to as 'PDUFA VII'.

48 For fiscal year 2023, the fees are as follows: for an application containing clinical data, US$3,242,026; for an application that does not contain clinical data, US$1,621,013; and the programme fee, US$393,933.

49 Priority designation generally 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.

50 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 ordinarily commits 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.

51 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).

52 21 USC, Section 355(j).

53 21 USC, Section 355(b)(2).

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).[54]

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 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 with avoid violating or infringing 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 in an ANDA 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.

Under the reauthorisation of the Generic Drug User Fee Act enacted in 2022, 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.[55] There is a 10-month target for standard review of new applications, and priority review is 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.[56]

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

55 Application fees for fiscal year 2023 are US$240,582 for new ANDAs; US$74,952 for DMFs; US$37,544 for domestic facilities that manufacturer active substances; US$52,544 for foreign facilities that manufacture active substances; US$213,134 for domestic facilities that manufacture finished products; and US$228,134 for foreign facilities that manufacture finished products.

56 See, e.g., FDA, Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019), at 3–4.

In 2010, Congress enacted legislation establishing an approval process for follow-on versions of biological products, or 'biosimilars'.[57] 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 is unnecessary. Additional showings are required for the FDA to make a determination that a biosimilar product is 'interchangeable' with a reference product.[58] In 2019, the FDA released final guidance describing its expectations for data and information, including from switching studies, needed to support interchangeability.[59]

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.[60] 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. In July 2021, the FDA approved the first interchangeable biosimilar product, Semglee (insulin glargine-yfgn), as interchangeable with Lantus (insulin glargine).

57 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 considered a constitutional challenge to provisions of this Act and determined that Plaintiffs lacked standing to challenge the provision at issue. See *California v. Texas*, 141 S. Ct. 2104 (2021).

58 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).

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

60 21 USC 379j-52; 86 Fed. Reg. 40,567 (28 July 2021).

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 –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).[61] 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 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.[62] 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.[63] The FDA has issued guidances describing proposed performance criteria to support use of the Safety and

61 FDA, Guidance: The New 510(k) Paradigm: Alternative Approaches to Demonstrating Substantial Equivalence in Pre-market Notifications (March 1998).

62 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).

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

Performance Based Pathway for spinal plating systems, cutaneous electrodes for recording purposes, conventional Foley catheters, orthopaedic non-spinal metallic bone screws and washers, magnetic resonance coils, fracture fixation plates, surgical sutures, denture base resin and facet screw systems.[64] 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. The FDA issued a final rule to implement the *de novo* classification process on 5 October 2021.[65] The rule largely aligns with the agency's existing guidance on the submission and review of *de novo* requests.[66]

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 may refer a PMA for a novel device 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.

FDA has also implemented two programmes to expedite access to certain types of devices. The Breakthrough Devices programme is intended to expedite devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. 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 patients' quality of life, facilitate patients' ability to manage their own care, or establish long-term clinical efficiencies.[67] The Safer Technologies Program (STeP) is intended to expedite devices that are reasonably expected to significantly improve the safety of currently available treatments or diagnostics and applies to devices that target an underlying disease or

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

65 86 Fed. Reg. 54826 (5 October 2021).

66 FDA, Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation) (October 2021).

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

condition associated with morbidities and mortalities less serious than devices eligible for the Breakthrough Devices programme.[68] Both the Breakthrough Devices programme and STeP feature more interactive communications with the agency during device development and increased flexibility in clinical study design.

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'.[69] 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'.[70]

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 rare disease or condition). 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.[71] 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 structures of their active substances or because they are clinically superior).[72] 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

68 FDA, Guidance for Industry and Food and Drug Administration Staff: Safer Technologies Program for Medical Devices (January 2021).

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

70 79 Fed. Reg. 16252, 16254 (25 March 2014).

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

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

or it expired.[73, 74] In 2021 litigation, the Eleventh Circuit held that the scope of orphan-drug exclusivity is not limited to the approved indication but instead covers the designated rare disease or condition.[75] This case may prompt future legislation that addresses the scope of orphan-drug exclusivity, but to date has not.

