Chapter 1: Statutory and Regulatory Controls for Drug Development

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Statutory and Regulatory Controls for Drug Development

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I. Regulation of Pharmaceuticals in the United States

In the United States, consumers obtain access to pharmaceuticals by presenting to a pharmacist a valid prescription signed by a licensed health care professional. Various drugs can also be purchased either with or without a prescription through over-the-counter (OTC) purchases. The U.S. Food and

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1In other cases, prescription and OTC products may be dispensed in a physician’s office, hospital, long-term care facility, drug rehabilitation facility, or any of a number of other pathways.
2Under some circumstances, providers may write prescriptions for OTC drugs so that patients can obtain these drugs through an insurance plan.
Drug Administration (FDA) determines the need to obtain a prescription for any given drug. This determination forms the basis for the legal classification of any specific drug and impacts the drug’s marketing and distribution. Prescription and nonprescription drugs may be available as brand-name or generic products; they may also be available as both. State and federal law requires that drugs may be prescribed and dispensed only by licensed health care professionals, and prescriptive authority is governed by individual state statutes—and is not restricted to physicians. There is no federal legislation regarding prescriptive authority; however, individuals licensed in a given state to prescribe pharmaceuticals within state boundaries must also apply for an additional federal license to prescribe controlled substances. Under the federal Controlled Substances Act (CSA), administered in part by the U.S. Drug Enforcement Agency (DEA), individual practitioners such as physicians are specifically granted the federal authority to prescribe controlled substances, such as narcotics.

The FDA has its origin in the Federal Food and Drugs Act of 1906 (1906 Act), which was the first federal legislation to address standards for the preparation and marketing of medicines. That 1906 Act was administered under the authority of the U.S. Bureau of Chemistry. Prior to the 1906 Act, medicinal

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3See 21 U.S.C. §384(a)(3)(2005), which provides: The term “prescription drug” means a drug subject to Section 503(b) [21 U.S.C. §353(b)], other than—

(A) a controlled substance (as defined in section 102 of the Controlled Substances Act (21 U.S.C. §802));

(B) a biological product (as defined in section 351 of the Public Health Service Act (42 U.S.C. §262));

(C) an infused drug (including a peritoneal dialysis solution);

(D) an intravenously injected drug;

(E) a drug that is inhaled during surgery; or

(F) a drug which is a parenteral drug, the importation of which pursuant to subsection (b) is determined by the Secretary to pose a threat to the public health, in which case section 801(d)(1) [21 U.S.C. §811(d)(1)] shall continue to apply.

4See 21 U.S.C. §353(b)(1)(A) (2005) (drugs that have potentially harmful effects require a physician’s prescription; stating that drugs “not safe for use except under the supervision of a practitioner licensed by law to administer such drug,” otherwise known as “prescription drugs”).


6See 21 U.S.C. §821 (2005) (“The Attorney General is authorized to promulgate rules and regulations and to charge reasonable fees relating to the registration and control of the manufacture, distribution, and dispensing of controlled substances and to listed chemicals.”).

7See 21 C.F.R. §1306.21 (2006); see also id. §1300.01(17) (The term “individual practitioner” is defined in the regulations as a “physician, dentist, veterinarian, or other individual licensed, [or] registered . . . to dispense a controlled substance in the course of professional practice, but [it] does not include a pharmacist, a pharmacy, or an institutional practitioner.”).

8CSA §102, 21 U.S.C. §802(10). The term “dispense” means “to deliver a controlled substance to an ultimate user . . . pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling, or compounding necessary to prepare the substance for such delivery.” See also 21 C.F.R. §1306.21 (2006).

products (then consisting largely of proprietary alcoholic tonics, patent medicines, and sometimes even toxic compounds sold as “remedies”) remained unregulated in terms of their content, purity, and safety. The 1906 Act represented the first statutory prohibition of the marketing for human consumption of compounds as either medicines or food additives when they were known to be poisonous or potentially harmful to human health.

In 1911, the U.S. Supreme Court limited the scope of the Bureau of Chemistry’s enforcement power over the misbranding of drugs. However, the Sherrill Amendment of 1912 expanded the definition of “misbranding” to specifically include “false and fraudulent” statements relating to “therapeutic effects.” The Bureau of Chemistry was officially renamed the U.S. Food, Drug, and Insecticide Administration in 1927. In 1930 its name was shortened to the Food and Drug Administration.

The Federal Food, Drug, and Cosmetic Act (FDCA) provides the modern statutory basis for the FDA’s authority and is the product of sequential legislative reforms and amendments. It took effect on June 25, 1938, superseding and repealing the 1906 Act. While the 1938 FDCA was first drafted in 1933 by the U.S. Department of Agriculture, it was later enacted in response to a national public health crisis caused by toxins found in a medicinal antibiotic compound, the “elixir of sulfanilamide.”

The FDCA delegated congressional power to the Secretary of the Department of Health, Education and Welfare (HEW), which was later renamed the Department of Health and Human Services (HHS), to regulate interstate and foreign commerce involving “drugs,” “foods,” “cosmetics,” medical “devices,” and related products. The FDCA was later amended to give the FDA, as the designee of the HHS Secretary, the statutory authority to regulate these products. Importantly, the FDCA also:

10 See United States v. Johnson, 221 U.S. 488 (1911).
11 Pure Food and Drug Act of Aug. 23, 1912, ch. 352, 37 Stat. 416. Note that the FDA was charged with the burden of proving fraudulent intent with respect to misstatements of therapeutic effect.
17 In April 1953, the FDA was brought under the authority of HEW; in 1968 the FDA was incorporated into the Public Health Service within HEW; and finally in 1980 the education function was removed from HEW to create the Department of Health and Human Services, the present parent agency for the FDA. See FDA, History of the FDA, available at http://www.fda.gov/oc/history/historyoffda/default.htm.
1. Added injunctive authority to augment the FDA’s seizure and enforce-
ment authority;19
2. Authorized standards of identity for a large variety of food products;20
3. Expanded requirements for manufacturers to list all the ingredients of
nonstandardized foods that contain two or more distinct ingredients;21
4. Required screening by the FDA of new drugs prior to their public mar-
keting;22
5. Significantly expanded the power and scope of the FDA’s enforcement
authority;23 and
6. Placed cosmetics and medical devices under the FDA regulation.24

In 1951, the Durham-Humphrey Amendment to the FDCA defined the
types of drugs that could not be safely used without medical supervision—effect-
ively creating the defined class of drugs known as “prescription drugs”—and
by exclusion simultaneously defined those drugs that could be used safely without medical supervision and could be marketed over the counter (1951 Amendment).25 The 1951 Amendment also provided statutorily defined criteria for prescription drugs: (1) habit-forming drugs; (2) drugs that can be used safely only when supervised by a licensed health care practitioner; and (3) drugs that can be used only under professional supervision because they were approved as the result of a New Drug Application (NDA). On the other hand, the 1951 Amendment permitted the FDA to assign OTC status to medications only if (1) a patient could self-diagnose safely or could understand drug usage require-
ments and restrictions, and (2) the drug was not known to cause any significant side effects.27

The 1962 Kefauver-Harris Amendments further amended the FDCA (1962 Amendments).28 These amendments explicitly required the FDA to review all NDAs to assess them for safety in humans and to ascertain that a drug manufac-
turer had provided “substantial evidence” through “adequate and well-controlled investigations” to demonstrate that a potential new drug is also effective for its intended use.29 As written, the 1962 Amendments required retroactive determi-
nation of the safety and effectiveness for drugs that had been approved from 1938 to 1962. To accomplish the effectiveness assessment of this large group of drugs, the FDA contracted with the National Research Council (NRC) of the

19Id. §332.
20Id. §341.
23Id. §331.
24Id. §§351, 361–63.
26These may include potential toxic or side effects, specific requirements or methods of administration, or requirements for close laboratory or clinical monitoring of drug levels or drug effects that necessitate professional oversight.
29Pub. L. No. 87-781, §§102(b), 102(c) (codified at 21 U.S.C. §§355(b), 355(d) (2005)).
National Academy of Sciences. The effectiveness review was named the Drug Effectiveness Study Implementation (DESI), and the NRC was required to formally present its findings to the FDA as to the safety, effectiveness, and appropriate labeling of drugs approved from 1938 to 1962.\textsuperscript{30} The FDA was also permitted to withdraw drugs introduced before 1962 if they were found to be ineffective. The 1962 Amendments also added new requirements: (1) a new drug or medical device could not be marketed until it was approved by the FDA,\textsuperscript{31} and (2) FDA approval must be issued prior to initiation of human clinical testing of a new drug.\textsuperscript{32} (Under prior law, if the FDA did not act within 180 days to exclude a drug after receiving an application, the drug was considered approved and could be legally marketed.\textsuperscript{33} The 1962 Amendments necessitated affirmative FDA premarket approvals for new drugs as a prerequisite to commercial development and marketing.)

The Food and Drug Administration Modernization Act of 1997 (FDAMA)\textsuperscript{34} further emphasized and reiterated the requirement that a manufacturer demonstrate a new drug’s effectiveness prior to FDA approval for marketing. Specifically, Section 115 of the FDAMA emphasized the term “substantial evidence” to represent the statutorily required standard of proof for drug “effectiveness.”\textsuperscript{35} The FDAMA also iterated a four-part FDA mission statement\textsuperscript{36} that stressed the promotion of the public health in addition to the FDA’s existing duty to protect the public health.\textsuperscript{37} The FDAMA also directed the FDA to take “prompt and efficient action” in approving new products for market.\textsuperscript{38}

\textsuperscript{32}Id. §106(b), codified at 21 U.S.C. §355(i).
\textsuperscript{33}Pub. L. No. 75-717, §505(c), 52 Stat. 052 (1938).
\textsuperscript{35}See 21 U.S.C. §355(d) (2005) (FDCA §505(d)).
\textsuperscript{37}Id. §406, 21 U.S.C. §903(b) (2005) provides:
MISSION—The Administration shall—
(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner; (2) with respect to such products, protect the public health by ensuring that—
(A) foods are safe, wholesome, sanitary, and properly labeled; (B) human and veterinary drugs are safe and effective; (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
(D) cosmetics are safe and properly labeled; and
(E) public health and safety are protected from electronic product radiation; (3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and
(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.
\textsuperscript{38}21 U.S.C. §903(b) (2005).
Statutory and Regulatory Controls for Drug Development

Now the FDA represents just one of the policymaking and enforcement units within HHS.\(^3^9\) The FDA’s Commissioner is charged by the Secretary of HHS (via the Assistant Secretary for Health who controls the PHS) with enforcing the FDCA and other statutes.\(^4^0\) The FDA Commissioner is “appointed by the President with the advice and consent of the Senate.”\(^4^1\) Thus, the FDA is empowered as an agency with a congressional mandate to oversee the safety and efficacy of the U.S. drug supply, among other things, and to enforce the FDCA’s requirements.\(^4^2\) However, the scope of its legislative mandate is frequently unclear.

The FDA’s actions are further circumscribed in part by the Administrative Procedure Act (APA), which provides the framework for agency rulemaking.\(^4^3\) In order for the FDA, as a federal agency, to develop new rules that will have the force of laws, it must have the authority to engage in rulemaking, summary judgment, and statutory guidelines.\(^4^4\) The FDA has made extensive use of rulemaking under a long-established statutory process, as well as informal notice and comment rulemaking\(^4^5\) and formal, evidentiary, on-the-record, quasi-judicial rulemaking\(^4^6\) in developing its policies.

Through its rulemaking power, the FDA has progressively broadened its scope of control to include:

1. Determinations of efficacy for stated indications;
2. Oversight regarding the conduct of preclinical and clinical research;
3. Continued evaluation of safety and efficacy through postmarketing surveillance and data collection; and
4. Attempts to directly and indirectly control the marketing practices of the pharmaceutical industry.

The FDA may also issue “guidance documents” prepared for the information of applicants or sponsors of drug approval applications. Guidance documents generally relate to administrative procedures (such as the processing, content, and evaluation/approval of applications) or they may pertain to the

\(^3^9\) The FDA was not specifically created by Congress; rather, it was merged into HEW in 1952 from its previous place in the Federal Security Administration.


\(^4^4\) See 21 U.S.C. §371(a) (“The authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in this section, is hereby vested in the Secretary.”).


\(^4^6\) Id. §704(e).
design, production, manufacturing, and testing of regulated products. Guidance documents may also be used to achieve consistency in regulatory approach. The purposes of guidance documents are to (1) assist the regulated industry by clarifying the requirements imposed by Congress or issued in FDA regulations and explaining how industrial users may comply with such requirements, and (2) illustrate specific review and enforcement approaches to help ensure that the FDA carries out its legislative mandate in an “effective, fair, and consistent manner.” To that end, the FDA has determined that all guidance documents must include the following:

1. The umbrella term “guidance”;
2. Information that identifies the center or office producing the document; and
3. The regulatory activity to which the document applies and/or the intended users of the document.

A guidance document is not binding on the FDA or the public; rather, it represents FDA current thinking on a certain subject. Because guidance documents are not regulations or laws, they are not enforceable, through either administrative actions or the courts. Notably, guidance documents do not include agency reports, general information provided to consumers, documents relating to solely internal FDA procedures, speeches, journal articles and editorials, media interviews, warning letters, or other communications or actions taken by individuals at the FDA or directed to individual persons or firms.

The FDA generally utilizes a two-tiered system of public involvement in developing its guidance documents: (1) solicitation of public comment prior to publication, used primarily for guidance documents that specify significant changes in existing policy, are controversial, or address complex issues; or (2) solicitation of public comment at publication, used primarily for guidance documents that constitute primarily a restatement of existing practices or represent relatively minor changes. This process is similar to the notice and comment process used in rulemaking.

The FDA also employs its summary judgment authority when necessary to enforce agency positions based upon the merits, when there are “no genuine and substantial issues of fact,” or when “data and information submitted are insufficient to justify the factual determination.”

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47 21 U.S.C. §371(h)(1)(A) (2005) (“The Secretary shall develop guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means. Such documents shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the . . . [FDA].”).
49 Id. at 8962.
50 Id.
51 Id. at 8961.
53 Id. §701(h)(1)(D).
54 See 21 C.F.R. §12.24(b) (2006); see also id. §12.24(b)(3) (“The data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue
Finally, when indicated, the FDA makes use of advisory committees, whereby it obtains independent advisory opinions at public hearings on matters of potentially controversial public policy or technical issues. An FDA advisory committee may be either a policy advisory committee or a technical advisory committee. A policy advisory committee advises the FDA on broad and general matters, whereas a technical advisory committee advises the FDA on specific technical or scientific issues.

An advisory committee typically “has a fixed membership, a defined purpose of providing advice to the agency on a particular subject, regular or periodic meetings, and an organizational structure.” In general, an advisory committee is defined as “any committee, board, commission, council, conference, panel, task force, or other similar group, which is established by statute, or established or utilized by the President or by an agency official, for the purpose of obtaining advice or recommendations for the President or on issues or policies within the scope of an agency official’s responsibilities.” In a strict sense, most agencies utilize “discretionary advisory committees,” which are advisory committees “established under the authority of an agency head or authorized by statute.” Federal regulations provide authority to the FDA’s Commissioner, “as a matter of discretion, that it is in the public interest for a standing or ad hoc policy or technical public advisory committee (advisory committee or committee) to hold a public hearing and to review and make recommendations on any matter before FDA.”

A. Identification and Classification of Pharmaceuticals

The word “drug” is a term of art under the FDCA. The early 1906 Act defined “drug” in a limited manner to mean (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (C) articles (other than food) in the way sought by the person. A hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate.”), and id. §16.26(b) (“After a hearing commences, the presiding officer may issue a summary decision on any issue in the hearing if the presiding officer determines from the material submitted in connection with the hearing, or from matters officially noticed, that there is no genuine and substantial issue of fact respecting that issue.”).

The Federal Advisory Committee Act forms the basis for convening an advisory committee. See 21 C.F.R. §14 and 5 U.S.C. §561 (“Agencies have the authority to establish negotiated rulemaking committees under the laws establishing such agencies and their activities and under the Federal Advisory Committee Act (5 U.S.C. App.).”).

Id. §14.1(b)(2).


41 C.F.R. §102-3.25 (2006); see also 16 C.F.R. §1018.2 (2003) (“Advisory Committee means any committee, board, commission, council, conference, panel, task force or other similar group, or any subcommittee or other subgroup, thereof, which is established or used by the Commission in the interest of obtaining advice or recommendations and which is not composed wholly of full-time officers or employees of the Federal Government.”).


intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Subsequent judicial statements have found that “if Congress had intended to limit the statutory definition of ‘drug’ to the medical definition, Congress would have so stated explicitly, or simply have made reference to the official United States Pharmacopoeia (or the National Formulary).” In fact, courts have ruled that “Congress fully intended that the Act’s coverage be as broad as its literal language indicates—and equally clearly, broader than any strict medical definition might otherwise allow.”

The definition of a “drug” is also based on a determination of its “intended use” or the objective intent of those responsible for labeling the product, where the compound has long been used for medicinal purposes, in terms of its common usage.

Drugs are distinct from devices. The FDCA defines the term “device” to mean:

[A]n instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopoeia, or any supplement to them; (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Technological advances in the scientific fields of tissue engineering, cell biology, pharmacology, gene therapy, and materials science have created some products that do not fit neatly into a single statutory definition. These products are termed “combinations” or “combination products” because they combine attributes of drugs, biologics, and/or medical devices. For example, antibiotic-impregnated catheters, heparin-bonded vascular devices, and antibiotic-coated orthopedic implants might represent combination products.

A combination product is defined to be:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are

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6134 Stat. 768, 769.
62Id. at 793.
63Id. at 798.
6421 C.F.R. §201.128 (2006). (The definition of “intent” makes use of advertising claims, company statements, patent applications, or SEC filings, for example); see also United States v. Bacto-Unidisc, 394 U.S. 784 (1969).
65Except where the term “device” is used in 21 U.S.C. §321(n); see also id. §§331(i), 343(f), 352(c), and 362(c) (2005).
6621 U.S.C. §332(g).
physically, chemically, or otherwise combined or mixed and produced as single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigation drug, device, or biological product where both are required to achieve the intended use, indication, or effect.68

Thus, combination products may include various drug-drug or drug-device combinations that the FDA may choose to regulate as either drugs or devices. Combination products provide a challenge to the FDA and the flexibility of its regulatory scheme.69

B. FDA Approval Process for New Pharmaceutical Drugs

The FDA imposes certain standards on the development and marketing of new drugs and requires all drugs to meet rigorous safety and effectiveness standards. The FDA's regulation of new drug development addresses two principal goals implied in the FDA’s mission statement: (1) FDA standards require empirical demonstration of both the safety and efficacy of new drugs prior to their approval for marketing; and (2) enforcement of the regulatory scheme is necessary to keep unapproved products from the market. FDA determinations regarding the safety and efficacy of new pharmaceutical products are based upon integration of an enormous amount of complex data from clinical medicine, pharmacology, biostatistics, and clinical trial design. The administrative infrastructure required to fulfill the FDA’s mission is therefore complex and costly.

FDA approval of new drugs also reflects the administrative tension between two important but competing public health risks: (1) the risk that a drug will be approved prematurely without an adequate demonstration of safety and efficacy; and (2) the risk of unnecessary delay in the availability of necessary medications required for disease treatment.70

In order to present data to the FDA that can satisfy FDA’s new drug approval requirements, a sponsor must first develop a new chemical entity, and

68 21 C.F.R. §3.2(e) (2006).
then file an Investigational New Drug Application (IND). Subsequently, if the drug testing is successful, the sponsor of the new drug must file an NDA.\footnote{Id. §355(a). Note that more than one IND can be filed for a potential drug.} All of these processes are discussed below.

1. **Stage 1: New Chemical Entity**

Successfully bringing a New Chemical Entity (NCE) to market requires a substantial investment of time and resources. Industry, universities, the National Institutes of Health (NIH), and other federal agencies collaboratively fund the complex process of clinical trials.\footnote{Pharmaceutical Research and Marketing Ass’n (PhRMA), Industry Profile 2005, available at http://www.phrma.org/2005_industry_profile/5/.} Research and development (R&D) expenses include basic science experimentation to produce possible compounds with biological activity, clinical testing, insurance, and marketing. A developer or manufacturer engaged in R&D must cover its operating costs, produce shareholder value, and allocate sufficient funds from profits to pay for the sunk costs of unapproved drugs and also fund future R&D. From an economic perspective, the revenues derived from successful medicines must not only cover the R&D expenses involved in their own development, but also the R&D costs of the unsuccessful medicines and future prospects. Economic modeling suggests that the optimal amount of pharmaceutical R&D spending, like any investment, depends on its future stream of expected marginal revenues and costs.\footnote{Henry G. Grabowski & John M. Vernon, The Determinants of R&D Expenditures in the Pharmaceutical Industry, in DRUGS & HEALTH: ECONOMIC ISSUES & POLICY OBJECTIVES 3 (Robert B. Helms ed., 1981); see also M. Scherer, The Link Between Gross Profitability and Pharmaceutical R&D Spending, 20(5) HEALTH AFF. 216 (2001).} Only three out of every 10 marketed drugs generate revenues that match or exceed average R&D costs.\footnote{PhRMA, What Goes into the Cost of Prescription Drugs (2005), available at http://www.phrma.org/files/Cost_of_Prescription_Drugs.pdf.}

industry in the United States on R&D totaled more than $33 billion, which represented approximately 17 percent of sales.78

NCEs that might possess biological activity and therefore potential medicinal utility are identified or developed during preclinical research. Preclinical research includes the isolation of naturally occurring plant, insect, mineral, or animal substances; synthetic compounds; or modifications of existing drugs. Research regarding a drug’s properties is typically initiated through a process of chemical analyses and laboratory animal studies. The FDA regulates “good laboratory practices” (GLPs) during drug testing in the laboratory stage. These preclinical animal studies include acute and short-term toxicity studies for assessing whether future human clinical studies would be acceptably safe. Once the properties of an NCE become sufficiently understood at the preclinical level, the FDA can engage in its risk-benefit calculus to decide whether benefits outweigh risks for further studies and potentially public distribution. Variability in the pharmacologic effects of compounds between various species means that results from animal studies cannot simply be extrapolated to humans. Thus, the “adequate and well-controlled” studies that generate the data required to substantiate that a drug is safe and effective must consist of both animal (preclinical) studies and human (clinical) studies.79

The FDA also requires that a sponsor of an NCE demonstrate the proposed production methods used in, and the facilities and controls used for the manufacturing, processing, and packaging of a new drug are adequate to preserve its identity, strength, quality, and purity80 throughout the testing process and in later marketing. Sponsors must submit information from preclinical testing in animal models as well as a detailed plan for investigation of the new drug in human clinical trials. Additionally, sponsors submit periodic progress reports to the FDA. The FDA may terminate clinical trials or order a modification of the investigation if the preliminary data suggest the drug is not safe or effective.

The FDA may establish or use panels of experts for the purpose of providing expert scientific advice and recommendations regarding a clinical investigation of a drug or the approval for marketing of a drug.81 Members of FDA review panels should be qualified by training and experience to evaluate the safety and effectiveness of the drugs; possess skill and experience in the development, manufacture, or utilization of such drugs; provide diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoconomics, biological and physical sciences, and other related professions; represent the interests of consumers and the drug manufacturing industry not directly affected; and be specialists in the particular disease or condition for which the drug under review is proposed to be indicated.82

81Id. §355(n).
82Id., §355(n)(3)(A).
2. Stage 2: The Investigational New Drug Application

a. Background on INDs

Once an NCE has been tested on animals in preclinical studies, the manufacturer may file an Investigational New Drug Application (IND) with the FDA. The term “investigational new drug” means “a new drug or biological drug that is used in a clinical investigation” and includes “a biological product that is used in vitro for diagnostic purposes.”

The IND represents an exemption from the statutory prohibition against shipping unapproved new drugs in interstate commerce. The IND process also provides the FDA with an opportunity to impose standards, restrictions, and ongoing oversight over the clinical drug research process.

The following regulations provide the major details about the IND application process:

1. 21 C.F.R. part 312: Investigational New Drug Application;
2. 21 C.F.R. part 314: IND and NDA Applications for FDA Approval to Market a New Drug;
3. 1 C.F.R. part 316: Orphan Drugs;
4. 21 C.F.R. part 58: Good Lab Practice for Nonclinical Laboratory [Animal] Studies;
5. 21 C.F.R. part 50: Protection of Human Subjects;
6. 21 C.F.R. part 56: Institutional Review Boards;
7. 21 C.F.R. part 201: Drug Labeling; and

When reviewing an IND, the FDA seeks to assure the safety and rights of subjects and that the quality of the scientific evaluation of drugs permits an evaluation of the drug’s effectiveness and safety. The FDA therefore evaluates the safety of proposed clinical experiments in the context of “unreasonable risk.” This assessment involves a balancing of the risks and the benefits associated with the proposed clinical trials. The IND includes all preclinical research data and a scientific design of the human studies to be conducted.