The Hatch-Waxman Act established 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.[76]

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 bioavailability 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 can be submitted during the three-year exclusivity period but approvals cannot be made effective for the innovator drug's conditions of approval until the period expires.[77] In 2019, the FDA was involved in litigation addressing the meaning of 'conditions of approval'.[78] 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.[79] In 2021, Congress enacted the Ensuring Innovation Act of 2021 (Section 415), which amended the provisions of the FDCA that confer NCE exclusivity and made conforming changes to other provisions.[80] As amended, these laws provide NCE exclusivity for a drug, 'no active moiety (as defined by [FDA] in Section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) of which has been approved in

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

74 *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).

75 *Catalyst Pharmaceuticals, Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), cert. dismissed, 142 S. Ct. 2904 (2022).

76 35 USC, Section 156.

77 21 USC, Section 355(j).

78 *Braeburn, Inc v. US Food & Drug Administration*, 389 F.Supp.3d 1 (D.D.C. 2019).

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

80 Pub. L. No. 117-9, 135 Stat. 256 (2021).

any other application', whereas the prior provision referred to a drug no 'active ingredient' of which had been previously approved. This change appears intended to overrule case law on NCE exclusivity for naturally derived mixture products.[81]

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.

In 2021, Congress passed the Orange Book Transparency Act, which amended the patent listing provisions of the FDCA and required the FDA to solicit public comment on the types of patent information that should be included or removed from the *Orange Book* and report to Congress on action FDA is considering taking, if any, in response to such comments.[82]

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 applicant believes that 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.[83]

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 that fairly responds to a written request from the FDA can receive a six-month extension of every form of regulatory exclusivity pertaining to its product, including five-year and

81 See *Amarin v. FDA*, 106 F.Supp.3d 196 (D.D.C. 2015); FDA, Justification of Estimates for Appropriations Committees (FY 2020), at 36.

82 Pub. L. No. 116–290, 134 Stat. 4889 (2021).

83 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.

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.[84]

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.[85]

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 that fairly respond to a written request from the FDA. A 'first licensure' provision limits availability of new exclusivity periods for modified versions of previously authorised reference products. In general, it allows for a new exclusivity period when the licence application for the subsequent product is submitted by an entity that is not related to the sponsor of the earlier product, or when the subsequent product differs from the earlier product in structure and in safety, purity or potency. In July 2018, the FDA sought public comment on whether it should adopt an 'umbrella' exclusivity policy for biologics as it has for drugs.[86] Under such a policy, new uses, dosage forms and other modifications to exclusivity-protected products that do not independently qualify for reference product exclusivity would benefit from the balance of reference product exclusivity on the first-licensed product. The FDA has not yet announced whether it will adopt an umbrella exclusivity policy.

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.[87] 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.[88] In late 2020, Congress passed the Biological Product Patent Transparency Act amendments to the BPCIA, which went into effect in June 2021.[89] These amendments require that FDA publish information about biological products in the Purple Book Database of Licensed Biological

84 21 USC, Section 355a.

85 21 USC, Section 355f.

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

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

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

89 Consolidated Appropriations Act, Pub. L. No. 116-260, Division BB, Title III, Subtitle C, § 325 (2020), 134 Stat. 1182, 2936.

Products, including information about the patents listed in an initial or supplemental patent list prepared by a reference product sponsor under certain provisions of Section 351(l) of the PHSA.

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. There are no regulatory exclusivity provisions for 510(k)-cleared devices or devices on the market through the *de novo* classification process.

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).

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 in the CIOMS[90] 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.[91] Manufacturers of approved drugs and biologics are also required to notify the FDA of

90 Council for International Organizations of Medical Sciences.

91 21 CFR, Sections 314.81(b)(1) (drugs), 600.14 (biologics).

discontinuance or certain interruptions in production of life-supporting and life-sustaining drugs, drugs 'intended for use in the prevention or treatment of a debilitating disease or condition,' and drugs 'critical to the public health during a public health emergency,' and NDA and ANDA holders are subject to an additional notification requirement for product withdrawals and products not available for sale.[92]

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.[93] 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). 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.[94] Minor changes (e.g., minor editorial changes in labelling) can be notified in annual reports to the NDA or BLA file. For drugs, the FDA has issued detailed guidance on classification of changes in the quality aspects of products (manufacturing facilities, manufacturing processes, components, containers, etc.), and in 2021 released guidance that addresses this topic for certain biologics.[95]

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

92 21 USC, Section 356c, 356i; 21 CFR Section 600.82.

93 21 CFR, Sections 314.70 (drugs), 601.12 (biologics).

94 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). Congress passed legislation in late 2020 that enables FDA to require updates to generic labelling where the listed drug has been withdrawn from the market and no longer has patent or exclusivity protection. 21 USC, Section 353d.

95 FDA, Guidance for Industry, Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (June 2021), https://www.fda.gov/media/109615/download.

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. 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 subject to expedited procedures.

Devices

The FDCA's 'general controls' apply to all devices, including Class I devices exempt from pre-market review.[96] 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.[97] 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 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.[98] Importers must complete their reports within 30 days; for user facilities, the deadline is 10 days.[99] 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.[100] 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.[101]

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,

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

97 21 CFR, Section 803.50(a).

98 21 CFR, Section 803.40.

99 21 CFR, Section 803.10.

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

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

whereas removals involve the physical removal of the device from its point of use to some other location for remediation or destruction.[102] 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'.[103] In October 2014, the agency issued a final guidance that distinguishes recalls from product enhancements.[104]

The FDA may require post-market surveillance and tracking of certain Class II and Class III devices.[105] 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 data in 510(k)s. The FDA also finalised regulations generally requiring the labels of devices to bear a unique device identifier.[106]

Different frameworks apply to post-market changes to PMA-approved and 510(k)-cleared devices. The PMA requirements are parallel to those for NDAs.[107] 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 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.[108] 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.[109]

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,[110] but subsequently withdrew

102 21 CFR, Section 806.2(d) and (i).

103 21 CFR, Section 806.10(a).

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

105 FDCA, Sections 519(e), 522.

106 78 Fed. Reg. 58,786 (24 September 2013).

107 See 21 CFR, Section 814.39.

108 21 CFR, Section 807.81(a)(3).

109 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).

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

the guidance in March 2020 without clarifying the reason for doing so. Generally, 510(k)s can be transferred to a new owner, and FDA notification of the transfer is accomplished through the establishment registration and device listing process.

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.[111] 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.[112] 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.[113] 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.[114]

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 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,[115] 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.[116] PMAs must contain a detailed description of methods, facilities and controls used in manufacturing the device.[117]

111 21 USC, Sections 360e(e), 360j(g)(5), 360j(m)(5).

112 66 Fed. Reg. 3523 (16 April 2001).

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

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

115 21 CFR, Parts 210, 211.

116 21 CFR, Part 820.

117 21 CFR, Section 814.20(b)(4)(v).

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.[118] 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.[119]

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 safety information (e.g., websites, print advertisements or other measures). Although FDA pre-clearance of DTC advertisements is not ordinarily required, companies often submit television advertisements for FDA review prior to use.

Oral statements by sales representatives and other agents of drug manufacturers may be taken as evidence of the intended uses of a drug product. If those statements recommend uses that are not included in the approved prescribing information, the FDA will take the position that the drug product is misbranded (and therefore in violation of the FDCA) because its labelling does not include adequate directions for such uses.[120]

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

118 21 CFR, Section 814.39(a)(3).

119 See 21 CFR, Part 202.

120 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 August 2021, the FDA finalised revisions to the intended use rule. In doing so, it asserted that the agency can establish intended use of a product based not only on advertising and promotional materials but also on the manufacturer's knowledge of actual use by customers, training programmes, financial analyses, and other internal documents. 86 Fed. Reg. 41,383 (2 August 2021).