There are three general types of IND applications:

1. Investigator IND;
2. Emergency Use IND; and
3. Treatment IND.

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8421 C.F.R. §312.3.
8621 C.F.R. §312.3.
8721 C.F.R. §312.22.
88See 21 U.S.C. §355(i)(3)(B)(i) (2005); see also 21 C.F.R. §312.23(a)(8) (2005) (requiring applicants to include pharmacological and toxicological studies that serve as the basis of their conclusion that clinical testing would be “reasonably safe”); id. §56.111(a)(2) (2004) (the Institutional Review Boards which oversee clinical trials must consider whether the “[r]isks to subjects are reasonable in relation to anticipated benefits”).
9021 C.F.R. §312.23 (outlining contents of an IND application).
The Investigator IND is submitted by a medical sponsor who both initiates and conducts the clinical investigation, and under whose immediate direction the investigational drug is administered or dispensed. There are two categories of Investigator INDs: (1) commercial, for industry sponsors; and (2) research (noncommercial), for physician or other clinical researchers. A sponsor can submit an Investigator IND proposal either to evaluate an unapproved drug, a previously approved pharmaceutical for a new indication, or an unapproved or approved drug in a different patient population.

The Emergency Use IND authorizes clinical therapeutic use of an experimental drug in an emergency situation. In such cases the Emergency Use IND temporarily circumvents 21 C.F.R. §§312.23 or 312.34 for a specific patient or population. The Emergency Use IND may also be used in the care of patients who do not meet the entry criteria to an existing study protocol.

The third type of IND, the Treatment IND, is a procedure that allows sponsors to expedite access to some drugs that are still in experimental or investigational stages. The Treatment IND makes drugs available for the treatment of individuals with imminently life-threatening diseases in cases where:

1. No effective alternative drugs or therapies are available;
2. The proposed drug is currently in controlled clinical trial stages or is listed under an effective IND and the sponsor of the clinical trial is actively pursuing approval; or
3. Such trial has been completed and the IND is pending FDA approval.

Nonetheless, there must be some reasonably acceptable preliminary evidence of the safety and effectiveness of the drug for which a Treatment IND is sought. Prescribers must obtain informed consent from each patient, obtain institutional review board oversight, and submit safety reports to the FDA.

The FDA’s Center for Drug Evaluation and Research (CDER) offers a Pre-Investigational IND Consultation Program to encourage early communications between sponsors and FDA new drug review divisions and to provide guidance on the data and procedural requirements necessary for a proper IND submission. The CDER initiatives were designed to accelerate the approval process for new drugs and to broaden preapproval access to the FDA. To that end, CDER has published numerous guidance documents to facilitate compliance with regulatory requirements for both INDs and NDAs.

b. IND Application Requirements

21 C.F.R. §312.23 specifies the required content of an IND application and the specified format. The principal forms for submitting an IND are (1) FDA 1571 (the IND Application) and (2) FDA 1572 (the Statement of Investigator).
The FDA also accepts electronic submissions of regulatory documents, including IND applications.96

The IND application must contain detailed information pertaining to three broad areas: (1) detailed data from preclinical testing in animal pharmacology and toxicology studies to permit a preliminary assessment of “reasonable safety”; (2) manufacturing specifications pertaining to the composition, manufacturer qualifications, stability, and controls used for manufacturing the drug substance and the drug product; and (3) detailed specifications of proposed clinical protocols and investigator qualifications. Finally, the investigators must commit to conduct the studies in an ethical manner, obtain informed consent from the research subjects, obtain review of the study by an institutional review board (IRB), and adhere to applicable regulations.97

Additionally, the IND application must contain information about the sponsor’s prior initial research on a drug including laboratory analysis, animal research, and proposed human study protocols.98 Investigators submitting the IND application must provide a detailed research plan that begins with summary statements detailing the investigation team and the compound to be studied.99

The protocols that constitute phases I through III of drug testing must be specified in detail, including a statement of the objectives and purpose; a statement of the qualifications of each investigator; criteria for selection and for exclusion of patients; the kind of control group to be used; methods to minimize bias; methods for determining dosages of drug, maximum dosage, and the duration of individual patient exposure; the observations and measurements to be made; and a description of clinical procedures to monitor the effects of the drug in human subjects and to minimize risk.100 Protocol changes and amendments must be submitted to and approved by the FDA.101

The IND application must be filed 30 days before beginning investigational testing in humans, and the FDA must either approve or reject the IND within that period.102 The FDA evaluates IND protocols to determine that the drug is reasonably safe for human testing, that human subjects in clinical trials have adequate protections and safeguards, and that the experimental design of the studies is appropriate to accomplish the goal of determining drug safety and effectiveness. During the IND phase, investigation of the drug normally proceeds through three progressive phases of premarketing human clinical testing.103

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97 The FDA’s IRB guidelines can be found at 21 C.F.R. §56.101 et seq., and are discussed in Chapter 5, Section II.A.
99 Id., §§312.23(a)(1)–(5). See also id., §312.22 (“The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies.”).
100 Id., §12, §312.23(a)(6).
101 Id. §312.30.
102 21 C.F.R. §312.40; see also 21 C.F.R. §312.20(a) (2004) (stating that “[a] sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug”).
103 In addition to statutory requirements and policies, the FDA publishes both “guidance documents” and “points to consider documents.” International research guidelines are increasingly relevant.
c. Post-Approval of the IND—Phase I through III Clinical Trials

Once approved, the “investigational new drug for which an IND application is in effect . . . is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.” 104 However, the packaging of an IND intended for human use must bear a label with the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” 105

The study sponsor is responsible for the prompt review of all information relevant to the safety of the drug and must notify the FDA and all participating investigators of any adverse experience associated with the use of the drug that is both serious and unexpected, and of any finding from tests in laboratory animals that suggests a significant risk for human subjects. 106 The sponsor must also submit annual progress reports to the FDA. 107

The filing of the IND also represents the applicant’s request to begin the conduct of human studies through designated clinical investigators. Phase I clinical trials may commence subsequent to FDA approval of the IND. Phase I clinical trials seek to establish the safety of a new drug, including the safe dosage range, and represent the first administration of a potential drug to a small test population of adults. Phase I trials typically involve approximately 20 to 100 normal, healthy volunteers. These trials generally occur over a period of several months.

In Phase I, the purpose of the trial is to determine the appropriate dosage, produce information about potential side effects, and ensure that the drug is generally safe for use in humans. Phase I testing involves a determination of basic metabolic, basic pharmacologic, and toxicologic properties of the IND in humans, with an emphasis on dose ranges and tolerance and metabolism (absorption, distribution, elimination, and excretion) of the compound as well as preliminary data regarding effectiveness of the drug in humans. 108 Given the nature of Phase I studies, a large majority are open-label studies, not blinded or controlled. Furthermore, it is increasingly recognized that intraspecies variability in the response of individuals to a drug is affected by factors such as race, gender, genetics, lifestyle, disease processes, and prior drug exposures. If problems in human toleration of the drug are detected, or if subjects exhibit otherwise unexplained adverse effects that would limit the use of the drug, the trial is concluded and the drug studies are terminated at this stage. Approximately 70 percent of drugs tested successfully complete Phase I.

If significant adverse effects are not detected in Phase I testing, the process continues through Phase II clinical trials; conducted on a larger population of adults. Phase II trials constitute the initial evaluation of a drug’s therapeutic effectiveness and involve larger numbers, in the range of 100 to 300 volunteer patients, diagnosed with the specific medical condition. 109 Phase II trials represent more detailed randomized, controlled studies to determine the safety and effectiveness of the drug compared against placebos, existing

10421 C.F.R. §312.1.
105Id. §312.6.
107Id. §312.33.
108Id., §312.21(a)(1).
109Id., §312.21(b).
alternative drugs, or other accepted standard agents for comparison.\footnote{110} If during this phase the drug appears to safely produce the expected therapeutic effect, it continues to Phase III. About 33 percent of drugs successfully complete Phase II.

The final phase, Phase III, is designed to compare the experimental treatment against the standard treatment to evaluate all aspects of human consumption of the drug: its safety, dosage, and effectiveness. Phase III clinical trials assume that, although the new treatment may ultimately prove to be more effective than the existing treatment, both are equally effective until proven otherwise. This null hypothesis is termed “equipoise” by researchers.

To be effective, Phase III clinical trials are large-scale (possibly thousands of patients), can last anywhere from one to four years, and provide information on safety and effectiveness important to the risk-benefit analysis of a drug.\footnote{111} This phase of clinical trials involves a large test population of patients afflicted with the condition of interest.\footnote{112} To establish efficacy and safety, clinical trials must be large and conducted at multiple centers. The gold standard is the multi-institutional double-blind placebo controlled randomized clinical trial.

In Phase III testing, adverse drug reactions and interactions of drugs are closely monitored and documented, and immediately reported to the FDA. These studies provide a basis for establishing the drug’s effectiveness for specific indications, calculating the overall risk-benefit relationship of the drug, verifying dosage range, identifying the best means of administering the drug for its intended effect, and determining the proper drug labeling information. About 25 to 33 percent of drugs successfully complete Phase III.

Once a drug has successfully completed\footnote{113} at least one adequate and well-controlled Phase III clinical trial,\footnote{114} an NDA may be submitted to the FDA for final approval.\footnote{115}

3. **Stage 3: The New Drug Application Process**

   a. **Background**

   The NDA process follows completion of appropriate clinical trials pursuant to an IND. An NDA is submitted by a sponsor.\footnote{116}
An NDA must contain:

1. Full reports of studies to show whether or not such drug is safe and whether it is effective;
2. A full list of the ingredients of the drug;
3. A full statement of the composition of the drug;
4. A full description of the “methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug”; and
5. Samples of the drug and of the articles used as components such as the Secretary may require.

In addition, the FDA requires an NDA sponsor to demonstrate that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality, and purity. The NDA may be submitted electronically, and manufacturers are required to pay fees to the FDA for the evaluation of NDAs and supplemental applications.

If the FDA approves the NDA, it publishes the drug and the patent information in Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book). Holders of approved NDAs are required to disclose all patents that they believe would be infringed by unauthorized sales of the approved drug. Thus, the NDA applicant must also file with the application “the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.”

The entire NDA process may last five to seven years, but there is a trend toward a more rapid approval of drugs than either biologics or implanted medical devices. In addition, a faster approval is possible for a “priority counter-

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Id. Debarment of a person other than an individual under 21 U.S.C. §355(a)(1) will be between one and 10 years, but subsequent debarment from the FDA program within 10 years of a first conviction will result in permanent exclusion from the NDA program. Id. §335(a)(C)(2)(a).

117 Id. §355(b)(1)(D).
118 Id. §355(b)(1).
119 Id. §§351(b), 351(h).
123 Applications for the approval of medical devices require the submission of an “investigational device exemption” (IDE). An important feature of the IDE is biocompatibility testing, which is necessary to assess the safety of a specific product material for sustained human contact. Devices
measure” drug or biological product that is determined to meet prioritization goals for approval fast tracking. In 1988, the FDA promulgated regulations to establish an expedited NDA process for certain types of drug therapies. Under this expedited approval system, qualifying drugs may reach the market after two, instead of three, phases of human clinical trials, although the FDA can demand post-approval studies to discover additional information about the drug’s safety and optimal use. “Fast track products” allow the sponsor and FDA to facilitate the development and expedite the review of a drug if that drug is intended to be marketed for the “treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition.” The drug sponsor may request fast track designation concurrently with, or at any time after, submission of an IND application under Section 505(i) (21 U.S.C. §355(i)) or Section 351(a)(3) of the Public Health Service Act (42 U.S.C. §262(a)(3)).

b. FDA Process for Evaluating NDAs

In 2015, the FDA established the Office of Pharmaceutical Quality (OPQ), which has the goal of standardizing and centralizing how drug quality is overseen by regulatory officials. All NDAs—both for new drugs and generic drugs—are now reviewed by OPQ.

Drug approval by the FDA is contingent on the demonstration of both safety and efficacy because the FDCA states: “no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.” Thus, the FDA approves new drugs for introduction or delivery into interstate commerce when the sponsor has supplied to the FDA data from “adequate and well-controlled” studies that provide “substantial evidence” of the safety of the drug and its effectiveness of the medication for the conditions for which it is intended to be prescribed, recommended, or suggested in the product’s proposed labeling, and also provide adequate scientific evidence that the drug is safe for use under the conditions under which it is to be used.

applications may be further subclassified into as “nonsignificant risk” (NSR) devices, which allow clinical studies to proceed under an abbreviated IDE. Under the abbreviated IDE, IRB approval and informed consent are required; however, FDA approval of an IDE application is not required.
The FDA interprets the substantial evidence requirement to mean that at least two adequate and well-controlled studies have been completed. It considers uncontrolled clinical studies to represent merely corroborating evidence.\textsuperscript{133} The substantial evidence requirement also includes “the conclusion of Congress, based upon hearings, that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy.”\textsuperscript{134} Clinical investigations must therefore be performed “by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”\textsuperscript{135} Furthermore, the “adequate and well-controlled” studies must include data from both animal (preclinical) studies and human (clinical) studies.\textsuperscript{136}

With respect to a drug’s “safety,” the FDCA requires that the FDA prevent any marketing of any drug or device if the potential for inflicting death or physical injury is not clearly offset by the possibility of therapeutic benefit.\textsuperscript{137} Examples of some presently available classes of medications with significant risk-benefit tradeoffs include:

1. Chemotherapeutic agents essential for treating cancer, which have the recognized associated side effects of suppressing the immune system and bone marrow as well as other end-organ toxicities;
2. Statins, which are clinically important in controlling serum cholesterol levels, but which have the potential for liver and muscle toxicities; and
3. Blood thinners, which are important in treating cardiovascular disorders and blood clots, but which also increase the risk for hemorrhage.

In general, the FDA may be more likely to approve a drug associated with higher risks if its potential benefits are substantial, for example, a drug that effectively treats a severe life-threatening disease or condition or a drug that is the only one available for that particular disease or condition.

In addition, the FDA has the authority to control certain aspects of the label, to enforce the requirement of truthful and nonmisleading label representations, and to ensure that the label contains adequate directions for use and appropriate safety warnings.”\textsuperscript{138} Thus, draft labeling must also be submitted to the FDA for review. Such labeling will necessarily describe the medical condition for which the drug is to be prescribed, instructions on use of the drug, warnings, and contraindications.\textsuperscript{139} Warnings about a drug’s side effects must also be included for intended use within the meaning of the Act only when that expert consensus is founded upon ‘substantial evidence’ as defined in §505(d).”).

\textsuperscript{133}21 C.F.R. §314.126 (2006).
\textsuperscript{134}Weinberger, 412 U.S. at 630.
\textsuperscript{136}Id. §355.
\textsuperscript{137}Id. §301.
\textsuperscript{138}See 21 U.S.C. §352(f) (2005) (requiring directions for use and warnings on labels in order not to be considered misbranded).
\textsuperscript{139}21 C.F.R. §314.50(e) (2006).
whenever there is “reasonable evidence” linking it to those side effects.140 At bottom, promotion of the drug can claim no more than the clinical effects established before the FDA, and must also include a summary of side effects and contraindications. The package insert that physically accompanies an FDA-approved product describes and determines the uses for which the product has been demonstrated to be safe and effective.141 In other words, the product’s labeling at the time of marketing approval only represents what is known about the drug’s risks and side effects based on the narrow parameters of existing data from completed clinical trials.

The FDA evaluates an NDA for approval within the statutorily required 180-day period142 if the application demonstrates the safety and effectiveness of the drug for its intended conditions of use. Specifically, within 180 days after the filing of the NDA, or such additional mutually agreed upon periods, the Secretary must either approve the application if none of the grounds for denying approval are found to exist or give the applicant notice of an opportunity for a hearing before the Secretary.143 If the opportunity for a hearing is accepted in writing within 30 days after notice of the hearing, it must be held not more than 90 days following the expiration of the 30 days unless the Secretary and the applicant otherwise agree.144 “If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6)145 do not apply, he or she shall issue an order approving the application.”146

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142The 180-day approval period can be extended by mutual agreement between the sponsor and the FDA, 21 C.F.R. §314.100.
145Clauses (1) to (6) state:
(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
(2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;
(3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;
(4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or
(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or
(6) the application failed to contain the patent information prescribed . . . .”
146Id. §355(d)(7).
c. FDA Standards for Denying an NDA

The FDA must refuse approval of a new drug if test results suggest or demonstrate that the drug is either unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions, or if there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Specifically, the FDCA requires the FDA to disapprove an NDA if:

1. The investigations, reports of which are required to be submitted to the Secretary . . . , do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
2. The results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;
3. Upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or
4. Evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or
5. Based on a fair evaluation of all material facts, such labeling is false or misleading . . . .

Appeals of FDA denials are possible. “[A]n order denying an NDA or withdrawing one is reviewable by the Court of Appeals, Section 505 (h); . . . and . . . an order that does not deny or withdraw an NDA is reviewable under the Administrative Procedure Act . . . .” Applicants may appeal an order of the Secretary, a refusal to approve, or the withdrawal of an existing approval of an NDA. The appeal must be filed in the U.S. Court of Appeal for the Circuit wherein the applicant resides or has his or her principal place of business, or it may be filed in the U.S. Court of Appeals for the District of Columbia Circuit.

d. Unique FDA Approval Procedures for Certain Drugs

There are several subsets of new drugs that are subject to unique FDA approval procedures. For example, a specific subset of FDA approval concerns drugs for rare diseases. The Orphan Drug Act of 1983 (ODA) intends to offset the key drug development constraints of cost and duration of the FDA approval process, as well as the issue of intellectual property protection. Orphan drug

development is limited, in part, by a general lack of knowledge about the pathophysiology of these diseases and the relative unavailability of subjects for clinical trials. The sponsor may seek orphan drug status at any phase of the R&D process before submitting an application for marketing approval. A sponsor seeks orphan status designation for a drug by (1) certifying that the product is for a rare condition, (2) providing a scientific rationale for using the drug for that rare condition, and (3) providing supporting epidemiologic data. The FDCA defines the term “rare disease or condition” to mean any disease or condition that affects fewer than 200,000 persons in the United States or affects more than 200,000 in the United States but for which there is no reasonable expectation that the cost of developing and marketing the drug in the United States will be recovered from sales revenue. The sponsor of a drug for a disease or condition that is rare may request written recommendations from the FDA for the “non-clinical and clinical investigations which must be conducted with the drug before (1) it may be approved for such disease or condition under section 505 [21 U.S.C. §355], or (2) if the drug is a biological product, it may be licensed for such disease or condition under section 351 of the Public Health Service Act [42 U.S.C. §262].

Congress enacted the ODA to encourage research and development of treatment for rare diseases, as the market for treatments of rare diseases, by nature, is not highly profitable. The ODA promotes innovation by reducing the development costs of orphan drugs before FDA approval and by increasing the financial returns from the orphan drugs after approval. The ODA provides for federal funding for research and clinical trials, beneficial tax credits, and the exclusive right to market a qualified drug for a limited period. The ODA also attempts to reduce development costs by streamlining FDA’s approval process for orphan drugs by providing tax breaks for expenses related to orphan drug development, authorizing the FDA to assist in funding the clinical testing necessary for approval of an orphan drug, and creating an Orphan Products Board to coordinate public and private development efforts.

The ODA also seeks to enhance the orphan drug manufacturer’s ability to recover its investment by granting the manufacturer seven years of exclusive marketing rights. The ODA’s market protection is narrow because only the

154 See 21 C.F.R. §316.23 (1999) (“(a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication. (b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.”).
158 Id. §360aa.
use of that particular drug for treating the designated rare disease is protected. 164 Although any NDA sponsor for an orphan drug may receive the development-phase benefits of the ODA, only the first manufacturer to receive full FDA drug approval receives the exclusive marketing rights for any one drug. 165 The FDA also bars other approvals for the “same drug” for the “same disease or condition” as a first-approved drug until the seven-year period of exclusivity expires. 166

On November 7, 2002, the Rare Diseases Act of 2002 and the Rare Diseases Orphan Product Development Act were signed into law. These acts established an Office of Rare Diseases within the NIH and authorized appropriations for Rare Disease Regional Centers of Excellence. 167 The FDA also maintains an Office of Orphan Products Development (OOPD) which “evaluates scientific and clinical data submissions from sponsors to identify and designate products as promising for rare diseases and to further advance scientific development of such promising medical products.” 168

Another specific subset of the FDA’s drug approval process concerns drugs that are specifically marketed for use in children. It is estimated that less than one-third of drugs that are used to treat children have been specifically tested or studied experimentally in the pediatric population. “Pediatric studies” are defined by the FDA to mean that at least one clinical investigation (which may include pharmacokinetic studies) has been performed in patients who fall into pediatric age groups (may include neonates) in whom the drug is to be used. 169 The FDA also has discretion to extrapolate pediatric effectiveness from adequate and well-controlled adult studies, although this usually requires supplementation with other information such as pharmacokinetic studies obtained from pediatric patients. 170 Studies can also be extrapolated between pediatric age groups. 171

In general, pediatric studies may include studies of new active ingredient(s), new indication(s), new dosage form(s), new dosing regimen(s), or new route(s) of administration, 172 or studies “to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and . . . to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.” 173 The majority of information regarding safety and efficacy for the

165 See 21 C.F.R. §316.31 (“After approval of a sponsor’s marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan-drug designation was granted, FDA will not approve another sponsor’s marketing application for the same drug before the expiration of 7 years from the date of such approval . . . .”).
169 Id. §355a(a); see also FDA, GUIDANCE FOR INDUSTRY: QUALIFYING FOR PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT (1999).
171 Id. §355c(a)(2)(B)(ii).
173 Id. §§355c(a)(2)(A)(i)–(ii).
pediatric utility of currently marketed drugs is insufficient or absent and the younger the age group, the more likely the lack of information.\footnote{174}

The Pediatric Exclusivity Section of the 1997 FDAMA includes incentive-based legislation regarding pediatric clinical studies, and FDAMA added a provision for six months of exclusivity in return for performing pediatric clinical trials.\footnote{175} Notably, the six-month pediatric exclusivity extension also applies if the pediatric trials are conducted for an “orphan drug.”\footnote{176} This six-month period of exclusivity is not contingent upon approval of the drug as safe and effective in children and is not limited to pediatric use of the drug. It simply extends any existing market exclusivity held by the submitter, whether under a patent, the Orphan Drug Act, or Hatch-Waxman exclusivity provisions, and thus it further defers the time during which when the FDA might approve a competing generic product.\footnote{177}

Finally, sponsors who represent the only manufacturer of a drug that is life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition must notify the FDA at least six months prior to the date of a planned discontinuance or withdrawal from market.\footnote{178}

4. When an Abbreviated New Drug Application Is Required

Congress, through the Hatch-Waxman Act (which significantly altered sections of both the FDCA and the Patent Act), allowed the FDA to proceed with a faster, less expensive drug approval for certain drugs through the Abbreviated New Drug Application (ANDA) process.\footnote{179} The ANDA process applies to generic drugs, which contain the identical active ingredients as a “listed drug” or “pioneer drug” that has received prior FDA approval either under Section 355(a) based on safety and effectiveness, or under Section 355(j).\footnote{180} This section discusses in detail the ANDA process.

\footnote{174}{FDA, Pediatric Exclusivity Provision: Status Report to Congress (2001).}
\footnote{175}{21 U.S.C. §355a(b)(1)(A) (2005) (“(i) the period referred to in subsection (c)(3)(D)(ii) of section 505 [21 U.S.C. §355(c)(3)(D)(ii)], and in subsection (j)(5)(f)(ii) of such section, is deemed to be five years and six months rather than five years, and the references in subsections (c)(3)(D)(ii) and (j)(5)(f)(ii) of such section to four years, to forty-eight months, and to seven and one-half years are deemed to be four years and one-half years, fifty-four months, and eight years, respectively; or (ii) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(D) of such section, and in clauses (iii) and (iv) of subsection (j)(5)(f) of such section, is deemed to be three years and six months rather than three years.”).}
\footnote{176}{Id. §355a(b)(1)(B) (“[I]f the drug is designated under section 526 [21 U.S.C. §360bb] for a rare disease or condition, the period referred to in section 527(a) [21 U.S.C. §360cc(a)] is deemed to be seven years and six months rather than seven years”).}
\footnote{177}{Id. §355a.}
\footnote{178}{Id. §355c(a).}
\footnote{179}{21 U.S.C. §355(j).}
\footnote{180}{Id. §§355(a), 355(j). See also Abbreviated New Drug Application Regulations, Final Rule, 57 Fed. Reg. 17,953 (Apr. 28, 1992) (defining “listed drug status” as evidenced by the drug’s inclusion in the current edition of FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations”).}
a. Patent Law Protection and ANDAs

In the United States, brand-name pharmaceuticals are protected by patent laws. Intellectual property rights and the associated profit potential are important drivers of innovation in the pharmaceutical and biotechnology industries. Title 35 U.S.C. dictates that "whoever without authority makes, uses, offers to sell, or sells any patented invention . . . during the term of the patent . . . infringes the patent." The increased duration and complexity of the new drug approval regulatory process has not surprisingly increased the costs of bringing new drugs to market—which has also increased the importance of patent protection.

The patent system is designed to enable those who invest in the development of new technology to protect and recapture economic returns on their investment by conferring protection from competitors. The Patent Act provides for a 17-year statutory term of marketing exclusivity from the date of patent issuance. However, in practical terms, pharmaceutical manufacturers must file a patent application as soon as a substance with potentially therapeutic activity is identified and, therefore, the actual protective life of a new drug’s patent may be much shorter if the patent is issued prior to the drug’s approval by the FDA. The scope of patent protection may extend to the following:

1. The discovery of the existence of a substance or compound;
2. The method of manufacture or purification; and
3. Under some circumstances, the nature of its properties and its therapeutic applications.