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 have been concerns 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.[121] Decisions by the US Supreme Court in 2011,[122] an influential federal court of appeals in 2012,[123] and a federal district court in 2015,[124] 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.[125]

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.[126] Similarly, the principles for the FDA's regulation of device promotion and restricted device

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

122 *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.

123 *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.

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

125 See FDA, Guidance for Industry and Review Staff, Drug and Device Manufacturer Communications with Payors, Formulary Committees, and 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); FDA, Guidance for Industry, Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products – Questions and Answers (February 2020).

126 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.

advertising are generally consistent with those for regulation of drug promotional labelling and advertising.[127] 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.[128] Device promotion remains subject to the statutory prohibitions on false and misleading representations, however (including misleading omissions of material risk information).[129] The 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.[130]

The FDA regulations implementing the Prescription Drug Marketing Act establish a number of requirements that apply to manufacturers, wholesalers and distributors, including provisions governing distribution of samples and drugs supplied to charitable institutions, documentation of the chain of distribution and requirements for manufacturers to maintain lists of authorised distributors.[131] The Drug Supply Chain Security Act, signed in November 2013, provided 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, and in 2022, the FDA issued a proposed rule on additional conditions for non-prescription use.[132] 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'.[133] Possible restrictions include

127 ibid.
128 ibid.
129 21 USC, Sections 502(a) and (q).
130 21 CFR, Part 205.
131 21 CFR, Part 203.
132 See 87 Fed. Reg. 38212 (28 June 2022).
133 21 USC, Section 360j(e).

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

Subject to certain exceptions, such as import of products for processing and export, FDA-regulated products imported into the United States must comply with the same standards as domestic products.[134] During entry review, the FDA evaluates whether the products appear to violate the FDCA, such as products that appear to be adulterated, misbranded or lack required pre-market approval or clearance.[135] For products that appear violative, including those subject to an import alert providing for detention without physical examination, the FDA may detain the products and offer the importer a hearing to present evidence to overcome the appearance of a violation.[136] Should the FDA ultimately determine that the products appear violative, the FDA must refuse their admission into the United States.

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 by wholesalers and pharmacists without the manufacturer's permission.[137] 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 the US consumer.[138] The FDA promulgated a final rule implementing Section 804 through time-limited Section 804 Importation Programs to be authorised by the FDA and managed by states and Indian Tribes.[139] 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.[140]

The FDCA includes complex provisions governing the export of drugs and devices that do not comply with requirements for shipment in domestic commerce. Products that are ordinarily considered to be 'adulterated' or 'misbranded' are not deemed as such, and thus they may be exported, if 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.[141] The FDA has interpreted the export provisions to impose requirements for record-keeping and other forms of documentation.

134 21 USC, Section 381(a), (d)(3).

135 21 USC, Section 381(a).

136 21 CFR 1.94.

137 85 Fed. Reg. 62094 (1 October 2020).

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

139 21 CFR, Part 251.

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

141 21 USC, Section 381(e).

Exports of products that do not comply with requirements for FDA pre-market approval or clearance (e.g., NDAs, BLAs, PMAs, and 510(k)s) are subject to much more elaborate rules.[142]

xiv Enforcement

The principal formal enforcement measures under the FDCA are seizures of non-complying goods, injunction actions to restrain future violations and criminal prosecutions. The FDA lacks authority to initiate these actions on its own, but must refer them to the Department of Justice. The statute has been interpreted to impose strict criminal liability for 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*).[143] 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.[144] 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. 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 66 per cent of all patients have private insurance, often provided through their employer,[145] 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

142 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.

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

144 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.

145 United States Census Bureau, Health Insurance Coverage in the United States: 2020 (2021), https://www.census.gov/content/dam/Census/library/publications/2021/demo/p60-274.pdf.

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.

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.[146]

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 by reducing the beneficiary's financial responsibility to 25 per cent). 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.

Despite the availability of public and private insurance, many people (approximately 27 million by one estimate) lack coverage in the United States.[147] The Affordable Care Act (ACA), enacted in 2010, extended health coverage to many 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. There have been significant efforts to repeal the ACA in full, but these efforts have failed.

There also have been significant efforts aimed at reducing drug prices in the United States, including the August 2022 passage of the Inflation Reduction Act (IRA).[148] The IRA established a price negotiation programme for certain single-source Part B and Part D drugs,

146 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.

147 United States Census Bureau, Health Insurance Coverage in the United States: 2020 (2021), https://www.census.gov/content/dam/Census/library/publications/2021/demo/p60-274.pdf.

148 Inflation Reduction Act of 2022, Pub. L. No. 117-169, 136 Stat. 1818 (2022).

through which a 'maximum fair price' will be specified through price-capped 'negotiation' with Centers for Medicare & Medicaid Services. Single-source drugs and biologics generally are eligible for selection for the negotiation programme seven or 11 years after their approval or licensure, respectively. The IRA sets forth several potential price caps for the negotiation process, potentially leading to a maximum fair price at or under 40–75 per cent of the product's non-federal average manufacturer price. Failure to offer the drug at the maximum fair price can result in substantial penalties. The IRA drug pricing provisions also require manufacturers to pay inflation-based rebates for Medicare Part B and Part D utilisation of certain drugs and biologics with price increases that exceed the rate of inflation.

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.[149] Other states have enacted laws aimed at limiting manufacturers' ability to increase drug prices. 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. As required by statute, the FDA regulations establish a general right to 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 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

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

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

151 FDCA Section 562; 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 VII Commitment Letter, Section I.G.

153 FDA, Guidance for Industry and Review Staff, Formal Dispute Resolution: Sponsor Appeals Above the Division Level (May 2019).

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

155 FDCA Section 517A(b).

'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 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

156 FDA, Guidance for Industry and Food and Drug Administration Staff: Center for Devices and Radiological Health Appeals Processes: Questions and Answers About 517A (March 2020); FDA, Guidance for Industry and Food and Drug Administration Staff: Center for Devices and Radiological Health Appeals Processes (July 2019).

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 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.

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 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).

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 Statute[163] 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 under the Anti-Kickback Statute.[165] In addition, the OIG has issued guidance on compliance programmes for pharmaceutical manufacturers[166] and the principal trade association of the pharmaceutical industry has adopted a code of practice on interactions with healthcare professionals (most recently revised effective 1 January 2022), 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.

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 The 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.

165 42 CFR, Section 1001.952.

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

167 PhRMA Code on Interactions with Healthcare Professionals.

168 www.cms.gov/openpayments.

VI TRANSACTIONAL AND COMPETITION ISSUES

The interplay between the statutory mechanisms providing for approval of generic and 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.[169] 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. However, 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.

The FTC has taken the position that settlements that involve consideration flowing back to the generic company are anticompetitive. In June 2013, the Supreme Court held that such settlements can in some circumstances violate the antitrust laws and that they should be evaluated under a traditional rule-of-reason analysis, which involves comparing the likely anticompetitive effects of the settlement versus any pro-competitive benefits. The application of the *Actavis* ruling to particular cases is extremely fact-intensive and continues to be litigated.[170]

In addition, both state and federal legislators also have focused on patent settlement issues. For example, in 2019, 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]

169 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.

170 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').

product for any period of time'. This legislation was the subject of a constitutional challenge, and the district court determined that the law can be enforced 'with respect to settlement agreements negotiated, completed, or entered into within California's borders'.[171] In July 2021, the Senate Committee on the Judiciary reported federal legislation that would also presume certain patent settlement agreements have anticompetitive effect.[172] The legislation remains pending.