Patent protection is the primary defense available to pioneer pharmaceutical companies to prevent the forfeiture of research and development investments to market competitors or new market entrants. The effective patent life of a new drug is defined as the elapsed time between FDA approval and the expiration of the last patent provision that effectively protects the drug from competition from bioequivalent generic products. The American Inventors Protection Act of 1999 (AIPA), passed by Congress on November 29, 1999, represents broad intellectual property protection for a range of drugs without focusing on discrete areas such as “orphan” or “pediatric” drugs. AIPA affects patent terms and is therefore a type of incentive-based legislation. Subtitle D of Appendix I of AIPA, the Patent Term Guarantee Act of 1999 (PTGA) applies to patent applications.

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181 Id. §271(a); see also Glaxo Group Ltd. v. Apotex, Inc., 272 F. Supp. 2d 772 (N.D. Ill. 2003) (“The plain wording of 35 U.S.C. §271(e)(2) provides that the submission of an application under 35 U.S.C. §355 of the Federal FDCA is an act of infringement if the purpose is to obtain approval to engage in the commercial manufacture, use, or sale of a drug claimed in a patent before the expiration of that patent.”).
184 See generally id.
185 See Monsanto Co. v. Rohm & Haas Co., 312 F. Supp. 778 (E.D. Pa. 1970) (holding a patent application to be invalid in view of similar properties of chemically related compounds); see also Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 341 F. Supp. 1303 (E.D.N.Y. 1972) (holding that patenting of uses alone was inconsistent with the intent of Congress to reward inventions).
filed on or after May 29, 2000. The PTGA provides for patent extensions to compensate for marketing delays that last longer than three years. Because the statutory patent term is 20 years from the date of filing, the PTGA extension guarantees most patents a minimum 17-year patent term. This extension also is available for some pharmaceutical patents. The average effective patent life for products other than pharmaceuticals is 18.5 years, but this is significantly shorter for pharmaceuticals—due in part to the lengthy testing and approval process that occurs after patent filing.

b. Hatch-Waxman Exceptions to Patent Infringement for Pharmaceuticals

To counter the effects of delay in the approval of generic drugs by the FDA, the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, was enacted on September 24, 1984. Before the enactment of Hatch-Waxman, a generic manufacturer could not begin making and testing a generic drug until after the brand-name manufacturer’s patent expired.

Title I of Hatch-Waxman therefore modified the FDCA to create the ANDA process for the purpose of increasing access to generic drugs at a lower cost to consumers and allowed generic drug firms to introduce equivalent copies of brand-name pioneer drugs to the marketplace without repeating expensive and lengthy clinical trials. Thus, Title I authorized the approval of duplicate versions of approved drug products under an ANDA procedure.

Title II of Hatch-Waxman was designed to benefit pioneer drug companies for the purpose of providing incentives for increased research and development of new drugs. To that end, Title II modified the Patent Code by providing both a safe harbor provision to the general prohibition against patent infringement and a patent term extension provision. Title II authorized the extension

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191Hatch-Waxman represented a legislative compromise attempting to balance the competing interests of promotion of innovation and discovery of new drugs while simultaneously encouraging development and market entry of lower-cost alternatives by establishing an abbreviated regulatory pathway. See AndrX Pharms., Inc. v. Biovail Corp., 276 F.3d 1368, 1371 (Fed. Cir. 2002).
194Drugs other than those reviewed and approved under §507 of the Act at 21 U.S.C. §357 (2005).
197Id.
198Id. §271(e)(1). The patent term extension provision is codified in 35 U.S.C. §156.
of patent terms for approved new drug products such as antibiotics and biologicals, some medical devices, food additives, and color additives.199

Hatch-Waxman also codified the experimental use infringement exemption200 that eliminated de facto patent term extension for brand-name drugs and specifically provided:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product . . .) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.201

Thus, Title II of Hatch-Waxman created a previously nonexistent exception to patent infringement,202 also known as the “Bolar Amendment” because it overruled Roche Products, Inc. v. Bolar Pharmaceutical Co.203 Roche held that a generic company’s use of a patented product for performing the bioequivalence testing required by the FDA constituted patent infringement.204 The safe harbor provision was intended to protect the manufacturers of generic drugs from claims of patent infringement while they were conducting research205 on an

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200 The Hatch-Waxman Act’s “experimental use” exception was based in part on the “experimental use” exception to patent infringement protection that originated in the 1813 decision of Whitemore v. Cutter, 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600), and permitted experimental use of protected material. The judicially created doctrine exempting experimental use from patent protection was based on the Court’s reasoning that “it could never have been the intention of the legislature to punish a man who constructed . . . a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.” Id. By 1861, the law was considered to be “well-settled . . . that an experiment with a patented article for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement [was] not an infringement of the rights of the patentee.” Poppenhusen v. Falke, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y. 1861) (No. 11,279).


202 Id. §271(e)(1) (“It shall not be an act of infringement to make, use, or sell a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs. . . .”).

203 733 F.2d 858 (Fed. Cir. 1984). Note that the federal circuit decided two similar cases in 1984: Roche Products, Inc. v. Bolar Pharmaceutical Co. and Paper Converting Machine Co. v. Magna-Graphics Corp., 745 F.2d 11 (Fed. Cir. 1984). In both cases, the court held that the commercial development by the defendant of a product that was patented by the plaintiff during the effective term of the patent constituted infringement. In Bolar, the product was a drug; in Magna-Graphics, the product was a machine. Hatch-Waxman specifically carved out a patent infringement exception for pharmaceuticals by overruling Bolar but not Magna-Graphics.

204 Plaintiff Roche, holder of the patent for flurazepam hydrochloride, the active ingredient in its prescription sleeping pill marketed under the brand name of Dalmane®, sued Bolar alleging patent infringement. Roche sought to enjoin Bolar from using a small quantity of flurazepam hydrochloride that it had obtained from a foreign manufacturer to conduct the tests and gather information required for FDA approval of generic flurazepam. The court held that Bolar’s intended use of the patented compound did not constitute patent infringement because the use was experimental and was de minimis.

205 The courts addressing the safe harbor provision limited the “uses” that are “solely” or “reasonably related” to FDA approval. For example, in Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991), Genentech was not found exempt from patent infringement because its experimentation was also related to the preparation of a patent application and the development of a process for commercial-scale production. In Intermedics, Inc. v. Ventri-
already patented product, research that would be reasonably and solely related in an effort to create an ANDA for a generic equivalent that would be marketable once the patent on the brand-name drug had expired. Through the enactment of the safe harbor provision, Congress overruled Roche’s holding that a generic drug developer’s use of a patented drug for FDA approval process constituted patent infringement. With a shortened FDA approval timeline and the Bolar Amendment’s testing exception to patent infringement, a generic manufacturer may obtain approval to market a generic version of an approved drug prior to all of the patents listed in the Orange Book expiring.

Because a patent holder cannot market its drug while awaiting approval, Hatch-Waxman also restored a portion of the patent term that had previously been regularly lost during the FDA approval process. Patent restoration limits the patent life extension and mandates that the maximum patent term may not exceed 14 years.

Congress added two more provisions for FDA-administered market exclusivity in the Hatch-Waxman Act of 1984, directing the FDA to award five years of market exclusivity for NCEs not previously approved by the FDA, and three years of exclusivity for making changes in a previously approved product that require conducting new clinical trials to win FDA approval. In other words, Hatch-Waxman made it possible for new pioneer drugs that were approved for the first time to be eligible for exclusivity market protection for a period of up to five years. The effect of Hatch-Waxman was to add a new section to the Patent Code providing for an extension of the statutory 17-year patent term to cover certain products, such as pharmaceuticals, that are subject to premarket

208Id. §156(c)(3). See also id. §271(e)(1) (“the extension is limited to a fourteen-year effective term”).
211Id. §355(j)(4)(D)(ii) (1988). In October 2014, the FDA published its final guidance for industry on the issue of New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf. The final guidance details the circumstances under which a fixed-combination drug (FCD) product may be entitled to five-year NCE exclusivity. In relevant part, the final guidance indicates that more FCDs may obtain five-year NCE exclusivity. It also appears that ANDA applicants will not even be able to submit an ANDA for an FCD enjoying NCE exclusivity until the five-year period expires, unless the ANDA was filed at the NCE-1 date with Paragraph IV certification.
approval to protect novel and nonobvious new indications for use or useful improvements\textsuperscript{212} within set limits.\textsuperscript{213}

To better protect the interests of manufacturers of pioneer drugs and encourage new drug innovation, the Hatch-Waxman Act allows pioneer patent holders to obtain an automatic 30-month stay against ANDA approval. Specifically, title 35 U.S.C. §156(a) states:

The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent if—

(1) the term of the patent has not expired before an application is submitted under subsection (d)(1) for its extension;

(2) the term of the patent has never been extended under subsection (e)(1) of this section;

(3) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);

(4) the product has been subject to a regulatory review period before its commercial marketing or use.

Also, Sections 505(c)(3)(D) and 505(j)(4)(D) of the FDCA contain “exclusivity provisions” which protect certain listed drugs, or certain changes in listed drugs, from generic copying for specified periods of time by placing a moratorium on the submission, or by delaying the effective date of approval, of ANDAs and 505(b)(2) applications for those listed drugs.\textsuperscript{214}

The major difference between an NDA and an ANDA is that the ANDA allows generic drug manufacturers to rely primarily on the scientific studies submitted in support of the NDA to support safety and effectiveness requirements. The ANDA applicant can substitute bioequivalence data for the extensive animal and human studies of safety and effectiveness that must accompany a full NDA.\textsuperscript{215} A drug is “bioequivalent” when the “rate and extent of absorption of the generic drug is not significantly different from the rate and extent of

\textsuperscript{213}Id. §156(c), 156(g)(6)(A)–(C).
\textsuperscript{214}Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338–39 (Oct. 3, 1994) (provide for “(1) A 10-year period of exclusivity for new chemical entities approved during the period January 1, 1982, to September 24, 1984, the date of enactment of the 1984 amendments; (2) a 5-year period of exclusivity for new chemical entities approved after September 24, 1984; (3) a 3-year period of exclusivity for drugs that are not new chemical entities approved after September 24, 1984, if the applicant submitted an application containing reports of new clinical investigations (other than bioavailability studies) essential to approval and conducted or sponsored by the applicant; (4) a 3-year period of exclusivity for certain changes made after September 24, 1984, if the applicant submitted a supplement containing reports of new clinical investigations (other than bioavailability studies) essential to approval and conducted or sponsored by the person submitting the application; and (5) a 2-year period of exclusivity for drugs that are not new chemical entities, or for certain changes made to already approved drug products, approved during the period January 1, 1982, to September 24, 1984.”).
\textsuperscript{215}Id., citing Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 675 (1990) (comparing 21 U.S.C. §355(j)(2)(A)(iv) with §355(b)(1)) (“It shall not be an act of infringement to make, use, or sell a patented invention solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacture, use, or sale of drugs.”); see id.
absorption of the listed drug when administered at the same dosage."\textsuperscript{216} Generic companies therefore save substantial money in research costs, and the costs associated with generic drug approval are significantly less than those associated with the NDA.

The ANDA permits an abbreviated application to be submitted because the scientific data for the compound and its active ingredients have previously been filed with and reviewed by the FDA during the initial NDA process. The ANDA applicant must demonstrate that the generic drug product has the same active ingredient, route of administration, dosage form and strength, and proposed labeling as the brand-name drug;\textsuperscript{217} the generic manufacturer must sufficiently demonstrate that the proposed generic drug is bioequivalent to the relevant brand-name product.\textsuperscript{218}

Title 21 U.S.C. §355(j) lists the requirements and 21 C.F.R. §314.71 defines the procedural process for submitting a supplement to an approved application. The ANDA must contain a showing that:

1. The conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for the previously approved drug as listed under paragraph (7); (requiring in effect that the application contain a certification of prior approval)
2. The active ingredient(s) of the new drug are the same as that of the listed drug;
3. The route of administration, the dosage form, and the strength of the new drug are identical to those of the listed drug;
4. The new drug is bioequivalent\textsuperscript{219} to the listed drug and the active ingredients of the new drug are of the same pharmacological or therapeutic

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\textsuperscript{216}See FTC, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (July 2002), available at http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf; see also 21 C.F.R. §320.1(e) (defining regulations for bioequivalence).
\textsuperscript{217}Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,343 (Oct. 3, 1994) (explaining the rule codified at 21 C.F.R. pt. 314). Exceptions to some of these requirements, for example, dosage form, may be obtained from the FDA.
\textsuperscript{219}See id. §355(j)(8)(A)(i) ("The term ‘bioavailability’ means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available online at the site of drug action."). However, note that under 21 U.S.C. §355(j)(8)(B), a drug is considered to be the bioequivalent of a listed drug if either (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Alternatively the Secretary may establish alternative, scientifically valid methods to show bioequivalence. Id., §355(j)(8)(C).\
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class as those of the listed drug so that the new drug can be expected to have the same therapeutic effect as the listed drug; and
5. The labeling proposed for the new drug is the same as the labeling approved for the listed drug except for those changes required because the new drug and the listed drug are produced or distributed by different manufacturers.

Once an ANDA application is approved, the generic drug may enter the market unless the patent holder asserts a patent infringement claim; however, the patent holder’s claim must be both timely and specific. In *Teva Pharmaceuticals USA v. Novartis Pharmaceuticals*, Teva, for example, a generic drug manufacturer, brought an action against patent owners Novartis, seeking a declaration that its drug did not infringe the owners’ patents. Novartis held an NDA for three strengths of the antiviral drug Famvir®, which had as an active ingredient the compound famciclovir. The existing Novartis patent would not expire until 2010, and the related therapeutic use patents would not expire until 2014–15. In 2004, Teva filed an ANDA with FDA for generic famciclovir tablets. Novartis brought an infringement suit against Teva on the basis of one patent alone and did not include in the action the related therapeutic use patents. After Novartis filed suit, Teva brought a declaratory judgment action on the four remaining method patents under 21 U.S.C. §355(j)(5)(C) and 35 U.S.C. §271(e)(5) to establish “patent certainty.”

The district court dismissed Teva’s declaratory judgment action requesting patent certainty. In doing so, the district court applied a two-pronged test requiring “both (1) an explicit threat or other action by the patentee which creates a reasonable apprehension on the part of the declaratory judgment plaintiff that it will face an infringement suit; and (2) present activity by the declaratory judgment plaintiff which could constitute infringement, or concrete steps taken with the intent to conduct such activity.” The U.S. Court of Appeals for the Federal Circuit reversed, relying on the decision in *MedImmune*, and stated that in “MedImmune, the Court disagreed with our ‘reasonable apprehension of imminent suit’ test and re-affirmed that the ‘actual controversy’ requirement in the Declaratory Judgment Act is the same as the ‘Cases’ and ‘Controversies’ requirement in Article III.” The appellate court held that “MedImmune applies

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220 *Id.* §355(j)(5)(B)(iii).
221 Title 21 U.S.C. §355(j)(5)(C) represents a 2003 amendment to the ANDA process. The statute is entitled “civil action to obtain patent certainty” and provides that if the patent or NDA holder fails to bring an infringement suit within 45 days after receiving notice of a paragraph IV certification, then the ANDA applicant may instead file a civil action for a declaratory judgment on the basis that the patent at issue either is invalid or will not be infringed by the drug for which the ANDA was submitted.
222 Title 35 U.S.C. §271(e)(5) is a 2003 amendment to the Patent Act which provides that in a civil action to obtain “patent certainty,” the federal courts “shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought . . . under §2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.”
223 *Teva Pharm., USA, Inc. v. Novartis Pharm. Corp.*, No. 05-2881, 2005 U.S. Dist. LEXIS 38649 at *10 (D.N.J. Dec. 12, 2005), rev’d by 482 F.3d 1330, 1339 (Fed. Cir. 2007).
224 *Id.* at *3.
226 *Teva Pharmas. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1339 (Fed. Cir. 2007).
to Teva’s declaratory judgment action and takes precedence over the district court’s application of *Pfizer*, which required Teva to show a single type of Article III injury-in-fact, ‘a reasonable apprehension of imminent suit.’"  

Therefore, under a totality of the circumstances analysis, the court determined that Teva had suffered an injury-in-fact due to the legal uncertainty that arose from Novartis’ single patent claim. The court opined that:

Congress created the ANDA declaratory judgment action for generic drug companies specifically to avoid the type of legal uncertainty that Novartis has created. The legislative history of the ANDA declaratory judgment amendment explicitly states that the “uncertainty” caused by a brand-name company when it chooses to sue on only selective patents submitted in a single ANDA is an injury sufficient to support a justiciable controversy . . . .

By its action, Novartis is insulating its Famvir (R) Orange Book patents from any challenge of invalidity or non-infringement until all the patents expire. This threat of protracted litigation creates a present and real harm that is a relevant circumstance in finding whether a justiciable controversy exists.  

When submitting an ANDA an applicant must make one of four certifications (paragraph I–IV certifications) for each patent listed in the Orange Book:

1. Paragraph I applies if the brand-name company has not filed the required patent information for the drug product that is the subject of the ANDA with the FDA, that is, patents are not listed in the Orange Book;  
2. Paragraph II applies for patent(s) listed in the Orange Book that have expired;  
3. Paragraph III applies if the patent on the brand-name product has not yet expired but will expire on a stated date and the generic manufacturer does not seek approval to market before that date; or  
4. Paragraph IV applies if the patent held by the brand-name drug manufacturer is invalid or will otherwise not be infringed by the manufacture, use, or sale of the drug for which the ANDA applicant seeks approval.  

Certifications under Paragraph I or II normally cause no delay in approval of an ANDA. A Paragraph III certification can be approved only on or after the date of existing patent expiration. Paragraphs I–III do not create causes of action because the FDA can easily determine whether a patent has been submitted or when a patent expires.

In contrast, a Paragraph IV certification is a technical act of infringement outside the scope of FDA review but subject to jurisdiction in federal court. This “Paragraph IV” certification by a generic drug manufacturer implicates two

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227 *Id.*
228 *Id.* at 1345.
233 *Id.* §355(j)(5)(B)(i).
234 *Id.* §355(j)(5)(B)(ii).
provisions of Hatch-Waxman; the 30-month stay and the 180-day marketing exclusivity period.

Under the 30-month stay provision, the ANDA filer is required to provide notice to the patent holder and the NDA holder, including a detailed factual and legal analysis of why the patent is not infringed or is invalid. Either may then sue for patent infringement. If the patent holder or the NDA filer do not bring suit within 45 days of notice, the FDA may approve an ANDA based on Paragraph IV certification without regard to the 30-month stay. If the patent or NDA holder duly files suit, the FDA automatically stays approval of the ANDA for 30 months until the earliest of the following events:

1. The date the patent or patents expire;
2. A final determination of noninfringement or patent invalidity by a court in the patent litigation; or
3. The expiration of 30 months from the receipt of notice of the above referenced certification.

If a 30-month stay has already begun when a new patent is listed, the generic drug manufacturers must recertify the new listing. At this point the brand-name drug manufacturer has 45 days to sue for patent infringement on this newly listed patent but does not receive the benefit of a new 30-month stay.

In 2003, the FDA released a final rule amending Hatch-Waxman in response to an ongoing Federal Trade Commission (FTC) study on the effect of Hatch-Waxman on generic drug entry into the market and comments received on a proposed rule. The final rule affected five aspects of Hatch-Waxman implementation regulations. The final rule:

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235 Id. §355(j)(2)(B)(i) (“An applicant who makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give the notice required by clause (ii) to: I. each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and II., the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.”).
236 Id. §355(j)(5)(B)(ii).
243 Abbreviated new drug applications certifying that patent claiming drug is invalid or will not be infringed; patent listing requirements and 30-month stays, 67 Fed. Reg. 65,448 (Oct. 24, 2002).
244 See 68 Fed. Reg. at 36,697.
1. Clarified which patents required listing in the Orange Book and which patents did not;\(^{245}\)
2. Ensured that only one 30-month stay is to be allowed per ANDA;\(^{246}\)
3. Changed patent declaration forms required when submitting or holding an NDA;\(^{247}\)
4. Modified the “statement used to describe the fact that the NDA applicant or holder believes there are no relevant patents to be submitted”;\(^{248}\) and
5. Comported with the proposed rule in that it did not affect the 180-day exclusivity period enjoyed by the first ANDA holder.\(^{249}\)

The 2003 rule\(^{250}\) reinforced the original intent of Hatch-Waxman by specifically allowing only one 30-month stay of generic approval for each brand-name drug, while also avoiding manipulation by ANDA filers. The new regulation also limited abuse of the Orange Book patent filing system by clarifying the types of patents that must be listed. However, the FDA refused to provide a definitive administrative process to review the appropriateness of Orange Book patent filings, reasoning that “[a]n administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside [FDA] expertise and . . . authority.”\(^{251}\)

Under the 180-day marketing exclusivity provision, the first generic applicant who submits a “substantially complete” ANDA with a Paragraph IV certification to the FDA is entitled to 180 days of marketing exclusivity, during which time the FDA may not approve other ANDAs for the same pharmaceutical, unless there is a judgment finding the brand-name’s patent can be shown to be invalid or not infringed.\(^{252}\) This 180-day period of market exclusivity represents

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\(^{245}\)Id. This aspect of the final rule changed 21 C.F.R. §314.53(b). Under the new regulation, the NDA holder must submit patents that claim the “drug substance (active ingredient), the drug product (formulation and composition), and [a] method of use.” Id. Additionally, patents that claim a polymorph of the active ingredient of the drug substance described in the NDA “must be submitted if the applicant has test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.” Id. Next, method-of-use patents must only be submitted if they “claim indications or other conditions of use that are the subject of a pending or approved application.” Id. Finally, “information one patents claiming packaging, patents claiming metabolites, and patents claiming intermediates must not be submitted.” Id.

\(^{246}\)Id. at 36,695: “Eligibility for 180-day exclusivity will follow the same general principles as before implementation of this final rule. . . . We are not altering our interpretation of exclusivity in the final rule.”

\(^{247}\)Id. This change affects 21 C.F.R. §314.53(c)(1) and subsection (c)(2)(i). Id. This change is notable because of the adoption of more specific attestation statements that must be signed by the applicant. Id. at 36,686. A warning is also included that informs “the submitter that a willfully and knowingly false statement is a criminal offense under 18 U.S.C. §1001.” Id.

\(^{248}\)Id. This aspect of the regulation affects 21 C.F.R. §314.53(c)(3).

\(^{249}\)Id. at 36,695: “Eligibility for 180-day exclusivity will follow the same general principles as before implementation of this final rule. . . . We are not altering our interpretation of exclusivity in the final rule.”

\(^{250}\)Id. at 36,676.

\(^{251}\)Id. at 36,683.

significant financial incentive for the first generic company to challenge an approved propriety drug’s patent, even where subsequent generic manufacturers will be able to follow at reduced cost.

However, the 180-day exclusivity period is forfeited if the first applicant fails to market the drug either within 75 days after the date on which the approval of the application of the first applicant is made effective or within 30 months after the date of submission of the application of the first applicant. The Secretary is authorized to:

[W]ithdraw approval of an abbreviated drug application if the Secretary finds that the approval was obtained, expedited, or otherwise facilitated through bribery, payment of an illegal gratuity, or fraud or material false statement, and (2) may withdraw approval of an abbreviated drug application if the Secretary finds that the applicant has repeatedly demonstrated a lack of ability to produce the drug for which the application was submitted in accordance with the formulations or manufacturing practice set forth in the abbreviated drug application and has introduced, or attempted to introduce, such adulterated or misbranded drug into commerce.

c. FTC Regulation of ANDA-Related Activities

The FTC Act of 1914 empowers the FTC to investigate and, where necessary, prohibit unfair methods of competition affecting commerce, thereby protecting consumers against unfair practices and anticompetitive conduct such as collusion, monopolization, and unlawful restraint of trade.

Over the last several years, the FTC has taken particular interest in settlement agreements entered into between generic drug manufacturers and brand-name manufacturers in the context of the patent infringement suits described above. These settlement agreements, referred to as “reverse payment” agreements, involve the brand-name drug manufacturer paying the generic drug manufacturer in ANDA patent litigation to refrain from marketing the generic version of a drug for a specified period of time. Several courts have analyzed whether these types of agreements are anticompetitive and per se unlawful restraints on trade.

On June 17, 2013, the United States Supreme Court weighed in with its opinion in FTC v. Actavis, Inc. In Actavis, Inc., the FTC filed an antitrust complaint against a brand-name manufacturer of AndroGel, alleging that the manufacturer’s reverse payment settlement agreements with certain generic drug manufacturers were unlawful agreements not to compete in violation of the FTC

253 Id. §355(j)(5)(D).
254 Id. §335c(a).
256 See, e.g., In re Cardizem CD Antitrust Litig., 105 F. Supp. 2d 682, 691 (E.D. Mich. 2000); Valley Drug Co. v. Geneva Pharm., 344 F.3d 1294, 1294 (11th Cir. 2003); In re Ciprofloxacin Hydrochloride Antitrust Litig., 544 F.3d 1323 (Fed. Cir. 2008); In re Tamoxifen Citrate Antitrust Litig., 466 F.3d 187 (2d Cir. 2006); Andrx Pharms. Inc. v. Elan Corp., 421 F.3d 1227 (11th Cir. 2005); Schering-Plough Corp. v. FTC, 402 F.3d 1056 (11th Cir. 2005); In re K-Dur Antitrust Litig., 686 F.3d 197 (3d Cir. 2012).
257 133 S. Ct. 2223 (2013).
Act. The Eleventh Circuit dismissed the FTC’s complaint, and the United States Supreme Court reversed, finding that while reverse payment settlement agreements are not per se lawful, although in some instances they may violate antitrust laws. Specifically, the Court held that:

[A] reverse payment, where large and unjustified, can bring with it the risk of significant anticompetitive effects; one who makes such a payment may be unable to explain and to justify it; such a firm or individual may well possess market power derived from the patent; a court, by examining the size of the payment, may well be able to assess its likely anticompetitive effects along with its potential justifications without litigating the validity of the patent; and parties may well find ways to settle patent disputes without the use of reverse payments.

5. How the Supplemental New Drug Application Process Operates

Following FDA approval, any changes in particulars as described by the NDA or ANDA must be further approved by the FDA by the filing of a Supplemental NDA (sNDA) or Supplemental ANDA (sANDA).

A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

The purpose of the sNDA is to “validate . . . the effects of the change [in manufacturing] on the identity, strength, quality, purity, and potency of the drug as [they] may relate to the safety or effectiveness of the drug.”

The sNDA and sANDA approval processes are intended to maximally protect the public against material changes to a drug, the manufacturing process, or drug labeling that may adversely affect the drug’s safety or effectiveness. For example, a sponsor seeking to obtain FDA approval for an additional use of a previously approved drug must submit a supplemental application (either an sNDA or a Supplemental Biologics License Application (sBLA)) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication.

Failure to file the sNDA or sANDA required by FDA regulations or failure to obtain necessary FDA approval before a “modified drug” is introduced into the market may result in the punitive withdrawal of the approved original NDA or sNDA.

259Id. at 2227.
260Id. at 2237.
262Id. §§314.70(b)(1); 314.70(c) (for a more complete listing of the permissible and nonpermissible changes that may be made and the indications for sNDA or sANDA filings).
263Id. §356a(b).
264See 21 C.F.R. §314.70 (for drugs) and §601.12 (for biologics).
The sNDA is also a mechanism to change a drug’s status from prescription to OTC status or to make changes in its labeling.\(^\text{265}\) 21 C.F.R. §314.8(d) provides that changes to the following be implemented as expeditiously as possible: “(1) The addition to package labeling, promotional labeling, and prescription drug advertising of additional warning, contraindication, side-effect, and precaution information; (2) The deletion from package labeling, promotional labeling, and drug advertising of false, misleading, or unsupported indications for use of claims for effectiveness.”\(^\text{266}\)

The sNDA can also potentially be used to extend patent life for three years (under Hatch-Waxman). The three-year period of exclusivity for sNDAs begins with the approval date of the sNDA.

C. The Approval Process for Human Biologics

Until the end of the nineteenth century, Congress had only limited involvement in the national regulatory schemes for biologics. One such regulatory statute was the Vaccine Act of 1813.\(^\text{267}\) The intent of the Vaccine Act was to provide for a public supply of smallpox vaccine. The U.S. Postal Service was an integral component of the Vaccine Act, as citizens could apply to receive a vaccine only at a Post Office, which was obligated to assist the vaccine agent in the distribution of vaccine by mail. Although the Vaccine Act was repealed in 1822, it was not until the 1890s that the federal government again became involved in vaccination science and policy, instructing state and local officials in methods of producing vaccines and antitoxins.

Concurrent with a rising demand for treatments for the major nineteenth-century diseases, private entities began to manufacture vaccines and antitoxins. In the early 1800s, counterfeit smallpox vaccine was distributed. Also, instances of contamination of commercial products became a recognized problem. Outbreaks of tetanus occurred via contamination of diphtheria antitoxin in the late 1890s and contamination of smallpox vaccine in 1901.\(^\text{268}\)

The federal government has had the authority to regulate biological products for medical use since the passage of the Biologics Act in 1902,\(^\text{269}\) when the purity of diphtheria vaccine was at issue. The Biologics Act exerted jurisdiction over “viruses, therapeutic serums, toxins, anti-toxins, or analogous products” as “biologics” that were intended for the “prevention, and cure of diseases of man.” This authority was expanded subsequently with the passage of the Public Health Service Act of 1912 (PHSA)\(^\text{270}\) and by the inclusion of biologics in key provi-


\(^{267}\) Available at http://biotech.law.lsu.edu/cases/vaccines/vac_act_1813.pdf.


\(^{269}\) Pub. L. No. 57-244, 32 Stat. 728 (1902).

sions of the federal FDCA. Biologics refer to structurally complex molecular entities that are often created by recombinant deoxyribonucleic acid (DNA) technology. The FDCA definition of a drug is in fact sufficiently broad as to encompass most biologics. The Biologics Act was revised in 1944 as part of the PHSA and provided for mandatory product licensure and also specified the criteria for the issuance of license approvals. In the 1960s, case-by-case adjudication was used to regulate blood-related biologics, such as packed cells and plasma proteins.

A biologic is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsenic or derivative of arsenic (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Designation of a product “biologic” infers a status or classification that triggers protective measures that require extensive testing and analysis prior to human clinical trials. The safety of biologics is a key concern and, therefore, the human testing process is subject to close regulatory oversight.

The Center for Biologics Evaluation and Research (CBER) reviews the safety and efficacy of biologics, monitors clinical testing of biological products, establishes product standards, conducts some specialized research, and administers the licensing of blood banks and vaccine manufacturers. In 2003, the FDA

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274Public Health Service Act, ch. 373, 351, 58 Stat. 682, 702 (1944) (current version at 42 U.S.C. §262 (2005)).
275See United States v. Steinschreiber, 219 F. Supp. 373, 383 (S.D.N.Y. 1963) ("[T]he activity of the defendants in the processing and drying of liquid blood plasma and in performing steps necessary to prepare the dried plasma for ultimate use falls within the statute" and therefore is subject to biologics regulations). See also Blank v. United States, 400 F.2d 302 (5th Cir. 1968) ("The court considered whether as a matter of statutory construction citrated whole blood and packed red blood cells were analogous products to a therapeutic serum. At the time of §262’s predecessor, the process of blood transfusion was unknown and Congress could not have intended to include citrated whole blood or packed red blood cells within the term ‘analogous product’ in the statute. The court determined that the products named in the indictment were not within the terms of §262.").
27621 C.F.R. §600.3(i). See also 42 U.S.C. §262(i).
278For example, in July 1995 the FDA published its Guidance Concerning Use of Pilot Facilities for the Development and Manufacture of Biological Products. This guidance document clearly stated that pilot facilities are eligible for licensure. Prior to this guidance, the agency position was that clinical trials must have been conducted with materials made in the facility that is intended to be licensed. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Availability, 60 Fed. Reg. 35,750 (July 11, 1995).
transferred some product oversight responsibilities from the CBER to the Center for Drug Evaluation and Research in order to facilitate coordination of scientific and regulatory activities between CBER and CDER, and to functionally provide increased efficiency, effectiveness, and a consistent review process. This transfer of review and approval responsibilities did not affect the applicable legal requirements for biologics approval. The Office of Therapeutics Research and Review (OTRR) oversees CDER’s Office of New Drugs: Office of Drug Evaluation VI and CDER’s Office of Pharmaceutical Science: Office of Biotechnology Products. Therapeutic biological products under CDER review include:

1. Monoclonal antibodies for in vivo use;
2. Cytokines, growth factors, enzymes, immunomodulators, and thrombolytics;
3. Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products; and

Biological products are regulated under the PHSA and require a biologics licensure application (BLA). Biologics that are drugs under 21 U.S.C. §331(g)(1) are subject jointly to Biologics Act and FDCA provisions, with the important exception that if a biologic is licensed, no NDA filing is necessary; however, biologics are subject to IND regulations.

The NDA route is available for FDA approval of all molecular entities, regardless of whether the FDA previously has considered the safety and effectiveness of that molecule; new biologics may similarly seek biologics licensing.

To qualify for a biologics license, a manufacturer must “submit an application to the Director . . . [of] CBER . . . [as well as] data derived from nonclinical laboratory and clinical studies . . . demonstrating that the manufactured product meets prescribed requirements of safety, purity, and potency.” Specifically, the BLA must contain, among other things:

1. A full description of manufacturing methods;
2. Data establishing stability of the product through the dating period;

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280 See Drug and Biological Product Consolidation, 68 Fed. Reg. 38,067–68 (June 26, 2003) (“As of June 30, 2003, responsibility for regulating most therapeutic biologics, with certain exceptions (e.g., cell and gene therapy products and therapeutic vaccines) will be transferred from the Office of Therapeutics Research and Review (OTRR), CBER, to the Office of New Drugs (OND), and the Office of Pharmaceutical Science (OPS), CDER.”).
282 See Biologics; Products Subject to License Control, id. §310.4(a).
284 See id. §610.4.
285 See id.
3. Sample(s) representative of the product for introduction or delivery for introduction into interstate commerce;
4. Summaries of results of tests performed on the lot(s) represented by the submitted sample(s);
5. Specimens of the labels, enclosures, and containers;
6. Any medication guide proposed in the use of the product; and
7. The address of each location involved in the manufacture of the biological product.286

Manufacturing and processing protocols as well as quality controls must also be detailed as part of a BLA and must be rigidly monitored as a means of ensuring that impurities, contaminants, or colonizing or mutant strains do not inoculate the biological products.287 All biotechnology products are thus rigorously characterized for identity, purity, stability, and potency.

The approval of generic biological products must be supported by a full data package, without reliance on the innovator’s safety and effectiveness data. 42 U.S.C. §262 addresses the FDA’s process for approval of biologics and states in relevant part that:

The Secretary shall approve a biologics license application (i) on the basis of a demonstration that: (I) the biological product that is the subject of the application is safe, pure, and potent; and (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and (ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application.288

Approval of the BLA depends on a demonstration of:
1. No microbial or viral contamination;
2. No endotoxin, exotoxins, or pyrogens; and
3. No nucleic acids (which were thought capable of delivering oncogenes and transforming the DNA of a potential patient).289

Manufacturers are required to test every lot of biological product and submit samples of every lot to the FDA for clearance for marketing.290

This current BLA process represents a streamlining of the biologics approval process, which previously consisted a two-part process with an ELA and PLA, and results from FDAMA.291 The FDA has further streamlined bio-

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286 Id.
288 42 U.S.C. §§262(a)(2)(I)-(II) (2005); see also 21 C.F.R. §601.2(d) (“Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products.”).
290 Tests Prior to Release Required for Each Lot, 21 C.F.R. §610.1; Requests for Samples and Protocols; Official Release, id. §610.2(a).
logics regulation by refining requirements for “well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products.” The “well-characterized” qualifier refers to:

1. Products with definable, measurable, and controllable identity, purity, impurities, potency/biological activity, and quantity;
2. Recombinant DNA biotechnology products with known amino acid sequence, known secondary structure (including disulfide bonds), and post-translational modifications (such as glycosylation); or
3. Monoclonal antibodies with an identity that could be determined by rigorous physicochemical and immunological tests without full knowledge of chemical structure.

Lot-by-lot release is not required for well-characterized biotechnology products. In 2010, Congress formally enacted the Biologics Price Competition and Innovation Act of 2009 (BPCIA) which provides a pathway for “biosimilars” to enter the market. The BPCIA is discussed more fully below.

D. FDA Postmarket Surveillance Program

The FDA’s authority over drugs does not stop after the drug is approved for manufacturing, distribution, and marketing. Specifically, the FDCA requires drug manufacturers to continuously monitor drug effects that are seen by physicians and patients after a drug is approved for marketing, including adverse drug events. An ADE that is not listed in the drug’s labeling for the drug product is defined to be an “unexpected adverse drug experience.”

Regulations define an ADE as:

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in

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293. Id. at 63,048–49.
294. Id. at 63,048.
295. PPACA, §7001 et seq., 124 Stat. at 804.
296. See Section II.B.1.
297. Id. §314.80. This is true for many reasons, including that premarketing human clinical studies have inherent limitations such as short duration, narrow subject population, and small sample size. For example, clinical trials during the NDA process rarely include special at-risk populations such as pregnant women or children. Timothy Brewer & Graham A. Colditz, Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs, 281 JAMA 824–29 (1999). Statistical analyses further suggest that, “in order to detect the difference between an adverse reaction incidence rate of 1/5000 and 1/10,000, approximately 306,000 patients would have to be observed.” Am. Med. Ass’n, Reporting Adverse Drug and Medical Device Events: Report of the AMA’s Council on Ethical and Judicial Affairs, 49 FOOD & DRUG L.J. 359, 360 (1994). Thus, because clinical trials typically involve fewer than 3,000 to 4,000 patients, Phase II and III studies will only detect adverse reactions that occur at a rate of 1 in 1,000 or higher. C. Anello & R.T. O’Neill, Does Research Synthesis Have a Place in Drug Regulatory Policy? Synopsis of Issues: Assessment of Safety and Postmarketing Surveillance, 13 CLIN. RES. REG. AFF. 13–21 (1996).
298. Id.
the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.\(^{299}\)

In turn, the FDCA defines “unexpected” in the context of an ADE to be “an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.”\(^{300}\)

ADEs can be divided into two broad categories: events that otherwise occur rarely in the population and events that represent an increased frequency over a relatively common rate in the general population. These two categories can be further subdivided into three groups based on the occurrence of the event relative to the use of the drug: those that occur shortly after initiation of drug use, those that occur with long-term use, and those that occur remotely after the drug has been discontinued. Both the frequency of the event, rare or relatively common, and the timing of the event relative to drug use influence the likelihood of detecting the ADE with different surveillance methods.\(^{301}\)

An ADE that places the patient at immediate risk of death is considered to be a “life threatening adverse drug experience.”\(^{302}\) An ADE at any dose that results in death, a life-threatening event, inpatient hospitalization or the prolongation of a hospitalization, a persistent significant disability/incapacity, or a congenital anomaly/birth defect is defined as a “serious ADE.”\(^{303}\)

ADE reports must be submitted to the FDA Division of Pharmacovigilance and Epidemiology.\(^{304}\) Postmarketing 15-day “alert reports” convey reports of adverse drug experiences using an FDA Form 3500A,\(^{305}\) or computer-generated FDA-1639,\(^{306}\) which must be submitted no later than 15 calendar days of initial receipt of the information by the sponsor and must be accompanied by a copy of the current labeling for the drug product.\(^{307}\) Manufacturers, packers, and distributors must maintain records of all reported adverse drug experiences for a period of 10 years.\(^{308}\)

Periodic adverse drug experience reports must also be submitted by drug sponsors to the FDA at quarterly intervals\(^{309}\) for three years from the date of

\(^{299}\) 21 C.F.R. §310.305(b).

\(^{300}\) Id.


\(^{302}\) 21 C.F.R. §310.305(b).

\(^{303}\) Id.

\(^{304}\) FDA Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

\(^{305}\) 21 C.F.R. §310.305(d).

\(^{306}\) Id. §310.305(d)(3).

\(^{307}\) Id. §310.305(c)(1).

\(^{308}\) Id. §310.305(f)(1); see also id. §314.80(i).

\(^{309}\) Id. §314.80(c)(2)(i) (“The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application.”).
approval of an NDA, and then at annual intervals. Each periodic report must contain (1) a narrative summary and analysis of the reported information and an analysis of all 15-day alert reports that have been submitted; (2) the FDA Form 3500A (adverse reaction report) for each adverse drug experience not reported; and (3) a history of actions taken because the last report. In addition, adverse reports within the scientific literature and medical journals or adverse results of formal clinical trials must be reported in the form of a 15-day alert. Reports must respect patient privacy and must not include the names and addresses of individual patients; instead, the each report must be identified by a unique code. The applicant should include the name of the reporter from whom the information was received; however, the names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not to be released to the public. Failure to comply with the adverse drug event reporting or record-keeping requirements is a ground for withdrawal of drug approval.

Following approval of an NDA, and perpetually thereafter, the FDA continues to monitor a drug’s safety. The FDA’s system for detecting post-approval toxicity includes the FDA Adverse Events Reporting System (FAERS), which gathers and analyzes adverse event and medication error reports submitted to the FDA. Postmarketing surveillance is mandated by the FDA and includes review of postmarketing clinical trial data, epidemiologic analyses of large numbers of ADEs, and review of voluntary case reports submitted to the AERS or the Manufacturers’ User and Device Experience (MAUDE). Post-approval monitoring detects problems that do not arise in the carefully controlled environment of premarket clinical trials. Once a drug becomes available for general use, a wide variety of patients with varying health conditions may take the drug, often in combination with other prescriptions. In particular, post-approval (Phase IV) studies can be useful for various purposes including:

1. Identifying and adjusting optimal dosage for the drug product;
2. Confirming the safety of the product and identifying new risks;

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310 See id. §314.80(c)(2)(i).
311 If preferred, on a CIOMS I form, per id. §310.305(f).
312 Id. §314.80(c)(2)(ii).
313 Id. §314.80(d).
314 Id. §314.80(h).
315 Id. §314.80(j).
3. Evaluating the product’s safety and efficacy in special populations such as pediatric or elderly patients; and
4. Discovering new uses for the product. $320$

Each year, the FDA receives several hundred thousand reports of possible adverse drug reactions, many of which are expedited reports that contain at least one even that is not described on a production’s labeling and for which the patient outcome is serious. $321$ ADEs may account for as many as 100,000 deaths annually. $322$

Where a potential problem is detected, a detailed follow-up analysis is performed. Clinical reviewers in CDER and CBER evaluate the FAERS reports to detect signal events regarding safety and to monitor drug safety. The FAERS reports can result in further epidemiological studies. Based on the FAERS, the FDA “may take regulatory actions to improve product safety and protect the public health, such as updating a product’s labeling information, sending out a ‘Dear Health Care Professional’ letter, or re-evaluating a prior drug approval decision.” $323$

The tort system is an additional source of information regarding ADEs.

ADE reports may result in requirements for changes in product labeling, “Dear Doctor” letters, bold-type warnings without boxes, further study by the manufacturer, or withdrawal of the product. $324$ ADEs that might cause death or serious injury may be required by the FDA to be placed in a prominently displayed box within the product labeling: the so-called black box.

A black-box warning represents the highest level of five possible warning categories found in the package insert. The black-box warning is generally assumed to be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. $325$ The FDA may not articulate the specific basis for the black box warning. $326$ The most serious warning placed in the labeling of a prescription medication, a black box warning can have serious ramifications for drug sales, marketing, and even the prescription


$324$Id.

$325$Food and Drugs: Labeling, 21 C.F.R. §201.

process. For example, the principles of informed consent require that a patient be informed of the risks of any recommended medication to aid them in deciding whether they are willing to assume the potential risks associated with a medication; this consent process is significantly more important with the use of drugs that have an associated black box warning. Black box warnings are prominently displayed in the Physicians’ Desk Reference to alert practitioners to serious risks. Advertisements that serve to remind health care professionals of a product’s availability (so-called reminder ads) are not allowed for products with black box warnings.327

Under 21 U.S.C. §355(e), the FDA may also withdraw an existing approval or immediately suspend approval “upon finding imminent hazard to public health.” Such action may be predicated on finding that:

1. “[C]linical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved”;

2. New evidence of clinical experience evaluated together with the evidence previously available shows that the drug is “not shown to be safe for use under the conditions of use upon the basis of which the application was approved”;

3. “[O]n the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, [. . .] there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof”, or

4. The patent information on which the NDA was based is either flawed or remains lacking.

Adverse events related to the use of vaccines are reported through a different mechanism; the Vaccine Adverse Event Reporting System (VAERS), a unified national system managed jointly by the FDA and the Centers for Disease Control and Prevention (CDC).331

As a result of withdrawal of certain drugs from the market,332 several additional postmarketing surveillance programs have been developed to run adjunct with and independently from FDA programs. For example, the Research on Adverse Drug Events and Reports (RADAR) project is funded independently of

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329Id. §355(e)(2).
330Id. §355(e)(3).
the pharmaceutical industry and its goals are to evaluate initial reports of previ-
ously unrecognized but serious ADEs, identify additional reports of each ADR, de-
velop hypotheses for mechanistic pathways, evaluate related laboratory and pathologic findings, derive reporting and incidence rate estimates, and identify new patient populations at high risk. Summary safety information is then synthesized into concise reports disseminated in medical journals, revised package inserts, and Dear Doctor letters, and is presented at medical conferences and at meetings with officials of the FDA, the relevant pharmaceutical manufacturers, and officials in the public sector who are evaluating pharmaceutical safety issues. The principal difference between RADAR and FDA surveillance is the greater frequency and timeliness of interactions between RADAR investigators and clinicians actively treating affected patients.

Finally, the FDA may require drugs with a significant abuse potential or with high risk to the patient to have a Risk Evaluation and Mitigation Strategy (REMS) to assure safe use.

E. Complying with FDCA Prohibitions Against Misbranding and Adulteration

In addition to complying with the FDA’s applicable drug approval process, drug manufacturers must comply with the FDCA’s prohibition against the misbranding or adulteration of drugs.

1. Background

The FDCA prohibits the:

1. “[I]ntroduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded”; 338
2. “[A]dulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce”; 339
3. “[R]eceipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise”; 340 and
4. “[I]ntroduction or delivery for introduction into interstate commerce of any article in violation of section 404, 505, or 564 [21 U.S.C. §§344, 355, or 360bbb-3].” 341

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335Id.
337Discussed more fully below at Section II.A.6.
33821 U.S.C. §331(a).
339Id. §331(b)(2).
340Id. §331(c).
341Id. §331(d).
Moreover, the “alteration, mutilation, destruction, obliteration, or removal of the wholesale or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded,” is prohibited. A drug is considered to be misbranded if:

- It has a false or misleading label;
- It lacks “a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count,” or
- “[A]ny word, statement, or other information required by or under authority of [the FDCA] to appear on the label or labeling is not prominently placed thereon,” or otherwise violates the specified labeling standards iterated in 21 U.S.C. §352.

Similarly, a drug is misbranded if it lacks appropriate and adequate directions for use, sufficient warnings regarding interactions and contraindications, or information regarding unsafe dosages, methods of administration, or duration of use on the label.

The term “label” means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of the FDCA that any word, statement, or other information appearing on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper. Each “package of a prescription drug . . . must contain or be accompanied by labeling setting forth information for its use.”

This labeling, commonly referred to as the “package insert,” provides information about the drug’s indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions. The requirements of 21 C.F.R. §201.100 apply to all prescription drugs, whether or not the drugs are subject to premarket approval by the FDA.

The FDA considers a product’s proposed labeling to be crucial in its determination of whether a drug is safe. Labeling is used to inform physicians (and consumers) about the drug’s uses and risks. FDA regulations therefore man-

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342 Id. §331(k).
343 Id. §352.
344 Id. §352(b).
345 Id. §352(c).
346 Id. §352(f).
349 See id. §201.56, 201.57 (regulations concerning the requirements for content and format of labeling for human prescription drugs); see also Purnell ex rel. Estate of Purnell v. United States, Case No. 86-4475, 1987 U.S. Dist. LEXIS 6237, *2–*3 (E.D. Pa. July 9, 1987).
date the format and content of all the labeling sections including “Contraindications,” “Warnings,” “Precautions,” and “Adverse Reactions.”351 The FDA details its product-specific labeling requirements to the manufacturer when it sends an “approvable” letter regarding the NDA.352 Approval of a new drug application is conditioned upon the NDA applicant incorporating the specified labeling changes exactly as directed by the FDA, and upon the applicant submitting to the FDA a copy of the final printed labeling prior to marketing.353 These requirements are viewed as consistent with a primary goal of Congress in enacting the FDCA: “to protect consumers from dangerous products.”354

FDA regulations permit a manufacturer to add or strengthen a contraindication, warning, precaution, or adverse reaction without prior approval.355 Similarly, a manufacturer is permitted to add or strengthen a statement about the potential for drug abuse, dependence, psychological effect, or overdosage without prior approval,356 or to add or strengthen labeling instructions regarding dosage and administration that are intended to increase the safe use of the drug without prior approval.357

The FDA’s position is that a manufacturer can, and should, provide stronger warnings as soon as such a warning is warranted. Furthermore, regulations require a manufacturer to issue a warning whenever there is reasonable evidence of an association of a serious hazard with a drug; this may occur in the absence of proof of a causal relationship.358

A drug is also considered to be adulterated if it:

• “[H]as been prepared, packed, or held under insanitary conditions”359 whereby “it may have been rendered injurious to health”;
• “[I]s a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess”360;
• “[I]s a compounded positron emission tomography drug and the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding do not conform to . . . standards”361

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351 21 C.F.R. §§201.56, 201.57.
352 Id. §314.110(a).
353 Id. §314.105(b).
355 21 C.F.R. §314.70(c)(6)(iii)(A).
356 Id. §314.70(c)(6)(iii)(B).
357 Id. §314.70(c)(6)(iii)(C).
358 Id. §201.57(e) (“The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.”).
359 Id. §351(a)(2)(A).
360 Id.
361 Id. §351(a)(2)(B).
362 Id. §351(a)(2)(C).
Statutory and Regulatory Controls for Drug Development

- Is in a container that “is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health”;
- “[B]ears or contains, for purposes of coloring only, a color additive which is unsafe” or “it is a color additive the intended use of which in or on drugs or devices is for purposes of coloring only and is unsafe.”

To ensure manufacturers’ compliance with these statutory requirements, the FDA has promulgated regulations concerning Current Good Manufacturing Practices (cGMPs). The guiding principles of cGMPs are (1) risk-based orientation, (2) science-based policies and standards, (3) integrated quality systems orientation, (4) international cooperation, and (5) public health protection. The FDA issues and regularly updates cGMP regulations for drugs, but the characteristics of these technology-based recommendations are necessarily such that the specifics must be continuously updated. Nonetheless, a failure to comply with the FDA’s cGMP guidelines means that a product is “adulterated.”