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.[173] Nevertheless, the FTC and private plaintiffs have continued to challenge alleged improper petitioning activity harming generic competition.[174] In July 2021, the Senate Committee on the Judiciary reported federal legislation that is intended to deter the filing of 'sham' petitions, which the bill defines as those that are 'objectively baseless and that attempt to use a governmental process, as opposed to the outcome of that process, to interfere with the business of a competitor, or a series of covered petitions that attempts to use a governmental process, as opposed to the outcome of that process, to interfere with the business of a competitor'.[175]

Other introduced legislation would target the alleged practice of 'product hopping',[176] which critics typically define as actions that force patients to switch to a new, trivially changed formulation of a drug with new patents on the eve of generic competition. The bill, however, is far broader and raises significant questions about how it might chill legitimate product improvements to the benefit of patients.

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 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

171 See *Ass'n for Accessible Meds. v. Bonta*, No. 20-01708 (E.D. Cal. 15 February 2022) (modifying earlier injunction).

172 S. 1428 (117th Cong. 2021) (as reported by the Senate Committee on the Judiciary).

173 21 USC, Section 355(q).

174 *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); see also FDA Response, Docket No. FDA-2021-P-1211 (15 December 2021).

175 S. 1425 (117th Cong. 2021) (as reported by the Senate Committee on the Judiciary).

176 S. 1435 (117th Cong. 2021) (as reported by the Senate Committee on the Judiciary).

from normal wholesale channels.[177] On 20 December 2019, Congress passed legislation, colloquially referred to as the CREATES Act, that provides 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.[178] The first lawsuit under CREATES was brought in 2021 and was voluntarily dismissed.[179]

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.[180] US antitrust laws normally favour discounting and other competitive responses to competitive entry, but the legal status of rebates or other discounts alleged offered to deter generic or biosimilar competition remains unclear as recent cases have settled short of a ruling on the merits.

VII CURRENT DEVELOPMENTS

A significant recent development is the passage of the Food and Drug Omnibus Reform Act of 2022 (FDORA) as part of the Consolidated Appropriations Act 2023, which was signed into law on 29 December 2022.[181] The FDORA contains various policy riders that had been considered during the user fee legislation that passed in September 2022, but were not included at that time. FDORA affects the FDA's authority over drugs, devices and cosmetics. For drugs approved under the accelerated approval process, FDORA codifies the FDA's authority to require that post-marketing confirmatory studies be underway at the time of accelerated approval and requires the sponsor to report on the post-approval study progress every 180 days. It also amends the statutory withdrawal procedures for accelerated approvals by replacing the right to an informal hearing with an opportunity for an in-person meeting with the commissioner or designee, a written appeals process, a public docket and requirement for the FDA to summarise and respond to public comments, and an opportunity for an advisory committee meeting if requested by the sponsor and no meeting has been convened previously on the topic. The law also has designated contrast agents, radioactive drugs and OTC monograph drugs as drugs, rather than devices, to partially overrule the *Genus Med Techs LLC v. FDA* decision. FDORA also requires clinical trial sponsors to submit diversity action plans for most Phase 3 and other pivotal studies. Subtitle E of FDORA contains the Modernization of Cosmetics Regulation Act of 2022, which overhauls the FDA's oversight of cosmetics, but other 'super-riders', including the aforementioned VALID Act and dietary supplement reform, were not included. Also excluded was the legislative proposal to overrule the mentioned *Catalyst* decision on orphan-drug exclusivity. Looking forward, government implementation of the FDORA as well as the Inflation Reduction Act's drug price negotiation provisions will be key areas of focus for stakeholders.

177 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 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.

178 Pub. L. No. 116-94, §610 (2019); (codified at Title 21 USC Section 355-2).

179 Notice of Voluntary Dismissal, *Teva Pharmaceuticals Development, Inc v. Amicus Therapeutics US Inc*, No. 2:21-cv-03105 (E.D. Penn. 2 September 2021), ECF No. 12.

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

181 Consolidated Appropriations Act, 2023, Pub. L. 117-328, Division FF, Title III, 136 Stat. 4459.

Appendix 1

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