The FDA enforces cGMP violations through the use of inspections. It employs investigators who conduct both periodic and “for cause” inspections of manufacturers to monitor for compliance with cGMPs. In the commercial context, the courts “have relaxed the warrant clause of the Fourth Amendment to account for the exigencies of administrative inspections ‘designed to enforce regulatory statutes.’” One court has gone so far as to hold that:

[C]ertain industries have such a history of government oversight that no reasonable expectation of privacy . . . could exist for a proprietor over the stock of such an enterprise. . . . When a dealer chooses to engage in [a] pervasively regulated business and to accept a federal license, he does so with the knowledge that his business records [and stock] will be subject to effective inspection. . . . So significant is the necessity for effective inspection that in such “pervasively regulated” industries, the Court has dispensed with the need for a warrant at all.

2. FDA Enforcement Powers and Remedies

The FDA’s principal enforcement remedies for cases of noncompliance with its adulteration and misbranding provisions include inspections, in rem

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363 Id. §351(a)(3).
364 Id. §351(a)(4)(A); within the meaning of §721(a) (21 U.S.C. §379e(a)).
365 Id. §351(a)(4)(B); within the meaning of §721(a) (21 U.S.C. §379e(a)).
367 See 21 C.F.R. pt. 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General) and pt. 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals).
369 See id. §351(a).
370 See In re Establishment Inspection of Wedgewood Vill. Pharm., Inc., 270 F. Supp. 2d 525, 534 (D.N.J. 2003) (in the context of the FDCA, U.S. Courts of Appeals for the Sixth, Eighth, and Ninth Circuits “have found the pharmaceutical industry to be so ‘pervasively regulated’ that a warrantless search is permissible under the Fourth Amendment”) (internal citations omitted).
372 The FDA has issued guidance to industry on FDA inspections. For example, FDA, Guidance for Industry, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a
product seizures, injunctions, and referrals for criminal prosecutions. In certain circumstances, the FDA may also have appropriate cases filed in the federal courts through the Department of Justice.

To prosecute a violation based on adulteration or misbranding of a drug, the FDA must generally prove that (1) the products are drugs within the meaning of the FDCA; (2) the drugs are in fact adulterated or misbranded; and (3) the drugs have moved or may move in interstate commerce. Violations of Section 331 may be enforced by injunction. The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown to restrain violations of section 301 [21 U.S.C. §331], except paragraphs (h), (i), and (j), and in the case of a “violation of an injunction or restraining order issued under this section, which also constitutes a violation of this Act, trial shall be by the court, or, upon demand of the accused, by a jury.” Also, violators of 21 U.S.C. §331 (1) may be “imprisoned for not more than one year or fined not more than $1,000, or both” and (2) “if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000 or both.” However, before “any violation of this Act is reported by the Secretary to any U.S. attorney for institution of a criminal proceeding, the person against whom such proceeding is contemplated shall be given appropriate notice and an opportunity to present his views, either orally or in writing, with regard to such contemplated proceeding.”

Civil penalties are possible if the Secretary finds:

1. A false statement or misrepresentation of a material fact in connection with an abbreviated drug application;
2. Bribery or attempted bribery in connection with an abbreviated drug application;
3. Destruction, alteration, removal, or secretion, or procurement of the destruction, alteration, removal, or secretion, of any material document in connection with an abbreviated drug application;
4. Knowing failure to disclose a material fact which such person had an obligation to disclose relating to any drug subject to an abbreviated drug application;
5. Knowing obstruction of an investigation of HHS into any drug subject to an abbreviated drug application.

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376Id. §332.
377Id. §333.
378Id. §335.
380Id. §332(a).
381Id. §332(b).
382Id. §333(a)(1).
383Id. §333(a)(2).
384Id. §335.
385Id. §335b(a)(1).
In such cases, the person “shall be liable to the United States for a civil penalty for each such violation in an amount not to exceed $250,000 in the case of an individual and $1,000,000 in the case of any other person.”\textsuperscript{384} Enforcement actions remove or bar further domestic shipments, and also restrict entry of international shipments of affected products where applicable.\textsuperscript{385} The authority of the FDA to deny border entry to imported products that “appear” to be adulterated or misbranded\textsuperscript{386} has also been interpreted as authority to deny entry to products that have been produced in facilities (or in countries) that have denied FDA investigators the right of inspection. Noncompliant imports are detained at points of entry through a program of cooperation between the FDA and customs officials of the Department of the Treasury.\textsuperscript{387}

Compliance with FDA regulations is also frequently negotiated and occurs through voluntary actions by responsible manufacturers including product recalls, often with the FDA’s strong encouragement, in private or public forums. To assist, the FDA has issued guidelines that govern pharmaceutical product recalls.\textsuperscript{388}

F. FDA Oversight of Compounded Drugs

Compounded drugs are generally drugs that are “prepar[ed], mix[ed], assembl[ed], alter[ed], packag[ed], and label[ed] . . . in accordance with a licensed practitioner’s prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice.”\textsuperscript{389} Traditionally, the regulation of compounded drugs fell to the states and specifically, state boards of pharmacies. However, the FDA developed concerns in the 1990s that certain pharmacies were using their status as pharmacies to manufacture new drugs under the guise of compounding, and outside the scope of the NDA process.\textsuperscript{390} The FDA therefore developed a \textit{Compliance Policy Guide} (CPG) in 1992 concerning the FDA’s regulatory authority over compounded drugs,\textsuperscript{391} and that CPG was partially enacted into law as part of the
FDAMA. The FDA’s authority to regulate compounding pharmacies was quickly challenged, and debates over the existence and scope of the FDA’s authority over compounded drugs continued for years.

The debates concerning the FDA’s authority over compounding pharmacies culminated in the passage of the Drug Quality and Security Act (DQSA) on November 18, 2013. The DQSA establishes three primary changes to the FDA’s authority over compounding legislation. First, the DQSA creates a new regulated entity, Section 503B outsourcing facilities, that are permitted to engage in large-scale pharmacy compounding without a patient-specific prescription. Second, the DQSA resurrects Section 503A of the FDCA, which details the requirements that must be met for traditional compounding pharmacies to remain exempt from the FDCA’s new drug, adequate use for labeling, and cGMP requirements. Third, the DQSA establishes new criminal penalties for several categories of conduct prohibited under the Act, including reselling compounded drugs that are labeled “not for resale”; intentionally falsifying a prescription for a compounded drug; failing to report drugs or adverse events for an outsourcing facility; and using advertisements or promotions of compounded drugs that are false or misleading in any particular. Since the passage of the DQSA, FDA has implemented the DQSA by issuing various guidance documents on subjects concerning compounded drugs including the requirements under Section 503A, cGMP requirements for Section 503B facilities, and adverse event reporting requirements for Section 503B facilities.

**II. Significant Changes to FDA Authority to Regulate Drug Development and Marketing**

The FDA’s authority to regulate drug development and marketing has undergone substantial changes in recent years. The Food & Drug Administration Amendments Act of 2007 and the Patient Protection and Affordable Care Act are the two most recent of those changes, each of which is discussed in greater detail below.

**A. Food & Drug Administration Amendments Act of 2007**

The Food & Drug Administration Amendments Act of 2007 (FDAAA) was arguably the most important legislative development in U.S. food and drug law in decades. It addresses issues for which the FDA has been criticized: insufficient oversight and regulatory support. Although parts of the FDAAA extend and reaffirm previous programs with some modifications, other sections dra-
matically change the FDA’s regulatory authority. The FDAAA provides the FDA with new resources to monitor the safety of drugs, and authorizes and empowers the FDA to compel manufacturers to make labeling changes, and allows the FDA to require manufacturers to undertake postmarketing safety studies.

The FDAAA is divided into Titles I–X, addressed below, and further into subtitles and sections. The portions of the FDAAA relating to the FDA’s authority over the drug development process are discussed in greater detail below.

1. Title I—Prescription Drug User Fee Amendments of 2007 and Title II—Medical Device User Fee Amendments of 2007

The Prescription Drug User Fee Act of 1992 (PDUFA I) was signed into law on October 29, 1992. PDUFA I amended the FDCA to authorize the FDA to collect user fees with respect to “human drug applications, prescription drug establishments, and prescription drug products” and thereby supplement the review activity resources of the FDA by making those additional funds available for the review of drug applications. PDUFA was legislatively reauthorized in 1997 (PDUFA II) and 2002 (PDUFA III).

The FDAAA extended and reaffirmed PDUFA’s targeted fiscal budgetary requirements. The FDAAA amended FDCA Chapter VII by adding a new Section 736A, empowering the FDA to collect fees (“to generate revenue amounts of $6,250,000 for each of fiscal years 2008 through 2012”) deemed necessary to fund oversight (“advisory review”) operations of Direct-to-Consumer (DTC) advertisements.

In September 2011, the FDA issued a guidance addressing requests for waivers, refunds, and reductions of user fees under Sections 735 and 736 of the FDCA. The guidance describes the types of waivers and reductions, as well as the eligibility criteria and procedures for applying for a waiver or reduction. Waivers or reductions are available if necessary to protect the public health, if

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398Id. §505(o)(3), 121 Stat. at 923–24.
40021 U.S.C. §379(g) (2008) (note that PDUFA I was amended by PDUFA II).
40321 U.S.C. §§379g et seq.
404Id. §379h-1.
406“The term ‘advisory review’ means reviewing and providing advisory comments on DTC advertisements regarding compliance of a proposed advertisement with the requirements of this Act prior to its initial public dissemination.” See FDAAA, tit. I, §104(h)(1), 121 Stat. 823.
407“The term ‘direct-to-consumer television advertisement’ means an advertisement for a prescription drug product (as defined in section 735(3)) intended to be displayed on any television channel for less than 3 minutes.” See FDAAA, tit. I, §104(h)(4), 121 Stat. 823.
the assessment of the fee presents a significant barrier to innovation, or if the applicant is a small business submitting its first human drug application. Waivers or reductions may also be available if the fees imposed exceed the costs of conducting the human drug application process, although the guidance does not address that type of waiver. Several products are exempt from fees, including orphan-designated products, applications by state or federal agencies for drugs that are not distributed commercially, and applications or supplements withdrawn before any substantial work is performed on the application or supplement. Finally, the guidance describes the procedure for submitting requests for waivers, reductions, and refunds.409

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 was signed into law.410 The FDASIA included the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V),411 new provisions for the new Generic Drug User Fee Amendments of 2012 (GDUFA),412 and the Biosimilars User Fee Act of 2012 (BUFA).413 The GDUFA provides for (1) a one-time backlog fee, (2) a drug master file fee, (3) an ANDA and prior approval supplemental filing fee, (4) a generic drug facility fee, and (5) an active pharmaceutical ingredient facility fee. The FDA’s goal with the GDUFA is to enhance safety, access, and transparency of generic drugs. In August 2012, the FDA issued a draft guidance for industry on the application of the GDUFA.414 The draft guidance clarified the FDA’s current thinking on the application of the GDUFA and details industry requirements for backlog fees, drug master file fees, ANDA and prior approval supplement fees, facility fees, and other fee-related issues. In July 2014, FDA issued two additional guidances for industry on GDUFA and that relate to Prior Approval Supplements Under GDUFA and Amendments and Easily Correctable Deficiencies Under GDUFA.415

Like the GDUFA, the BUFA would authorize the FDA to collect fees such as a (1) biosimilar development program fee, (2) annual biosimilar biological product application and supplement fee, (3) biosimilar biological product establishment fee, and (4) biosimilar biological product fee. The goal of the BUFA is to expedite the review process for biosimilar biological products.

409Requests for waivers or reductions—for application, product, or establishment fees—must be submitted no later than 180 calendar days after the fee is due, and may be submitted in advance to avoid having to pay the fee. The FDA recommends that advance requests be submitted three to four months before submission of the application or before the product and establishment fees are due. Id.
413Id. §379j-52.
2. Title IV—Pediatric Research Equity Act of 2007 and Title V—Best Pharmaceuticals for Children Act of 2007

On December 2, 1998, the FDA originally promulgated the “Pediatric Rule,” which asserted the FDA’s authority to compel drug manufacturers to complete pediatric testing for pharmaceuticals. The American Association of Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert subsequently litigated and successfully challenged the validity of the Pediatric Rule in the U.S. District Court for the District of Columbia. The result was that, in 2002, the Pediatric Rule was invalidated when the court held that the FDA lacked statutory authority to promulgate such a regulation.

The Best Pharmaceuticals for Children Act of 2002 (BPCA) and the Pediatric Research Equity Act of 2003 were designed to improve the quality and quantity of pharmaceuticals available to children, but included sunset provisions for 2007. The FDAAA reauthorized both acts for an additional five years, with relatively minor changes, and both were later reauthorized by the FDASIA in 2012.

The BPCA was passed to address the concern that, at that time, the majority of prescription medications were never tested in, and therefore not specifically approved for use in, children. The BPCA was passed after the Food and Drug Administration Modernization Act of 1997, and provided for pediatric exclusivity—six months of marketing exclusivity for pharmaceutical companies that conducted pediatric studies. The FDAAA prohibits pharmaceutical manufacturers from filing late applications to the FDA for pediatric testing, a practice that presumably had been engaged in with the intent of extending the life of the drug patent.

Moreover, the FDAAA empowers the HHS Secretary, after consultation with the sponsor, to issue a written request for the con-

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421 The term “pediatric studies” or “studies” means at least one clinical investigation (which, at the Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies. FDAAA, Pub. L. No. 110-85, tit. V, §505A(a), 121 Stat. 823 (2007); see also id. §505A(m)(1)–(2); FDA, THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS (2001), available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf.
422 “Exception—The Secretary shall not extend the period referred to in paragraph (1)(A) or (1)(B) if the determination made under subsection (d)(3) is made later than 9 months prior to the expiration of such period.” FDAAA, tit. V, §505A(b)(2), 121 Stat. 823 (2007).
duct of pediatric studies for such drug.\textsuperscript{423} Adverse-event reports by sponsors to the FDA are mandatory.\textsuperscript{424}

The pediatric mandate in the FDAAA also requires the National Institutes of Health (NIH) to develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study.\textsuperscript{425} The last published priority list identified diseases in each of the following 17 categories that the NIH determined were priority needs in pediatric therapeutics:

1. Infectious Disease;
2. Cardiovascular Disease;
3. Respiratory Disease;
4. Intensive Care;
5. Biodefense Research;
6. Pediatric Cancer;
7. Psychiatric Disorder;
8. Neurological Disease;
9. Neonatal Research;
10. Adolescent Research;
11. Hematologic Disease;
12. Endocrine Disease Priorities and Diseases with Limited Alternative Therapies;
13. Dermatologic Disease;
14. Gastrointestinal Disease;
15. Renal Disease;
16. Rheumatologic Disease;
17. Special Considerations.\textsuperscript{426}

Again, the FDAAA, and then the FDASIA, have both reauthorized the Pediatric Research Equity Act (PREA).\textsuperscript{427} The PREA requires a pharmaceutical manufacturer to supply greater documentation in order to receive a pediatric testing waiver. In addition, the FDAAA empowers the FDA with broader authority to mandate pediatric testing.\textsuperscript{428}

3. \textit{Title VI—Reagan-Udall Foundation}

Title VI, Section 601 of the FDAAA amends Chapter VII of the FDCA\textsuperscript{429} to establish the Reagan-Udall Foundation for the FDA. The foundation is a nonprofit corporation and “not [. . .] an agency or instrumentality of the United

\textsuperscript{423}Id. §505A(d)(1)(A).
\textsuperscript{424}Id. §505A(d)(2)(B); see also id. §505A(d)(2)(l)(1).
\textsuperscript{428}See FDAAA, tit. V, §505A (Pediatric Studies of Drugs).
\textsuperscript{429}21 U.S.C. §§371 et seq.
States Government.”430 The purpose of the foundation is “to advance the mission of the [FDA] to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety.”431

The duties of the foundation are enumerated broadly to include policy and program development and funding in the areas of safety, research, and education by doing the following:

1. Taking into consideration the Critical Path reports and priorities published by the Food and Drug Administration, identify unmet needs in the development, manufacture, and evaluation of the safety and effectiveness, including post approval, of devices, including diagnostics, biologics, and drugs, and the safety of food, food ingredients, and cosmetics, and including the incorporation of more sensitive and predictive tools and devices to measure safety;

2. Establish goals and priorities in order to meet the unmet needs . . . ;

3. In consultation with the Secretary, identify existing and proposed Federal intramural and extramural research and development programs relating to the goals and priorities established under paragraph (2), coordinate Foundation activities with such programs, and minimize Foundation duplication of existing efforts;

4. Award grants to, or enter into contracts, memoranda of understanding, or cooperative agreements with, scientists and entities, which may include the Food and Drug Administration, university consortia, public-private partnerships, institutions of higher education, entities described in section 501(c)(3) of the Internal Revenue Code . . . ;

5. Recruit meeting participants and hold or sponsor (in whole or in part) meetings as appropriate to further the goals and priorities established under paragraph (2);

6. Release and publish information and data and, to the extent practicable, license, distribute, and release material, reagents, and techniques to maximize, promote, and coordinate the availability of such material, reagents, and techniques for use by the Food and Drug Administration, nonprofit organizations, and academic and industrial researchers to further the goals and priorities established under paragraph (2); . . . .432

Title VI, Section 602 of the FDAAA amends Chapter IX of the FDCA433 by adding Section 910,434 “thereby establishing the Office of the Chief Scientist, a person appointed by the Secretary.” The duties of the Office include the mandate to

1. Oversee, coordinate, and ensure quality and regulatory focus of the intramural research programs of the Food and Drug Administration;

430FDAAA, tit. VI, §601(a).
431Id.
43321 U.S.C. §§391 et seq.
434Id. §399a.
2. Track and, to the extent necessary, coordinate intramural research awards made by each center of the Administration or science-based office within the Office of the Commissioner, and ensure that there is no duplication of research efforts supported by the Reagan-Udall Foundation for the Food and Drug Administration;

3. Develop and advocate for a budget to support intramural research;

4. Develop a peer review process by which intramural research can be evaluated;

5. Identify and solicit intramural research proposals from across the Food and Drug Administration through an advisory board composed of employees of the Administration that shall include—
   (A) Representatives of each of the centers and the science-based offices within the Office of the Commissioner; and
   (B) Experts on trial design, epidemiology, demographics, pharmacovigilance, basic science, and public health; and

6. Develop postmarked safety performance measures that are as measurable and rigorous as the ones already developed for premarket review . . . .

Title VI, Section 603 further amends Subchapter E of Chapter V of the FDCA\textsuperscript{436} to empower the Secretary, acting through the Commissioner of Food and Drugs, [to] enter into collaborative agreements, to be known as Critical Path Public-Private Partnerships, with one or more eligible entities to implement the Critical Path Initiative of the Food and Drug Administration by developing innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development, manufacturing, and translational therapeutics, and enhancing medical product safety.\textsuperscript{437}

4. Title VII—Conflicts of Interest

The issue of bias\textsuperscript{438} in drug development and pharmaceutical research continues to receive much attention in scientific and regulatory circles.\textsuperscript{439} In 1989, researchers detecting possible scientific bias suggested that the FDA implement measures such as certifying the competence of potential investigators; providing for peer-reviewed, competitive application for the opportunity to conduct FDA-authorized clinical trials; limiting an investigator’s level of participation in clinical trials; penalizing manufacturers who fail to detect their investigators’ misconduct; and permitting the FDA to suspend investigators prior to a hearing.\textsuperscript{440}

\textsuperscript{436}21 U.S.C. §§360bbb et seq.
\textsuperscript{437}FDAAA, tit. VI, §603(a), 121 Stat. 823.
Title VII of the FDAAA amends Subchapter A of Chapter VII of the FDCA by inserting a legislative mandate requiring:

[D]isclosure of any financial interest prior to any meeting of an advisory committee regarding a particular matter (as that term is used in Section 208 of Title 18 of the U.S. Code), [and providing that] each member of the committee who is a full-time Government employee or special Government employee shall disclose to the Secretary financial interests.

Thereafter, the:

member of an advisory committee may not participate with respect to a particular matter considered in an advisory committee meeting if such member (or an immediate family member of such member) has a financial interest that could be affected by the advice given to the Secretary with respect to such matter.

In keeping with the principle of transparency, the FDAAA mandates the Secretary to “ensure that the public record and transcript of each meeting of an advisory committee includes the [required] disclosure.”

Since that time, the FDA has addressed conflicts of interest in several guidance documents. For example, in August 2008, the FDA released a Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, dated August 2008, which describes the factors and analyses to be used in the consideration of whether an advisory committee member has a potential conflict of interest and whether participation in a meeting is appropriate. Then, in March 2014 the FDA released a final guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members’ Financial Interest Information and Waivers, which generally “describes the basis and provides a format for public disclosure of certain financial interests by special Government employees (SGEs) and regular Government employees participating in these advisory committee meetings, and provides a format for FDA waivers allowing participation in these meetings.”

443 Id. §701(c)(1).
444 Id. §701(c)(2)(A).
445 Id. §701(d).
448 Id.
5. Title VIII—Clinical Trial Databases

The FDAAA requires an expanded clinical trial registry data bank intending to “enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.” Pursuant to this enhanced requirement, the NIH improved the public clinical trial registry data bank to permit the public to search the entries of the registry data bank by the safety issue, if any, being studied in the clinical trial as a primary or secondary outcome.

This enhanced clinical trial database was enacted against the backdrop of prior efforts to increase public knowledge of clinical trials. For example, the American Medical Association (AMA) Council on Scientific Affairs approved a resolution in 2004 recommending the public registration of all clinical trials at inception, with the results from these trials to be made publicly available through either journal publication or an electronic data repository. The Pharmaceutical Research and Manufacturers of America (PhRMA) Principles were revised in June 2004 to improve public access to drug trial data. PhRMA has also established a centralized electronic database to facilitate the public’s access to clinical trial data and the results of unpublished clinical studies.

An Interagency Oncology Task Force (IOTF) was also established in 2003 to increase the efficiency of clinical research and the scientific evaluation of new potential cancer-treating pharmaceuticals and diagnostic modalities. In September 2006, HHS/FDA and the HHS/NIH/National Cancer Institute (NCI) jointly published a Memorandum of Understanding (MOU) to establish a formal collaboration designed to develop and implement the Federal Investigator Registry of Biomedical Information Research Data (FIREBIRD). This collaboration is designed to enable clinical investigators, NCI, FDA, and industry entities sponsoring clinical trials of investigational drugs (Sponsors) to manage clinical investigator information electronically in a fully secure manner. Information that is entered into FIREBIRD by a Sponsor may become a matter of “FDA record” (a submission to FDA) only if the submitter takes an affirmative step acknowledging that the data are accessible by FDA.

The MOU was codified in April 2007, under the designation Janus Study Data Repository, and notes that:

FDA and NCI both have interests in expediting the development of new drugs. One of the central goals of the IOTF is to implement an electronic drug application submission system that will help reduce the delays, errors, and costs associated with

450Id.
453PhRMA Clinical Study Results Database, available at http://www.clinicalstudyresults.org/.
drug development. Such a system is expected to speed the discovery and delivery of new therapies.\textsuperscript{456}

6. \textit{Title IX—Enhanced Authorities Regarding Postmarket Safety of Drugs}

The FDAAA also enacted several new sections relating to the FDA’s post-market review of drugs and the FDA’s communication with consumers about drug safety. For example, Section 901 of the FDAAA addresses postmarket safety for drugs and biologics by adding new sections 505(o)(3) and 505(o)(4) to the FDCA. Section 505(o)(3) authorizes the FDA to require postmarketing studies and clinical trials for prescription drugs approved under the FDCA and biological products approved under the Public Health Service Act, either at the time of approval or post-approval if the FDA becomes aware of new safety information.\textsuperscript{457} In turn, Section 505(o)(4) allows the FDA to order specific changes to the labeling for an approved drug based on new safety information since the drug was approved, since a REMS was required, or since the last assessment of an approved REMS; and, as indicated, post-new warnings. The FDA is empowered to impose fines\textsuperscript{458} if the sponsor fails to comply with agency requirements for further testing and warnings.\textsuperscript{459} The pharmaceutical manufacturers will bear user fees that will fund the active surveillance system intended to delineate such postmarket drug risks.\textsuperscript{460} Moreover, under the FDAAA, the agency has been granted the express authority to order such postmarket safety actions despite objections from the drug sponsor.

In April 2011, the FDA issued a guidance detailing the agency’s current thinking on the implementation of Section 505(o)(3). According to the guidance, the FDA will require a postmarketing study or clinical trial when the decision to require such study or trial is based on appropriate scientific data and where adverse-event reporting (for postmarketing studies) or a postmarketing study (for clinical trials) would be insufficient to meet one of the purposes for either. Under Section 505(o)(3)(B), the purposes for a postmarketing study or clinical trial may be to:

1. Assess a known serious risk related to the use of the drug;
2. Assess signals of serious risk related to the use of the drug; or
3. Identify an unexpected serious risk when available data indicate a potentially serious risk.

If these conditions are met, a postmarketing study or clinical trial may be required, and the FDA may describe the study or trial, including how it will be

\textsuperscript{456}Id.
\textsuperscript{457}See id. §901(a), 121 Stat. at 923; FDA, \textit{Guidance for Industry, Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act} (Apr. 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf. “New safety information” is defined to include information about a serious risk or unexpected serious risk associated with the use of the drug, or the effectiveness of the approved risk evaluation and mitigation strategy for the drug since the last assessment. \textit{Id.}
\textsuperscript{458}Id. §902(b), §303(f), 121 Stat. at 943.
\textsuperscript{459}Id.
\textsuperscript{460}Id. §905(a), §505(k), 121 Stat. at 944.
conducted, the population, and the indication. Additionally, the FDA may require a postmarketing study or clinical trial if it becomes aware of a risk and believes it is serious, but requires additional knowledge to determine the appropriate response to the risk.\footnote{Applicants may appeal the imposition of a postmarketing study or clinical trial through the FDA’s dispute resolution procedures. Id.; see also FDA, Draft Guidance for Industry, Guidance for Industry Formal Dispute Resolution: Appeals Above the Division Level (Feb. 2000), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf.}

The FDA has also issued a guidance detailing its current view on Section 505(o)(4) of the FDCA.\footnote{FDA, Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act (July 2013), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf.} As detailed in the guidance, Section 505(o)(4) was enacted to modify the past practice of protracted labeling negotiations, which ultimately left the FDA with limited options if an application holder failed to comply. New safety information may be from “a clinical trial, an adverse event report, a post approval study . . . [or] peer-reviewed biomedical literature, data derived from the post market risk identification and analysis system . . . or other scientific data deemed appropriate by [the Secretary].” As the guidance describes, when the FDA learns of the potential for new safety information, it will use a multidisciplinary team to review the information and determine whether a labeling change is necessary. The FDA anticipates that Section 505(o)(4) will be implemented when a change to the boxed warnings, contraindications, warnings and precautions, drug interactions, or adverse-reactions sections of the professional labeling is required. However, the FDA has indicated that if a change were warranted solely to the adverse-reactions section, FDA would be unlikely to exercise its authority under Section 505(o)(4).

The FDA’s use of Section 505(o)(4) may have one of several results: new labeling, an appeal of the FDA’s order, or an enforcement action if the application holder does not comply. With regard to revised labeling, the FDA’s guidance indicates that it should be available on the application holder’s Web site within 10 calendar days of approval. As for the timing of implementing revised labeling for package inserts and other printed materials, the FDA plans to issue guidance on this topic. Alternatively, the FDA’s guidance indicates that an appeals process is available for applicants who disagree with any ordered labeling changes. Should an application holder not comply with the FDA’s order, the application holder may face an enforcement action by the FDA. This may include unapproved new drug charges, misbranding charges, civil monetary penalties, or seizure of the product and an injunction. Nonetheless, the FDA’s guidance signals a willingness to negotiate labeling changes using the platform provided by Section 505(o)(4).

Title IX, subtitle A, section 901 of the FDAAA also created a new FDCA Section 505–1(a), “which authorized FDA to require persons submitting certain applications to submit and implement a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug
and informs the holder of the application for the drug.\textsuperscript{463} REMS are mandatory plans intended to ensure that the benefits of a prescription drug or biologic outweigh that product's risks.\textsuperscript{464}

Under this section, the FDA is authorized to consider the following factors at the time of initial approval of a new pharmaceutical:

1. The estimated size of the population likely to use the drug involved.
2. The seriousness of the disease or condition that is to be treated with the drug.
3. The expected benefit of the drug with respect to such disease or condition.
4. The expected or actual duration of treatment with the drug.
5. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
6. Whether the drug is a new molecular entity.\textsuperscript{465}

REMS also apply in the post-approval period requiring the Secretary, when he or she:

[H]as approved a covered application . . . and did not when approving the application require a risk evaluation and mitigation strategy . . . [to, as needed,] subsequently require such a strategy for the drug involved (including when acting on a supplemental application seeking approval of a new indication for use of the drug) if the Secretary becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.\textsuperscript{466}

The Chief Counsel of the FDA has noted that “[t]he most far reaching and restrictive elements of a REMS are what FDAAA calls ‘Evaluation of elements to assure safe use.’”\textsuperscript{467} This section of the FDAAA describes many of the elements that sponsors have used in the past under the rubric of “restricted distribution plans.” In order to impose elements to assure safe use, the FDA is required to first make a determination that the drug (1) is effective; (2) is associated with a “serious adverse drug experience,” as that term is defined by the statute; and (3) can be approved only if elements to assure safe use are imposed.

To facilitate the tracking of adverse events, product problems, and medication/device use errors related to FDA-regulated products, two reporting forms are available: (1) FDA 3500, which is used for reporting by health care professionals and the public; and (2) FDA 3500A, which is designed for mandatory reporting by manufacturers and health care professionals reporting under the National Childhood Vaccine Injury Act of 1986.\textsuperscript{468}

\textsuperscript{464}Gerald F. Masoudi, Legal Developments in the Enforcement of Food and Drug Law, 63 FOOD & DRUG L.J. 585, 586 (2008).
\textsuperscript{466}Id.
\textsuperscript{467}See id. tit. IX, §901(b), Postmarket Studies and Clinical Trials Regarding Human Drugs; Risk Evaluation and Mitigation Strategies.
\textsuperscript{468}National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§300aa-1 to -34 (2008). Mandatory reports of untoward reactions to immunization are not submitted to the FDA on either Form
FDAAA Section 917, entitled “Risk Communication,” also directs the Secretary to establish an Advisory Committee on Risk Communication. The drug safety program includes the following: (1) sponsoring an independent study by the Institute of Medicine of the National Academies of the effectiveness of the drug safety system, with emphasis on postmarketing risk assessment and surveillance; (2) conducting workshops and Advisory Committee meetings regarding complex drug safety and risk management issues, including emerging concerns; and (3) publishing three risk management guidance documents. In addition, the FDA augmented its drug safety initiative in February 2005 by creating an independent Drug Safety Oversight Board to enhance oversight of drug safety decision-making within CDER.469

The FDA is also taking a more comprehensive approach to making information on potential drug risks available to the public. The FDA believes that timely communication of drug safety information best provides health care professionals, patients, consumers, and other interested persons access to the most current information concerning the potential risks and benefits of a marketed drug, helping them to make more informed individual treatment choices.470 The heightened attention by the FDA to risk-communication efforts is considered to be an integral part of a larger drug safety initiative that dates back to November 2004.

For example, disclosures by manufacturers must note on FDA’s Web site the limits on information regarding drug safety where agency approvals were based on surrogate endpoints during the clinical trials, evolving information obtained through postmarket studies or surveillance, and the significance of any failure to complete postmarket studies.471 The FDA also makes drug information and postmarket safety information available online for consumers to access.472

B. The Patient Protection and Affordable Care Act

The Patient Protection and Affordable Care Act (PPACA) of 2010 also made numerous changes to the FDA’s authority to regulate drug development.473 The PPACA represents one of the most comprehensive health care reform efforts

FDA 3500 or Form FDA 3500A, but are instead submitted to the joint FDA/Centers for Disease Control and Prevention Vaccines Adverse Event Reporting System (VAERS) on the VAERS-1 form, available at http://www.vaers.hhs.gov.

469Id.
470Id.
since the creation of Medicare and Medicaid, and was enacted in response to
growing public concern regarding the disparities in the availability of health care and
health care insurance, the rising cost of health care both in the public and
private contexts, and the inequitable treatment of individuals covered by private
health insurance. The PPACA provides for incremental implementation of broad
reforms ranging from the immediate creation of a national high-risk insurance pool, enhanced quality improvement measures, the restructuring of payment and eligibility for Medicare and Medicaid, and provisions addressing concerns about the health care work force, preventative medicine, tax changes, and employer participation.474 Various aspects of the PPACA have been repeatedly challenged in court,475 although the provisions relating to the FDA’s authority have not been challenged.


The most significant expansion of FDA authority under the PPACA was enacted through Title VII, specifically, the Biologics Price Competition and Innovation Act of 2009.476 This provision gives the FDA authority “to approve generic versions of biologic drugs[,] grant biologics manufacturers 12 years of exclusive use before generics can be developed,”477 and grant exclusivity rights to the first generic applicant that receives a determination of interchangeability status.478

In order to receive a determination of biosimilarity,479 an applicant must demonstrate five criteria: (1) the applicant product is biosimilar to the reference product,480 (2) the applicant product and reference product481 use the same mechanism(s) of action for the condition(s) of use prescribed, recommended, or suggested, (3) such condition(s) of use in the labeling of the generic drug have previously been approved for the reference product, (4) the route of administra-

476PPACA, §7002, 124 Stat. at 804.
477Kaiser, Focus on Health Reform, at 1.
478PPACA, §7002(a), 124 Stat. at 807.
479Biosimilar or biosimilarity means “(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” §7002(b), 124 Stat. at 815.
480The determination that a generic is biosimilar to the reference product must be supported with data derived from:

(aa) analytical studies that demonstrate the [generic] is highly similar to the reference product[, excluding differences in clinically inactive components]; (bb) animal studies (including the assessment of toxicity); and (cc) clinical study[(ies)] . . . that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product. Id. §7002(a), 124 Stat. at 805.
481The term “reference product” refers to “the single biological product . . . against which a biological product is evaluated in an application submitted under” the BPCIA. Id. §7002(b), 124 Stat. at 815.
tion, dosage, and strength of the generic drug are the same as the reference product’s, and (5) the applicant’s manufacturing, processing, packing, or holding facility uses standards to assure the retention of safety, purity, and potency. 482

Similarly, a biosimilar product will be deemed interchangeable 483 if the product (1) is biosimilar to the reference product, (2) can be expected to produce the same clinical result, and (3) if intended for multiple administrations, has no greater risk of safety or diminished efficacy if used interchangeably with the reference product than the reference product would have without such interchangeability. 484

The first biosimilar application to receive a determination of interchangeability for a reference product will be granted exclusivity for a limited period. 485 Similarly, even though the BPCIA grants manufacturers the right to file an application for an interchangeable or biosimilar determination four years after the reference product is first licensed, 486 the reference product holds exclusivity for 12 years. 487

The biosimilar applicant must provide to the outside and in-house counsel of the reference product’s sponsor information pertaining to the biosimilar. 488 Moreover, the representative of the reference product’s patent owner may also request disclosure of this information, as long as the representative notifies the reference product’s sponsor and the generic applicant of its intent to maintain the requisite confidentiality of the applicant’s information. 489

In May 2011, the FDA proposed a User Fee Program for Biosimilar and Interchangeable Biological Product Applications. Pursuant to its obligation

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482 Id. §7002(a), 124 Stat. at 805.
483 Interchangeable or interchangeability “means that the biological product may be substituted for the reference product without the intervention of a health care provider who prescribed the reference product.” Id. §7002(b), 124 Stat. at 815.
484 Id. §7002(a), 124 Stat. at 806.
485 That period of time will be defined:
(U)pon the earlier of: (1) 1 year after the first commercial marketing of the interchangeable generic product, (2) 18 months after a final court decision on all patents in an action against the first generic applicant or the dismissal with or without prejudice of an action against the first generic applicant, (3) 42 months after approval of the generic as interchangeable if the applicant has been sued on the application and the litigation is pending, or (4) 18 months after approval of the generic as interchangeable if the generic has not been sued under (l)(6). Id. §7002(a), 124 Stat. at 807. Section (l)(6) of §7002 allows the patent owner of a reference product to file suit against the generic applicant for patent infringement within 30 days of the mutual exchange of patent lists or mutual agreement on patents. Id. §7002(a), 124 Stat. at 812–13.
486 Id. §7002(a), 124 Stat. at 807.
487 Id. Market exclusivity for new biological products and already marketed biological products may also be extended to 12 years and six months if the HHS Secretary determines that it requires information on the use of the reference product in the pediatric population. Id. §7002(g), 124 Stat. at 820. Similarly, the exclusivity period for a new or already marketed biological product licensed under Section 526 of the FDCA for use in a rare disease or condition is extended to seven years and six months if the HHS Secretary determines that it may be useful for pediatric populations. Id.
488 Id. §7002(a), 124 Stat. at 809. The applicant must disclose the following information within 20 days after the generic’s application has been accepted for review: (1) a copy of the application and information that describes the process(es) used to manufacture the generic drug, and (2) any other information requested by the reference product’s sponsor. Id.
489 Id.
under the BPCIA to consult with outside groups on user fee programs, the FDA sought comments in several areas of the BPCIA, including development and structure of the biosimilar user fee program, performance goals for the FDA’s review of applications under the Act, and performance goals for applications for which the FDA is unable to grant approval due to exclusivity provisions of the BPCIA. Under the BPCIA, the FDA was required to submit the FDA’s recommendations by January 15, 2012.\footnote{See also Vicki G. Norton & Lewis F. Gould, Alert: FDA Proposes Pre-marketing User Fees for Biosimilar Product Manufacturers Comparable to Fees for Branded Manufacturers (Duane Morris May 11, 2011), available at http://www.duanemorris.com/alerts/FDA_biologics_price_competition_innovation_act_user_fee_biosimilar_biological_4073.html.} These recommendations eventually became the Biosimilars User Fee Act of 2012, which was enacted on July 9, 2012 as part of the PDUFA V reauthorization.\footnote{21 U.S.C. §379j-52.}

As further implementation of the BPCIA, the FDA has issued four guidance documents on biosimilar product development that addressed (1) Questions and Answers Regarding Implementation of the BPCIA,\footnote{FDA, Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Apr. 2015), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf.} (2) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,\footnote{FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Apr. 2015), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.} (3) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product,\footnote{FDA, Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Apr. 2015), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.} and (4) Formal Meetings Between FDA and Biosimilar Biological Product Sponsors or Applicants.\footnote{FDA, Guidance for Industry, Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (Mar. 2013), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf.} The first guidance addresses public questions in the areas of biosimilarity or interchangeability, determining when a “biological product” is subject to a Biologics License Application (BLA) or NDA, and exclusivity. The second guidance, Scientific Considerations, reflects the FDA’s current plan to implement a \textit{totality-of-the-evidence} approach to reviewing biosimilar applications under the BPCIA, recommends that sponsors use a stepwise approach to demonstrate biosimilarity, and provides general scientific principles to use in conducting studies. The third guidance related to Quality Considerations details the FDA’s advice to applicants on the specific factors used in assessing a biological product’s biosimilarity. Finally, the fourth guidance was designed to create a unified approach to all formal meetings between sponsors or applicants and the FDA for biosimilar biological product development programs, as well as to assist sponsors or applicants in generating and submitting a meeting request to the FDA for biosimilar biological products.
2. Labeling Changes

The PPACA also amends Section 505(j) of the FDCA\textsuperscript{496} pertaining to the ANDA, and expands eligibility for FDA approval even if the proposed label of the drug differs from the listed drug.\textsuperscript{497} The drug on which the ANDA application was filed will no longer be considered misbranded if the label differs due to a labeling revision in Section (i) of the Act, the ANDA is otherwise eligible for approval,\textsuperscript{498} the labeling revision does not include a change to the “warnings” section, and the application sponsor agrees to submit revised labeling of the drug.\textsuperscript{499} This exception may be inapplicable, however, if the HHS Secretary determines that such labeling has an adverse impact on safe uses of the drug. In that event, the ANDA application will not retain eligibility for approval if it does not implement revised labeling.\textsuperscript{500} On February 12, 2013, the Office of Generic Drugs/Office of Pharmaceutical Science issued a policy addressing how the Office of Generic Drugs (OGD) should implement Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (OGD Policy).\textsuperscript{501} The OGD Policy states that the FDA may approve an ANDA, even though certain changes have been made to the labeling for the reference listed drug (RLD), if: (1) “the approval of the RLD’s labeling revision is made within 60 days before the expiration of a listed patent, an exclusivity period, or a 30-month stay delaying ANDA approval”; (2) “the approved revision to the labeling of the RLD does not include a change to the ‘Warnings’ section”; and (3) “the FDA has determined that the continued presence of the labeling in effect before the revision will not adversely impact the safe use of the drug product.”\textsuperscript{502}

3. Sunshine Act Reporting Requirements

Section 6002 of PPACA also now requires “applicable manufacturers” to report payments or other transfers of value to physicians or teaching hospitals that exceed $10 or, in the aggregate, exceed $100 in a calendar year.\textsuperscript{503} A large number of entities fall within the definition of an applicable manufacturer, including entities that are engaged in the production, preparation, propagation,
compounding, or conversion of a covered drug for sale or distribution in the United States, including foreign manufacturers that operate in the United States by selling a product (regardless of where the product is physically manufactured); or entities under common ownership with such an entity with respect to such acts. There are several notable exceptions to this definition, including:

1. Raw materials and component manufacturers;
2. Hospitals, pharmacies, and laboratories that produce or manufacture materials solely for their own use or use by their patients; or
3. Pharmacies/compounding pharmacies that (a) maintain establishments that are compliant with state and local laws, (b) regularly engage in distributing prescription drugs or devices, and (c) do not produce, propagate, compound, or convert drugs/devices for sale other than in the regular course of their business of selling devices or drugs at retail to individual patients.\footnote{504}

The reporting provisions are also broad, requiring applicable manufacturers to disclose practically all transfers of value or other payments made to teaching hospitals or physicians, and to report the name of the recipient, the business address of the recipient, the amount of the payment or transfer of value, the dates on which the payment or transfer of value was made, and a description of the form of the payment or other transfer of value.\footnote{505} There are also special reporting requirements with respect to research-related payments, which must be reported if they are made pursuant to a written agreement or contract between the applicable manufacturer and entity conducting the research or a written protocol. The substantive reporting requirements for research-related payments are slightly different to accommodate the payment stream for research, and require applicable manufacturers to report the entity that received the payment, the principal investigator for the study, the name of the study, and other related items.

Finally, the Sunshine Act and its implementing regulations require applicable manufacturers and group purchasing organizations to make annual reports of physician ownership or investment interests in the applicable manufacturer or group purchasing organization. The definitions of ownership and investment interests mirror those in the physician self-referral law, commonly referred to as the Stark Law, and include both direct and indirect interests, such as stock; stock options; partnership shares; limited liability company memberships; loans; bonds; and any other interest through debt, equity, or other means. Such interests do not include interests arising out of retirement plans, stock options, or convertible securities received as compensation, or unsecured loans subordinate to credit facilities.


\footnote{505} PPACA, Pub. L. No. 111-148, tit. VI, §6002, 124 Stat. at 689–90. Examples of payments or transfers that merit reporting include the transfer of stock or stock options, consulting fees, and grants. \textit{Id}. There are also several exceptions to the reporting requirements, including but not limited to: product samples not intended for sale or patient use, educational materials that benefit patients or are intended for patient use, discounts, and “in-kind items used for the provision of charity care.” \textit{Id}. §6002, 124 Stat. at 696.
Under the final rules, data collection under Section 6002 was set to begin on August 31, 2013, and the first reports were due on March 13, 2014.506

4. Prescription Drug Transparency

Section 6004 of the PPACA also imposes new reporting requirements for manufacturers and authorized distributors of record. No earlier than October 1, 2012,507 and annually thereafter, manufacturers and distributors of prescription drugs were required to start tracking and report certain information regarding the distribution of drug samples to licensed practitioners or to pharmacies of hospitals or other health care entities. The report must include information such as the identity and quantity of drug samples requested by a licensed practitioner; the identity and quantity of drug samples distributed pursuant to such request; the name, address, professional designation, and signature of the practitioner (or his or her designee) making the request; and any other information deemed appropriate by HHS.508

5. The Cures Acceleration Network

The PPACA additionally established the Cures Acceleration Network (CAN) in an effort to facilitate the development of high-need cures.509 Although the CAN will operate under the authority of the National Institutes of Health,510 the FDA will play a pivotal role in guiding the development of high-need cures, as it is a member of the board of the CAN.511 The purposes of the CAN are to:

1. Conduct and support revolutionary advances in basic research, translating scientific discoveries from bench to bedside;
2. Award grants and contracts to eligible entities to accelerate the development of high-need cures;

50842 U.S.C. §1320a–7i.
509A “high need cure” is:
[A] drug (as that term is defined by section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act), biological product (as that term is defined by section 262(i)), or device (as that term is defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act) that, in the determination of the Director of NIH—
(A) is a priority to diagnose, mitigate, prevent, or treat harm from any disease or condition; and
(B) for which the incentives of the commercial market are unlikely to result in its adequate or timely development.
510Id. tit. X, §10409(d), 124 Stat. at 978–79.
511Id. §10409(d), 124 Stat. at 979.
512In addition to sending a representative to serve on the board of the CAN, the FDA may participate in regular and ongoing communication with the entities engaged in research, and will provide approval for such activities. Id. §10409(d), 124 Stat. at 979–81.
3. Provide the resources necessary for government agencies, independent investigators, research organizations, biotechnology companies, academic research institutions, and other entities to develop high-need cures;
4. Reduce the barriers between laboratory discoveries and clinical trials for new therapies; and
5. Facilitate review in the Food and Drug Administration for the high-need cures funded by the [CAN].

Among other institutions, both pharmaceutical companies and biotechnology companies are eligible to receive grants under the CAN. In conjunction with the CAN and the FDA, pharmaceutical companies awarded grants will promote technologies supporting advanced research, development, and production of high-need cures. Grant recipients will also receive assistance from the CAN in the areas of establishing FDA and other regulatory compliant protocols for the development, manufacturing, review, approval, and safety surveillance of the high-need cure. The CAN focus is on rescuing and repurposing drugs, tissue chip for drug screening, and identifying and validating drug targets.

C. The Future of FDA Regulatory Authority

The FDA’s strategic priorities for the years 2011–2015 detail the focus of the FDA’s regulatory efforts and future regulatory goals. First, the FDA described its guiding principles for regulatory efforts including science-based decision-making, innovation and collaboration, transparency, and accountability. With these guiding principles in mind, the FDA’s cross-cutting strategic priorities include advancing regulatory science and innovation, strengthening the safety and integrity of the global supply chain, strengthening compliance and enforcement activities to support public health, expanding efforts to meet the needs of special populations, and advancing medical countermeasures and emergency preparedness. From a long-term perspective, the FDA plans to advance food safety and nutrition; promote public health by advancing the safety and effectiveness of medical products; establish an effective tobacco regulation, prevention, and control program; and manage organizational excellence and accountability. As these priorities make clear, the FDA anticipates that its regulatory role will continue to expand.

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512 Id. §10409(d), 124 Stat. at 979.
513 Id. §10409(d), 124 Stat. at 982.
514 The development of high-need cures will include “the development of medical products, behavioral therapies, and biomarkers that demonstrate the safety or effectiveness of medical products.” Id.
515 Id.
III. LIMITS OF FDA JURISDICTION

As set forth above, the FDA’s jurisdiction over the new drug development process is broad. There are numerous important exceptions to the FDA’s ability to regulate the drug development and marketing process, however, certain of which are described in greater detail below.

A. The Exception for Clinical Trials of Medical Procedures Not Involving Drugs or Medical Devices

Prescription drugs are subject to a significantly more rigorous evaluation process than are medical devices, whereas medical procedures are not subject to a formal FDA regulatory process to determine safety or efficacy. The process by which medical procedures are developed, tested, and disseminated within the practice of medicine differs significantly from that of pharmaceuticals.

Specifically, the FDCA governs drugs and devices, and the processes by which they are manufactured. Moreover, in any clinical investigation the “investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator’s care, and for the control of devices under investigation,” including informed consent.\textsuperscript{518}

The FDCA does not, however, address the performance and development of medical procedures. Clinical experimentation with new medical procedures and deviations from standard methods is recognized but is regulated primarily under the tort doctrines.\textsuperscript{519} Hospitals also assume a duty “to ensure that any patient involved in a clinical study was made aware of the clinical nature of the procedure and the risks associated with such experimentation, and had signed a consent form acknowledging that fact.”\textsuperscript{520} In other words, the FDA’s ability to regulate the performance and development of medical procedures is limited where such procedures fall outside the FDCA’s definition of “drug,” “device,” or the processes by which they are manufactured.

B. The “Practice of Medicine” Exception: Off-Label Uses of Drugs and Medical Devices

The FDA’s authority to regulate the off-label use of drugs and medical devices is also limited by several common law doctrines including the “practice of medicine” exception and the “learned intermediary” doctrine. Specifically, medical practitioners may prescribe FDA-approved drugs for certain “off-label

\textsuperscript{518}21 C.F.R. §812.100.
\textsuperscript{519}See Fortner v. Koch, 272 Mich. 273, 282 (1935) (“We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him and must not vary too radically from the accepted method of procedure.”).
uses,” which occurs when the drug is used in a manner that is either inconsistent with or is not described in the product’s FDA-approved labeling. Off-label uses, by definition, have not undergone testing and review by the FDA, and therefore are not FDA-approved as safe or efficacious.521

The FDA does not regulate the practice of medicine, however, and therefore does not have the authority to regulate medical practitioners’ prescribing of drugs for off-label uses.522 In other words, once the FDA approves a drug for any use, the actual prescription choices regarding those drugs are left to the discretion of the physician.523 A physician may prescribe an approved drug for any medical condition, irrespective of whether the FDA has determined that the drug is safe and effective with respect to that illness.

Similarly, the FDA does not regulate off-label drug uses by physicians that involve the “learned intermediary” doctrine. The learned intermediary rule states that it is the duty of the prescribing physician to be fully aware of (1) the characteristics of the drug he or she is prescribing, (2) the amount of the drug that can be safely administered, and (3) the different medications the patient is taking. The doctrine provides that a pharmaceutical manufacturer owes a duty to warn prescribing physicians of the risks associated with the use of a pharmaceutical; the physician then acts as a “learned intermediary” between the manufacturer and the patient.524 It is then the duty of the prescribing physician to advise the patient of any dangers or side effects associated with the use of the drug as well as how and when to take the drug. The FDA has recognized this concept since at least 1982, when the FDA issued a Drug Bulletin which states that “once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling.” The FDA also noted that off-label (“unapproved” or “unlabeled”) uses may in fact be appropriate in some circumstances, and may represent a kind of therapeutic innovation.525

521 See FDA Approval Process, 1996: Hearings Before Subcomm. on Health and Env’t of the House Comm. on Commerce, 104th Cong. (1996) (testimony of David A. Kessler, M.D., Comm’r of Food & Drugs,HHS) (stating that the only way to ensure safety and efficacy is through the collection and analysis of the data supporting such off-label uses). See also More Information for Better Patient Care, 1996: Hearings Before Senate Comm. on Labor & Human Resources, 104th Cong. (1996) (testimony of Paul D. Stolley, M.D., M.P.H., F.A.C.P, Chairperson of the Dep’t of Epidemiology & Preventive Med., Univ. of Md. Sch. of Med.) (stating that that testimonials, anecdotes, and preliminary data are no substitute for rigorous scientific evaluation of drugs). For nonprescription or OTC drugs, off-label use occurs when a consumer fails to follow the directions for use. For prescription medications, off-label uses may include prescribed changes in dosage, route of administration, use in a new patient population, or use in a new therapeutic indication.


523 See, e.g., Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994) (noting that the agency has restated this policy on numerous occasions).


Pharmaceutical and Medical Device Law

The learned intermediary doctrine and practice of medicine exception also intersect with a manufacturer’s duty to warn patients about potentially adverse side effects or drug reactions. This is because certain warnings on drug labeling are directed to the medical professional instead of the patient. Thus, “it is for the prescribing physician to use his independent judgment, taking into account the data supplied to him from the manufacturer, other medical literature, and any other sources available to him, and weighing that knowledge against the personal medical history of his patient, whether to prescribe a given drug.”

In certain cases, then, a warning to an intermediary such as a physician may fulfill a supplier’s duty to warn ultimate consumers. Courts have upheld the rule, finding that it is reasonable for a manufacturer to rely on the learned intermediary to communicate warnings to patients.

On the flip side, courts have held that manufacturers have a strict duty to warn and can still be held liable directly to plaintiffs if the warnings that the manufacturer gave the learned intermediary are deemed inadequate. In other words, “[u]nless the individual prescribing physician receives specific, relevant warnings, he or she cannot make a careful, balanced assessment of the risks and benefits to her patient, nor can the patient herself be adequately informed.”

The learned intermediary rule also provides that a failure of the manufacturer to provide a physician with adequate warnings of risks associated with a prescription pharmaceutical cannot be considered the proximate cause of patient injury if that prescribing physician had independent knowledge of the risks.

For example, in United States v. Evers, the court noted that a physician may, as part of the practice of medicine, “lawfully prescribe a different dosage for his patient or may otherwise vary the conditions of use from those approved in the package insert without informing or obtaining the approval of the Food and Drug Administration.”

The court went on to say that when “physicians go beyond the directions given in the package insert it does not mean they are acting illegally or unethically and Congress did not intend to empower the FDA to interfere with medical practice by limiting the ability of physicians to prescribe according to their best judgment.”

Nonetheless, physicians who prescribe drugs for off-label indications must comply with generally accepted standards of medical practice.

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528 Id. at 94.
530 Christopher v. Cutter Lab., 53 F.3d 1184, 1192 (11th Cir. 1995).
531 453 F. Supp. 1141, 1149 (M.D. Ala. 1978) (citing FTC v. Simeon Mgmt. Corp., 532 F.2d 708 (9th Cir. 1976)); see also American Standard, Inc. v. Pfizer, Inc., 722 F. Supp. 86, 103 (D. Del. 1989) (“[T]he FDA has no jurisdiction to prevent a doctor from using an approved drug or device in a manner different from the labeling instructions on the package.”); see also Planned Parenthood Ariz., Inc. v. Humble, 2014 U.S. App. LEXIS 10260 (9th Cir. June 3, 2014) (affirming that FDA “consistently maintained” the position that physicians may prescribe FDA-approved drugs for off-label uses); United States v. King-Vassel, 728 F.3d 707, 709 (7th Cir. 2013) (“Once a drug has been approved for one use, however, the FDA cannot prevent physicians from prescribing the drug for other uses.”).
532 Evers, 453 F. Supp. at 1150.
C. Extraterritorial Limitations: Harmonization With Research Conducted Outside the United States

Given the FDA’s territorial limitations, the FDA is also increasingly attempting to harmonize its own regulatory requirements with those of other nations, particularly Europe. The shift to an international perspective in food and drug law reflects broad economic trends generally referred to as globalization. The FDA, in its policies and strategies, must increasingly consider:

1. The impact of general economic globalization;
2. The increasingly international character of both pharmaceutical products and multinational corporations; and
3. World Trade Organization agreements.\textsuperscript{533}

Time and resources could logically be conserved through efficient international harmonization because the drug development and drug approval process would not require duplication in the United States prior to allowing drug marketability. In addition, the public could have accelerated access to therapies that are developed outside the United States. “One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.”\textsuperscript{534}

Harmonization has legislative support in the APA\textsuperscript{535} as well as FDA administrative statutes and procedures.\textsuperscript{536} International activities consistent with the statutes that the FDA administers and that support the purposes of the FDA may be initiated under the auspices of either the product-specific provisions of the FDCA, or under more general mandates such as the broad rulemaking authority found under Section 701(a) of the FDCA.\textsuperscript{537}

The FDA’s agreements fall into the category of executive branch agreements that are negotiated and entered into under an agency’s statutory authority, which derives from the statutes it administers, principally the FDCA and the PHSA. The authority of the FDA to enter into agreements with other countries is supported under sections of the PHSA such as the following:

1. Section 301 (granting broad authority for public health cooperation);
2. Section 307 (authorizing international cooperation);
3. Section 351 (controlling biological products, most of which are also drugs or medical devices, e.g., certain in vitro diagnostic products and tissue-derived devices); and
4. Section 361 (authorizing regulations to control communicable diseases).\textsuperscript{538}

The FDA clears its proposed foreign agreements with foreign counterparts with the Department of State, under procedures governing clearance of agency agreements.

\textsuperscript{534}64 Fed. Reg. 44,928, 44,929 (Aug. 18, 1999).
\textsuperscript{536}The FDA’s rules on administrative practices and procedures are set forth in 21 C.F.R. pts. 10–17 (1998).
\textsuperscript{537}21 U.S.C. §371(a).
\textsuperscript{538}42 U.S.C. §§241, 242, 262, 264.
agreements. In addition, the FDA agreements with other nations are not binding and lack mandatory language.

FDA published a “harmonization policy” on World Standards Day 1995, which summarized FDA strategy and vision even before the FDAMA explicitly added harmonization provisions. The FDAMA also clearly articulated a harmonization policy within the statutory mission statement of the FDA, and directed the FDA to “participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements.”

Standardization of requirements for product testing and approval could be accomplished through bilateral governmental agreements such as Memoranda of Understanding (MOUs) or Mutual Recognition Agreements (MRAs). The FDA has MRA authority based in the Trade Agreements Act as well as in the FDCA. The MRA generally refers to other countries’ systems of conformity assessment or to an exchange of the results of conformity assessments to assure that another country’s statutory requirements are met.

The FDA also has product-specific authority to enter into MOUs regarding food, drugs, and devices. In addition to MOUs, the FDA sends inspectors abroad to ensure that foreign plants exporting products to the United States adhere to the FDA’s cGMPs, as do domestic firms.

Standardization can also occur through the collaboration of international standards setting or facilitating bodies such as the following:

1. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH);
2. World Health Organization (WHO);
3. International Conference of Drug Regulatory Authorities (ICDRA);
4. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH);
4. Council for International Organizations of Medical Sciences (CIOMS);
5. Organisation for Economic Co-operation and Development (OECD); or

The principal active harmonization program is based in the ICH, which was established in 1990. The ICH has adopted approximately 50 guidelines classified into four categories: quality, safety, efficiency, and multidisciplinary. The ICH includes as participants the regulatory bodies and representatives of pharmaceutical industries from the United States, the EU, and Japan.

Phase I of the ICH (which ended in 1997 with the fourth ICH conference in Brussels, Belgium) proposed to reduce duplication and redundancy in the drug development process by harmonizing technical guidelines for drug testing. The next phase of ICH concentrates on consolidating, updating, and ensuring the acceptance of the guidelines developed in Phase I.

Harmonized ICH guidelines are created in five steps:

1. The selection of harmonization topics by the Steering Committee based on the advice of Expert Working Groups (EWG) and development of a draft guideline, policy statement, recommendation or “points to consider” document which is prepared by the “EWG Rapporteur”;
2. Approval by the six cosponsors of the Steering Committee and its subsequent transmittal transmitted to the three regulatory agencies (FDA, EMEA, and MHW) for formal review and internal consultation;
3. Selection of a Regulatory Rapporteur from one of the regulatory agencies whose duty it is to oversee the collection and incorporation of comments;
4. Collation of the EWG-approved document and presentation to the Steering Committee for acceptance by the three regulatory agencies; and
5. Incorporation of the harmonized guideline into domestic regulations (such as publication of a final guideline by the FDA in the Federal Register) or similar administrative mechanisms of all three regulatory authorities.

WHO, founded as a result of the 1946 International Health Conference, also plays a significant role in harmonization based on its general mandate to “attain the highest possible level of health for all people in the world.” WHO is involved in harmonization by providing advice regarding the development of

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551 *Id.* at 200.
552 Ward, 55 FOOD & DRUG L.J. at 241.
554 *Id.*
national drug laws and policies and by supporting the Action Program for Essential Drugs in an ongoing attempt to ensure the international availability of low-cost and necessary pharmaceuticals. WHO has also actively started developing an international model formulary with a special interest in new biological products based on its perceived present and future need for vaccines in the developing world.556

IV. FUNDING PHARMACEUTICAL RESEARCH

The Public Health Service Act557 is the federal law that regulates research where federal funds are involved. The FDA’s regulation applies to all clinical investigations regulated by the FDA as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA. The FDA may apportion grants558 to, and enter into contracts with, public and private entities and individuals to assist in defraying the costs (1) of qualified testing expenses incurred in connection with the development of drugs for rare diseases and conditions, (2) of developing medical devices for rare diseases or conditions, and (3) of developing medical foods for rare diseases or conditions.559

The NIH, a division of HHS, is the principal channel through which the federal government funds biomedical research in the United States.560

A. The Effect of Federal Funding on Research Spending

The NIH leads the public sector as the single largest source of funding for clinical research. The NIH budget receives significant congressional support, and according to the NIH Almanac, more than 83 percent of its $30 billion budget goes to more than 300,000 research personnel at over 3,000 universities.561 Two primary criteria determine the best possible level of research spending on a disease: (1) the potential benefit of finding a cure, measured by the disability, morbidity, premature mortality, and medical expenses prevented; and (2) the projected cost of finding a cure, measured as research productivity.562

The NIH evolved from numerous acts of Congress and funding programs.563 For example, in 1899 the Marine Hospital Service was directed by Congress to

556Ward, 55 FOOD & DRUG L.J. at 229.
558The principal data source for determining the level of federal support for biomedical research is the “National Health Expenditure Accounts,” published by HHS as an annual series of statistics presenting total health expenditures. See Health Accounts, available at http://www.cms.hhs.gov/NationalHealthExpendData/.
55921 U.S.C. §360ee(a).
562Robert I. Field et al., Toward a Policy Agenda on Medical Research Funding, HEALTH AFF. (May–June 2003).
investigate leprosy in the United States.\textsuperscript{564} In 1912 the name Public Health and Marine Hospital Service was changed to Public Health Service and the PHS research program was expanded to include “diseases of man.”\textsuperscript{565} The Ransdell Act of 1930 reorganized, expanded, and redesigned the National Advisory Health Council\textsuperscript{566} as the National Institute of Health, funded construction of a physical plant, and authorized a system of fellowships.\textsuperscript{567} In 1937 the National Cancer Institute was established to conduct and support research relating to the cause, diagnosis, and treatment of cancer.\textsuperscript{568} The 1948 National Heart Act authorized the National Heart Institute to conduct, assist, and foster research; provide training; and assist the states in the prevention, diagnosis, and treatment of heart diseases. The act also changed the name of National Institute of Health to National Institutes of Health.\textsuperscript{569}

Since that time, the scope of federal funding for various research initiatives has undergone numerous changes. For example, the Health Research Facilities Act of 1956 (Title VII of the PHSA) authorized a PHS program of federal matching grants to public and nonprofit institutions for the construction of health research facilities.\textsuperscript{570} Also, in 1960 the PHSA was amended to authorize grants-in-aid to universities, hospitals, laboratories, and other public and nonprofit institutions to strengthen their programs of research and research training in the sciences related to health. In 1963 the Health Research Facilities Act of 1956 (Title VII of the PHSA) was amended to allow grants for multipurpose facilities that would provide teaching space as well as essential research space.\textsuperscript{571}

The Health Services Research, Health Statistics, and Health Care Technology Act\textsuperscript{572} of 1978 established the National Center for Health Care Technology in the Office of the Assistant Secretary for Health. The Health Promotion and Disease Prevention Amendments of 1984 amended the PHSA, extended health promotion and disease prevention research, and required that the NIH director be consulted as to procedures for peer review of applications and that the director of the NIH serve on the National Advisory Council on Health Care Technology Assessment.\textsuperscript{573}

The ADAMHA Reorganization Act of 1992 further amended the PHSA to incorporate the National Institute of Mental Health (NIMH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and National Institute on Drug Abuse (NIDA) into the NIH.\textsuperscript{574} Also, a new section (Section 409) was added to the PHSA, which defined “health services research” to include research regarding the impact of organization, financing, and management of health services of the quality, cost, access to, and outcomes of care.\textsuperscript{575} The Agency for Health Care

\textsuperscript{564}30 Stat. 976.
\textsuperscript{565}37 Stat. 309.
\textsuperscript{568}Pub. L. No. 75-244, 50 Stat. 559 (1937).
\textsuperscript{574}Id.
Policy and Research Reauthorization Act of 1992 required that the National Library of Medicine establish an information center on health service research and on selected technology assessments and clinical practice guidelines.\(^{576}\)

The Children’s Health Act of 2000 authorized research related to autism, Fragile X syndrome, juvenile arthritis, juvenile diabetes, asthma, hearing loss, epilepsy, traumatic brain injuries, childhood skeletal malignancies, muscular dystrophy, autoimmune diseases, birth defects, and genetic mental impairment, among other conditions.\(^{577}\)

The Department of Defense Appropriations Act, 2002, provided funding for the NIH for bioterrorism under the Emergency Supplemental Act, 2002 (which is part of this legislation). In addition, funds were provided for the construction of a level-4 biosafety laboratory and related infrastructure costs at the National Institute of Allergy and Infectious Diseases (NIAID) and for improving laboratory security at the CDC and NIH. The bill also includes funds for the National Institute of Environmental Health Sciences (NIEHS) “for carrying out under current authorities, worker training, research, and education activities” in response to the September 11 terrorist attacks.\(^{578}\)

The Rare Diseases Act of 2002 provided statutory authorization for the existing NIH Office of Rare Diseases (ORD). The measure requires the director of the ORD to recommend an agenda for research on rare diseases, promote coordination and cooperation among NIH Institutes and Centers, promote sufficient allocation of NIH resources related to rare diseases, and serve as the principal advisor on orphan diseases to the director of the NIH. In addition, the legislation established regional Centers of Excellence on Rare Diseases.\(^{579}\)

The Homeland Security Act of 2002 established a new executive branch agency known as the U.S. Department of Homeland Security (DHS). Among its research provisions, the act:

1. Established within DHS a Directorate of Science and Technology, to conduct basic and applied research, development, demonstration, testing, and evaluation activities that are relevant to any or all elements of DHS with the exception of human health-related research and development activities;
2. Required the Secretary of HHS to set priorities, goals, objectives, and policies and to develop a coordinated strategy for these activities in collaboration with the Secretary of Homeland Security; and
3. Authorized the Secretary of Homeland Security to draw upon the expertise of any federally supported laboratory, and to establish a headquarters laboratory and additional laboratory units for DHS at any laboratory or site.\(^{580}\)

Finally, the Project Bioshield Act of 2004 authorized NIAID to award grants or contracts to public and nonprofit private entities to expand, remodel,
renovate, or alter existing research facilities or construct new research facilities.\textsuperscript{581}

\textbf{B. Private Industry and Academic Clinical Research}

In addition to the NIH, private industry has become an increasingly important sponsor of clinical research. PhRMA members have increased domestic research and development spending from $6.8 billion in 1990 to an estimated $23.9 billion in 2001.\textsuperscript{582} Also, health foundations with assets totaling $15.2 billion have been established through the conversion of nonprofit hospitals, health plans, and health systems to for-profit entities.\textsuperscript{583}

The rapid growth in clinical research and clinical research funding over the past two decades has fostered the emergence of the contract research industry, which focuses on the management of outsourced clinical trials for pharmaceutical companies, biotechnology and medical device firms, and universities. An estimated $5 billion to $8 billion of pharmaceutical R&D is used to fund clinical trials conducted by contract research organizations (CROs). Examples of CROs include Quintiles,\textsuperscript{584} Covance (formerly Corning Pharmaceutical Services Inc.),\textsuperscript{585} and PAREXEL (research bases in at least 29 countries).\textsuperscript{586}

CROs increase the efficiency of the research pipeline through focused expertise. CROs also increase the effectiveness of clinical trials by promoting inter-institutional collaboration at a national and even international level, helping to minimize institutional, regional, or investigator biases. Centralized clinical laboratory services allow consistency of laboratory methods, reagent manufacturers, and clinical trial reference ranges; equipment calibration; and standardized reporting of data.\textsuperscript{587}

Clinical trial management services for all phases include project management, study and protocol design, case report form development, clinical database design, data entry and verification, data management, statistical analysis and reporting, investigator and site selection, healthy volunteer and special population recruitment, investigator meetings, clinical monitoring, centralized clinical trial laboratory, bioanalytical and clinical chemistry laboratory services, pharmacokinetics and pharmacodynamics, expert report writing, and regulatory applications.\textsuperscript{588} The international reach of CROs facilitates regulatory approval in multinational markets simultaneously rather than sequentially in the setting of increasing harmonization of U.S., European, and Japanese drug evaluation procedures.

\textsuperscript{582}Pharmaceutical Research and Manufacturers of America 2005 Industry Profile, available at http://www.phrma.org/2005_industry_profile/1/.
\textsuperscript{584}Incorporated in 1982; see http://www.quintiles.com.
\textsuperscript{585}Incorporated in 1996; see http://www.covance.com.
\textsuperscript{586}Founded in 1983; see http://www.PAREXEL.com.
\textsuperscript{588}Id.
Site management organizations (SMOs) are “centrally managed groups of multiple investigative sites that work on behalf of biopharmaceutical companies or contract research organizations and focus on the front-end aspects of clinical studies.”\(^{589}\) These include marketing investigative sites (to sponsors or CROs), negotiating contracts, obtaining IRB approval and handling regulatory documents, enlisting clinical investigators, training investigators and coordinators, recruiting and enrolling patients, and improving and standardizing sites and practices.

However, a significant amount of medical research, both primary and clinical, occurs at universities and medical schools. Academic medicine is organized around three interrelated activities: medical education, research, and patient care. Universities obtain their funding for research from the NIH, private foundation grants, and, increasingly, private industry/corporate funding. In addition, research at medical schools is further partially subsidized by the government because some patient care costs (in addition to the funded research costs) are indirectly or directly passed on to the Centers for Medicare and Medicaid Services (CMS).

The Morrill Act of 1862 was the first to suggest that universities could foster economic development through technology transfer.\(^{590}\) Technology transfer refers to translational research—research that could be subsequently translated into pharmaceutical development and profit. Historically, the principal acceptable mode of the transfer of research data from the public to the private sector was by way of scientific publication; this was primarily a result of university-based research. Because industry funding had outpaced NIH funding, the priorities of academic research centers shifted to pursue technology transfer goals. In 1950, Congress allocated $15 million to establish the National Science Foundation (NSF) to support basic scientific research at universities. The Stevenson-Wydler Technology Innovation Act of 1980 made technology transfer a mission of government-owned, contractor-operated laboratories,\(^{591}\) a decision based in part on the determination that technology and industrial innovations are central to the economic, environmental, and social well-being of U.S. citizens.

The Bayh-Dole Act of 1980 specifically permitted universities and other federally funded institutions to patent and profit from inventions arising from federally funded research.\(^{592}\) The goal of this legislation was to spur the development and commercialization of technology by providing universities and researchers with incentives to focus their research on marketable products. The Bayh-Dole Act is generally recognized as a primary cause of the increasingly commercial orientation of American medical research.\(^{593}\)

Although the NIH has a strong interest in ensuring widespread dissemination of broadly enabling research tools like stem cell lines for use across the

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\(^{590}\)7 U.S.C. §301 (providing for lending grant aid to colleges).


broad spectrum of biomedical research, the Bayh-Dole Act seriously limits the extent to which the NIH can oversee the use of intellectual property rights by its grantees. As long as the contractor is based in the United States, funding agencies such as the NIH may restrict patenting in “exceptional circumstances,” when the agency determines that withholding title to the invention from the contractor will better promote the goals of the Bayh-Dole Act, or when certain government interests are in play. If the Secretary of Commerce determines that “any individual determination or pattern of determinations is contrary to the policies and objectives of [the Bayh-Dole Act],” the Secretary must advise the head of the agency and the Administrator of the Office of Federal Procurement Policy and recommend corrective actions.

The Federal Technology Transfer Act of 1986 (FTTA) amended the Stevenson-Wydler Act, encouraging collaboration and cooperation between federal laboratories and universities or the private sector by permitting government-owned and government-operated laboratories to enter directly into cooperative research and development agreements (CRADAs) with industry and universities. However, Section 5171 of the Omnibus Trade and Competitiveness Act of 1988 clarified the FTTA, requiring that federally supported international science and technology agreements be negotiated so as to ensure that intellectual property rights are properly protected. The National Competitiveness Technology Transfer Act of 1989 further amended the Stevenson-Wydler Act by extending the CRADA authority of the FTTA to labs owned by the government and operated by private contractors.

The issues of private grants and of potential conflicts of interest that might occur as a result of financial incentives in research have necessitated increased oversight and disclosure requirements in the interest of public health and safety. Since 1995 the Public Health Service has attempted to regulate certain research relationships by requiring academic investigators who receive federal grants to disclose their personal financial relationships with for-profit companies. In particular, recipients of NIH or NSF funding are required to disclose to their institutions annual income in excess of $10,000 or equity ownership exceeding 5 percent in a company whose “financial interests would reasonably appear to be affected by the research.”

To minimize bias in clinical studies due to financial interests of the clinical investigator, the regulation requires “an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests

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594 Id. §202(a)(i)-(iv).
595 Id. §202(b)(1).
596 Id.
600 See Objectivity in Research, 60 Fed. Reg. 35,815 (July 11, 1995).
of the clinical investigators in the product under study or in the sponsor of the
covered study.”

C. The Effect of FDA Approval on Reimbursement and Coverage Under
Medicare & Medicaid

The Centers for Medicare and Medicaid Services is the subdivision of HHS charged with administering Medicare, which was established by Congress in 1965. Medicare and Medicaid are major purchasers of health care in the United States, so any requirements they impose on reimbursement have a major impact on what health care entities do. Both Medicare and Medicaid have jurisdiction relating to drug coverage. Coverage decisions for an increasing number of items, such as drugs, devices, and services, are made at a national level by CMS with the aid “of employed contractors.” The Social Security Act also authorizes state Medicaid programs to cover prescription drugs. However, a drug’s eligibility for purchase in the United States under Medicare and Medicaid depends on its FDA approval. Covered outpatient drugs include neither FDA-designated new drugs nor drugs that are the subject of FDA administrative action. The FDAMA also provides that patients and providers must have access to information on all clinical drug trials being conducted for serious or life-threatening diseases.

CMS places limitations on the drugs that are available under its reimbursement rules. In general, this limitation is similar to that of a formulary which defines preferred drugs based on both cost and benefit. Drugs provided under state Medicaid plans “are drugs purchased by the entity for which payment is made by the State under the State plan for medical assistance under title XIX of the Social Security Act [42 U.S.C. §1396 et seq.].”

Reimbursement for non–FDA approved drugs in clinical trials under an IND is generally decided on a case-by-case basis. Two types of costs are associated with clinical trials: research costs and patient care costs. Research costs generally include costs for “data collection and management, research physician and nurse time, analysis of results, and tests purely performed for research purposes.” Although research costs may be paid by the sponsor of the trial, pharmaceutical companies, the federal government (through the NIH), or the patients and/or their insurers are most commonly responsible for patient care costs.

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601 21 C.F.R. §54.1(b).
603 42 U.S.C. §1395d(a)(1) (Scope of benefits); id. §1395x(t)(1), (2) (Definitions); id. §1396a(a)(10)(A); §1396d(a)(12) (State plans for medical assistance).
605 42 U.S.C. §§1396a(a)(10)(A), 1396d(a)(12). “A State plan for medical assistance must . . . . provide for making medical assistance available . . . . [including] payment of part or all the cost . . . . prescription drugs.”
606 Medicare & Medicaid Guide (CCH) ¶17,432K.
607 42 U.S.C. §256b(a)(1) (2005). (“The Secretary shall enter into an agreement with each manufacturer of covered drugs under which the amount required to be paid (taking into account any rebate or discount, as provided by the Secretary) to the manufacturer for covered drugs . . . .”).
608 Id. §256b(a)(3).
Patient care costs fall into two categories: usual care costs and extra care costs. Usual care costs include doctor visits, hospital stays, clinical laboratory tests, X-rays, and other similar costs that would occur during treatment whether or not the patient is participating in a clinical trial. Extra care costs are costs directly attributable to participation in the clinical trial, which include, for example, hospitalization due to unexpected side effects of an investigational drug. Thus, these are the costs for which patients seek reimbursement from third-party payors.

Most third parties, including private insurers and federal programs such as Medicare, have not traditionally reimbursed patients for costs associated with participation in clinical trials. The principal argument is that clinical trials are “experimental” or not “medically necessary” and, therefore, they fall outside the scope of coverage. Most of the litigation challenging denial of coverage for participation in a clinical trial is brought under the Employee Retirement Income Security Act of 1974 (ERISA).

V. MARKETING AND ADVERTISING ISSUES

Advertisers of prescription drugs must navigate several federal agencies and laws when developing and publishing advertisements for a given drug. The major legal issues concerning drug advertising are discussed in detail below. A more detailed discussion of marketing and advertising issues affecting the marketing and advertising of drugs is included in Chapter 3.

A. FTC and FDA Shared Regulation of Drug Marketing

The FTC and FDA share exclusive jurisdiction over regulation of drug marketing per the Memorandum of Understanding Between the FTC and the

611 ERISA preempts any state law claims based on denial of coverage. See Kentucky Ass’n of Health Plans, Inc. v. Miller, 538 U.S. 329 (2003) (“Despite the statutory focus upon the relationship between the HMOs and third-party providers, the statutory prohibition substantially affected the type of risk pooling arrangements that the HMOs could offer and thus constituted regulation of the business of insurance.”).
612 Pilot Life Ins. Co., 481 U.S. at 45 (“To summarize the pure mechanics of the provisions quoted above: If a state law ‘relate[s] to . . . employee benefit plan[s],’ it is pre-empted. §514(a). The saving clause excepts from the pre-emption clause laws that ‘regulate[s] insurance.’ §514(b)(2)(A). The deemer clause makes clear that a state law that ‘purport[s] to regulate insurance’ cannot deem an employee benefit plan to be an insurance company, §514(b)(2)(B).”).
614 36 Fed. Reg. 18,539 (Sept. 16, 1971) (“The Food and Drug Administration has primary responsibility with respect to the regulation of the truth or falsity of prescription drug advertising.”).
The FDA maintains primary jurisdiction over the labeling of prescription drugs and restricted medical devices. The FTC, on the other hand, retains primary jurisdiction over OTC medications, foods (including dietary supplements), nonrestricted medical devices, and cosmetics. The FDA’s goal is to assure the safety and efficacy of drugs; on the other hand, the primary mission of the FTC is to maintain the smooth operation of the commercial market through the detection and elimination of acts or practices that are unfair or deceptive.

Specifically, the FTC Act, as enacted in 1914, gives the FTC power to enact rules that define unfair or deceptive trade practices. Section 5(a) of the Act provides that “[u]nfair methods of competition in commerce are hereby declared unlawful” and that the “[Federal Trade] Commission is hereby empowered and directed to prevent persons, partnerships, or corporations . . . from using unfair methods of competition in commerce.” The FTC, in addition to its recognized responsibility to “ensure that the nation’s markets function competitively, and are vigorous, efficient, and free of undue restrictions,” has a broad jurisdictional mandate to investigate allegations of “unfair or deceptive acts or practices in or affecting commerce,” including the “dissemination” of any “false advertisement . . . for the purpose of inducing, directly or indirectly the purchase of . . . drugs.”

Thus, in general the FTC’s efforts are directed toward stopping actions that threaten consumers’ opportunities to exercise informed choice. The FTC relies on two major principles to reach its regulatory goals: (1) advertising must be truthful, and not confusing to consumers (including claims that are reasonably implied as well as express claims); and (2) the advertiser must substantiate objectively, advertising claims prior to their dissemination.

A false advertisement is statutorily defined in the FTC Act as “an advertisement, other than labeling, which is misleading in a material respect.” The FTC has further stated that an advertisement or practice is “deceptive” if there

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615 See 15 U.S.C. §§41, 52–55 (1994); see also 36 Fed. Reg. at 18,589 (stating that FTC has primary responsibility for regulation of the truth or falsity of all advertising (other than labeling) of food, drugs and cosmetics).


617 See 15 U.S.C. §§41, 52–53 (describing the FTC’s creation and its authority to act against anyone it believes is violating the advertising restrictions); see also 36 Fed. Reg. at 18,539 (explaining that the FTC, not the FDA, has authority over OTC drugs and medical devices).

618 Id., §§45(a), 52.

619 Id., §57(a)(1)(B) (FTC rules can also contain provisions to prevent unfair or deceptive trade practices).


621 15 U.S.C. §§45(a)(1)–(2), 52(a). Section 5(a) of the Act declares unlawful “unfair or deceptive acts or practices in or affecting commerce” and empowers the Commission to prevent such acts or practices. Under 15 U.S.C. §52(a)(2), Section 12 of the Act is specifically directed to false advertising and prohibits the dissemination of “any false advertisement” in order to induce the purchase of “food, drugs, devices, or cosmetics.” Under U.S.C. §52(b), the Act also provides that the dissemination of any such false advertisement is an “unfair or deceptive act or practice in or affecting commerce” within the meaning of Section 5.

622 K.M. Friedman, Internet Prescribing Limitations and Alternatives, 10 ANN. HEALTH L. 139, 149 (2001).

is a material “misrepresentation, omission, or other practice, that misleads the consumer acting reasonably in the circumstances, to the consumer’s detriment.” 624 In order to prove that an act or practice is deceptive or constitutes a false advertisement, the FTC uses the “Cliffdale Standard.” 625 Under this test, the FTC must prove “first, [that] there is a representation, omission, or practice that, second, is likely to mislead consumers acting reasonably under the circumstances, and third, that the representation, omission, or practice is material.” 626

On the other hand, the FDA defines advertising to include “advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.” 627 The FDCA requires advertisements that make claims regarding the efficacy of prescription drugs or medical devices to contain brief summaries of the indications, contraindications, side effects, and warnings for use of the products 628—a provision termed “fair balance.” 629 To meet FDA requirements, fair balance information “must be provided along with, and must be reasonably prominent with respect to, any claim of safety and/or effectiveness.” 630

Advertising must also be a “true statement” of information relating to side effects, contraindications, and effectiveness, 631 and where possible, provide easy and ready access to the actual package insert. 632 An advertisement does not meet the requirements of a “true statement” if it:

1. Is “false or misleading with respect to side effects, contraindications, or effectiveness”;  
2. Fails to present a fair balance between information relating to side effects and contraindications and information relating to effectiveness of the drug; or  
3. Fails to reveal material facts. 633

The “brief summary” aspect of the “true statement” requirement provides the FDA with the basis to propose advertising regulations consistent with the FDCA 634 and includes highly technical information concerning product labeling and the product’s side effects, contraindications, and effectiveness. 635 The prescription drug advertising regulations distinguish between print and broadcast

626 FTC v. Pantron I Corp., 33 F.3d 1088, 1095 (9th Cir. 1994).
628 21 C.F.R. §202.1(e)(5)(ii). This includes material published on some Web sites, some social media, or the like.
631 21 C.F.R. §202.1(e).
632 Id. §202.1.
633 Id. §202.1(5).
634 Id. §202.1(k)(1)(1).
635 Id. §202.1(l)(1).
In order to effectively comply, only print advertisements need include the brief summary. Sponsors of broadcast advertisements may make an “adequate provision” to offer to disseminate “the approved or permitted package labeling in connection with the broadcast presentation” as an alternative to the brief summary required of printed advertising. The “major statement” requires the prominent disclosure of information concerning major side effects and contraindications of the prescription drug.

Thus, an advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading if, among other things, it:

1. “[C]ontains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients . . . safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience . . . whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references”;
2. Contains undemonstrated comparisons with respect to drug safety or effectiveness;
3. Contains information or opinions that have been rendered invalid by contrary and more credible recent information;
4. Contains selective presentation of information from published articles or other references;
5. Implies that the study represents larger or more general experience than it actually does;
6. Fails to disclose that claimed results may be due to concomitant therapy or placebo effect (information concerning placebo effect is not required unless the advertisement promotes the drug for use by man);
7. Contains favorable data or conclusions from nonclinical studies of a drug in a way that suggests clinical significance;
8. Fails to refer to concurrent or more recent unfavorable data or statements from the same authority on the same subject or subjects;
9. Selectively uses a “quote or paraphrase out of context to convey a false or misleading idea”;
10. Cites “literature, quotations, or references that purport to support an advertising claim but in fact do not support the claim or have relevance to the claim”;
11. Cites “literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling”;
12. “[O]ffers a combination of drugs for the treatment of patients suffering from a condition amenable to treatment by any of the components”;

See id. §202.1.

See id. §202.1.

21 C.F.R. §202.1(c)(1).
13. “[C]ites a study on normal individuals without disclosing that fact”;
14. Suggests that statistics used in the studies are valid if they are not;
15. Employs a statistical finding of “no significant difference” to “claim clinical equivalence or to deny or conceal the potential existence of a real clinical difference”;
16. States or represents that a drug differs from or does not contain a named drug or category of drugs;
17. Uses data derived from patients treated with differing dosages from those recommended or approved;
18. Employs a “headline, subheadline, or pictorial or other graphic matter in a way that is misleading”; or “represents or suggests that drug dosages properly recommended for use in the treatment of certain classes of patients or disease conditions are safe and effective” when such is not the case”; or
19. Presents required information relating to side effects or contraindications by means of a “general term . . . in place of disclosing each specific side effect and contraindication.”

B. The Prescription Drug Marketing Act

The Prescription Drug Marketing Act of 1987 (PDMA)\(^{640}\) regulates drug marketing in that it regulates the distribution of prescription drug samples to physicians and other licensed health providers. The PDMA allows manufacturers and authorized distributors to provide samples only upon written request “made on a form which contains the practitioner’s name, address, and professional designation, the identity of the drug sample requested, the quantity of drug samples requested, the name of the manufacturer or authorized distributor of the drug sample, the date of the request and signature of the practitioner making the request.”\(^{641}\) The PDMA also requires that pharmaceuticals manufacturers and distributors “conduct, at least annually, a complete and accurate inventory of all drug samples in the possession of [their] representatives” and to “maintain records for at least 3 years of all drug samples distributed, destroyed, or returned to the manufacturer or distributor, of all inventories maintained under this subparagraph, of all thefts or significant losses of drug samples, and of all requests [made by a practitioner pursuant to 21 U.S.C. §353(d)(3)(A)] for drug samples.”\(^{642}\)

The PDMA also provides in relevant part that “[n]o person may engage in the wholesale distribution in interstate commerce of drugs . . . in a State unless such person is licensed by the State in accordance with the guidelines issued.”\(^{643}\) The law forbids wholesale distribution of prescription drugs in interstate com-

\(^{639}\)See id., §202.1(6).
\(^{642}\)Id., §353(d)(2)(C).
merce without a state license, and forbids wholesale distribution of prescription drugs without providing a history of transactions from the original manufacturer.

C. Regulation of Direct-to-Consumer Advertising

Direct-to-consumer (DTC) marketing of drugs involves the advertisement of pharmaceuticals directly to the consumer. In general, there are three broad categories of DTC prescription drug advertisements:

1. Product claims provide an overview of the drug’s name and indications, and states the safety and efficacy of the drug;
2. Help-seeking advertisements seek to “encourage consumers with particular symptoms, conditions, or diseases to consult their physician to discuss general treatment options”; and
3. Reminder-type advertisements seek to reinforce brand-name recognition and brand loyalty, exclude all representations or suggestions about the drug, and are, therefore, associated with fewer regulatory restrictions.

DTC is widely accepted in the case of OTC products that do not require a prescription. In the case of drugs restricted to sale by prescription, DTC marketing suggests the availability and potential utility of a given prescription drug. Consumers may then ask their physician or other prescribing provider to furnish them with the necessary prescription.

The key issues regarding DTC marketing of prescription drugs can be summarized in this way:

Proponents argue that direct-to-consumer promotion is of educational value and will improve the physician-patient relationship, increase patient compliance with drug therapy and physician visits, and lower drug prices. The promise of DTC prescription drug advertisements lies in their potential to educate consumers about their medical conditions and the possibility of available treatment options; and that the information presented in DTC communications can inform patients’ decision making and leads to more productive physician-patient encounters. Opponents contend that consumers do not have the expertise to accurately evaluate and comprehend prescription drug

644 See id., §§331(t), 333(b)(1), 353(e)(2)(A).
645 See id., §§331(t), 333(a)(2), 353(e)(1)(A).
646 See K. Hanson, Marketing and Direct-to-Consumer Advertising (DTCA) of Pharmaceuticals (May 8, 2006), available at http://www.ncsl.org/programs/health/rxads.htm. Hanson provides an excellent compendium of state laws, bills not enacted, and related resources describing or affecting the marketing and advertising of pharmaceuticals, including disclosure of information relating to DTC advertising. DTC advertising regulations are also discussed in Chapter 3, Federal Regulation of Advertising, Promotion, and Distribution Practices, at Section II.
648 Id.
649 Interestingly, in 1983, the FDA requested a voluntary moratorium on DTC advertisements for prescription drugs in order to “allow time for a dialogue among consumers, health professionals, and industry on the issue of direct-to-consumer advertising of prescription drugs” and to “allow time for the conduct and interpretation of research by interested parties on aspects of consumer-oriented drug advertising.” Direct-to-Consumer Advertising of Prescription Drugs; Withdrawal of Moratorium, 50 Fed. Reg. 36,677 (Sept. 9, 1985). FDA subsequently announced its position on the dissemination of DTC advertising in September 1985. Id.
Opponents also argue that such promotion is misleading by failing to adequately communicate risk information, and that such promotion will damage the physician-patient relationship, increase drug prices, increase liability actions, and lead to over-medication and drug abuse.

The regulations governing DTC advertising of prescription drugs are implemented and enforced by FDA’s Office of Prescription Drug Promotion (OPDP). Generally, DTC advertising for prescription drug products, including both print (e.g., newspaper or magazine) and broadcast (e.g., television, radio, or telephone) advertising, must meet the requirements set forth in the FDA’s regulations which address the content, review, and approval process for such communications to consumers. Pharmaceutical manufacturers must submit copies of all drug advertisements to the FDA (specifically, the OPDP) before they are first broadcast, published, or otherwise disseminated to the public.

In the future, the FDA may also require prescription drug promotional labeling or print advertising to include a quantitative summary, in a standardized format, of the risks and benefits of prescription drugs. As mandated by the PPACA, the FDA’s commissioner must submit a report to the HHS Secretary determining the impact of such quantitative summaries on health care decision-making by clinicians, patients, and consumers. If the commissioner finds that such dissemination will positively impact such decision-making, the FDA will be required to promulgate associated regulations within three years of the report submission. The First Progress Report under this section was submitted to Congress on March 23, 2011, concluding that existing literature provided an insufficient basis to determine the impact of quantitative summaries. As a result, the First Progress Report recommended that the conducting of additional studies, a literature review, and consultation are necessary prior to the promulgation of regulations. In 2012, a final technical report on the presentation of quantitative benefit information in DTC television and print advertisements for prescription drugs was completed and a literature review of communicating quantitative risks and benefits in promotional prescription drug labeling or print

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650 See K.A. Kaphingst et al., Comprehension of Information in Three Direct-to-Consumer Television Prescription Drug Advertisements Among Adults With Limited Literacy, 10 J. HEALTH COMMUN. 609–19 (Oct.–Nov. 2005) (Participants correctly answered an average of 59% of comprehension questions. The percentage of respondents correctly answering individual comprehension questions ranged from 26% to 92%).


655 Id. §3507 (d), 124 Stat. at 530.


advertising was accepted on January 10, 2013. The final technical report generally concludes that “inclusion of quantitative benefit information in DTC print and television ads has the potential to help people make informed decisions about speaking with their health care professional about prescription drugs.”

D. Potential Sanctions for Violating FDA or FTC Rules and Regulations

Potential sanctions for violations of FDA or FTC rules and regulations pertaining to false or misleading advertising of pharmaceuticals traditionally have included the equitable remedies of disgorgement, restitution, cease and desist orders, and injunction. Disgorgement deters violations of statutory law by forcing violators to surrender that amount by which they have been unjustly enriched. Restitution restores to an aggrieved party the loss caused by the wrongdoing of another, i.e., returns “the parties to the position that existed before the transaction occurred.”

1. FDA Rules—Responsible Corporate Official Liability

In addition to the penalties discussed above, the FDCA also authorizes criminal prosecution of corporations and such persons who perform “prohibited acts.” To be held criminally liable under the FDCA, a person must have had “a responsible share in the furtherance of the transaction which the statute outlaws, namely, to put into the stream of interstate commerce adulterated or misbranded drugs.”

Corporate executives may also be held liable for a pharmaceutical company’s violations of the FDCA under the Park doctrine. In essence, the Park doctrine provides for criminal liability (first-time misdemeanor and possible subsequent felony) under the FDCA without proof that a corporate official acted with intent or even negligence. The FDA’s policies were recently set forth in the FDA’s Regulatory Procedures Manual for FDA personnel, which describes

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660 See also Chapter 3, Federal Regulation of Advertising, Promotion, and Distribution Practices.

661 SEC v. Commonwealth Chem. Sec., Inc., 574 F.2d 90, 102 (2d Cir. 1978) (“the primary purpose of disgorgement is not to compensate . . . it is a method of forcing a defendant to give up the amount by which he was unjustly enriched”).

662 See, e.g., In re First Penn Corp., 793 F.2d 270, 272 (10th Cir. 1986) (“The object of restitution is to return the parties to the position that existed before the transaction occurred.”).


664 United States v. Dotterweich, 320 U.S. 277, 284 (1943) (“The offense is committed, unless the enterprise which they are serving enjoys the immunity of a guaranty, by all who do have such a responsible share in the furtherance of the transaction which the statute outlaws, namely, to put into the stream of interstate commerce adulterated or misbranded drugs.”).

665 Responsible Corporate Officials are not limited to officers or directors. Rather, the term includes all corporate officials who could have prevented the violation.
the criteria for which FDA would refer a matter for potential prosecution under the Park doctrine.\textsuperscript{666} Thus, in the Regulatory Procedures Manual, the FDA stated it would consider several factors in determining if prosecution is warranted, including the corporate official’s knowledge of an actual participation in the violation, whether the violation involves actual or potential harm to the public, whether the violation is obvious, whether the violation reflects a pattern of illegal behavior and/or failure to heed prior warnings, whether the violation is widespread, whether the violation is serious, the quality of the legal and factual support for the proposed prosecution, and whether the prosecution is a prudent use of FDA resources.\textsuperscript{667}

Unfortunately, these criteria provide little additional guidance as to when the FDA will refer a matter for Park doctrine prosecution. That being said, responsible corporate officials at companies with a history of violations (evidenced by receiving Form FDA 483s and warning letters) or with violations that pose potential or actual harm to the public may be at particular risk for a Park doctrine referral. Moreover, the consequences of a Park conviction, even pursuant to a plea agreement, can include criminal liability as well as debarment from the industry.\textsuperscript{668}

Finally, if pharmaceutical companies fail to submit proposed DTC advertising for review and comment before use, the OPDP can exercise various statutory enforcement powers to bring a company into compliance, including:

1. Notices of violations directing discontinuance of violative false or misleading advertising;
2. Warning letters;
3. Injunctions and consent decrees;
4. Referrals for criminal investigation or prosecution; or
5. Seizures.\textsuperscript{669}

\textsuperscript{666}United States v. Park, 421 U.S. 658 (1975); see also United States v. Higgins, Case No. 09-403-4, 2011 U.S. Dist. LEXIS 140343 (E.D. Pa. Dec. 7, 2011), in which the court affirmed a severe sentence for a corporate officer who pled guilty under the Park doctrine to FDCA violations of bringing adulterated and misbranded medical devices into interstate commerce. In United States v. Undetermined Quantities of Articles of Drug, 145 F. Supp. 2d 692, 705 (D. Md. 2001), the court denied a defendant president’s partial summary judgment motion, finding that the “evidence indicates that Mr. Hitt was aware of potential FDCA violations and had the power to take preventive or corrective action,” and that such evidence was “sufficient to impose civil liability upon Mr. Hitt for the FDCA violations.” The FDA has also tried to prosecute the attorneys for pharmaceutical companies under the Park doctrine. For example, in United States v. Stevens, the FDA prosecuted GlaxoSmithKline’s in-house counsel under the Park doctrine, alleging that she obstructed justice and falsified documents regarding GlaxoSmithKline’s marketing activities. Eventually, the U.S. District Court for the District of Maryland granted Stevens’ motion for judgment as a matter of law and held that no reasonable jury could convict her of the alleged crimes. United States v. Stevens, Case No. RWT-10-694 (D. Md. May 10, 2011) (transcript of record), available at http://lawprofessors.typepad.com/files/110510stevens.pdf.


\textsuperscript{668}See generally Friedman et al. v. Sebelius et al., 686 F.3d 813 (D.C. Cir. 2012).

\textsuperscript{669}DTC Advertising Hearing (statement of Janet Woodcock, director of CDER).
2. FTC Rules

The FTC is also authorized to request that courts impose penalties for violations of final FTC orders, including those relating to violations of FTC rules on advertising.\(^{670}\) The FTC has asserted a restitutionary power primarily for remedying “unfair or deceptive acts or practices.”\(^ {671}\) In 1975, Congress added Section 19 to the FTC Act, effectively enabling the FTC to obtain restitution from the courts for injured consumers if qualifying criteria, such as proof of intent and a statute of limitations, are met.\(^ {672}\) In \textit{FTC v. Mylan Laboratories}, the FTC alleged price fixing in the generic drug market, and Mylan Laboratories was required to disgorge $100 million in profits.\(^ {673}\) The FTC also has authority to order companies to cease and desist violative conduct.\(^ {674}\) Specifically, under Section 13(b) of the FTC Act, the FTC has authority to petition federal district courts for preliminary injunctions to halt conduct allegedly violating Section 5 of the FTC Act pending administrative determination of the conduct’s legality.\(^ {675}\) Section 13(b) also authorizes courts to grant permanent injunctions in “proper cases.”\(^ {676}\)

VI. Federal Agency Discretion

When it enacts a particular statutory scheme, Congress often leaves legislative “gaps” with instructions to the specific department or agency charged with executing the statute to promulgate necessary regulations to fill the gaps with appropriate interpretations of statutory language.\(^ {677}\) In promulgating these regulations, an agency or department is always limited to the authority delegated by Congress, and must act consistently with congressional directive or intent.\(^ {678}\)

The FDA also has relied on flexible judicial interpretations of its statutory authority to fulfill its legislative and regulatory mandate.\(^ {679}\) The federal judiciary is the final authority\(^ {680}\) on issues of statutory construction and can reject those agency administrative interpretations or constructions found to be contrary to congressional intent.\(^ {681}\) When a court is faced with a “pure question of statutory

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\(^{674}\) Id. §13(b), tit. IV, §408(f), Pub. L. No. 93-153, 87 Stat. 576, 592 (1973) (codified as amended at 15 U.S.C. §53(b) (1988)) (allowing FTC to obtain preliminary injunctions when it believes FTC Act will be violated and when it is in public interest).

\(^{675}\) Id.


\(^{677}\) See \textit{Bowen}, 488 U.S. 204.

\(^{678}\) See \textit{Chevron}, 467 U.S. 837.


\(^{680}\) Chevron, 467 U.S. at 843.
interpretation,” it relies on traditional methods of statutory construction to determine the intent of Congress.682 Courts have long recognized that considerable weight should be accorded to an executive department’s construction of the statutory scheme which it is entrusted to administer, and the principle of deference to administrative interpretations “has been consistently followed . . . whenever decision as to the meaning or reach of a statute has involved reconciling conflicting policies, and a full understanding of the force of the statutory policy in the given situation has depended upon more than ordinary knowledge respecting the matters subject to agency regulations.”683

Accordingly, a reviewing court will employ a two-step analysis of agency mandate and congressional intent, widely known as the “Chevron analysis.”684 In Chevron v. Natural Resources Defense Council, Inc.,685 the U.S. Supreme Court addressed the degree of judicial deference to be given to an agency’s interpretation of a statute made during the rulemaking process.686 Coincident with the rise of textualism and the fall of intentionalism, a majority of the U.S. Supreme Court justices increasingly equate step one of the Chevron analysis with a simple search for statutory clarity: “the Supreme Court has resolved the nature of the inquiry at step one: it is no longer a search for congressional intent; rather, it is simply a search for statutory clarity.”687

The issue of deference to an agency’s rulemaking is entwined with consideration of issues outside the agency’s purview. It has been suggested that Congress would prefer increasing deference to agency interpretations as the interpretive issue becomes closely connected with everyday administration . . . . [F]actors such as the technical nature of the issue and its complexity reinforce the need to defer. Chevron deference is therefore analogous to the deference traditionally accorded to routine agency applications of statutory terms in agency adjudications. Deference in those situations is given because Congress wants the courts to accord administering agencies the scope to carry out the statutory program. Deference, however, ceases to be mandatory when issues attain levels of importance that affect the basic design of the regulatory scheme. These “boundary” issues differ from so-called “jurisdictional” issues, which can vary widely in their regulatory significance . . . . Sometimes an interpretive issue rises to a level that Judge Breyer had called “central to the statutory scheme.”688

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682 See Immigration and Naturalization Serv. v. Cardoza-Fonseca, 480 U.S. 421 (1987) (“In that process of filling any gap left, implicitly or explicitly, by Congress, the courts must respect the interpretation of the agency to which Congress has delegated the responsibility for administering the statutory program.”).
686 Id. at 842.
The importance of *Chevron* was its recognition of an implied intent of Congress to legislatively delegate authority to an agency. That framework, however subjective, facilitated legal strategy in litigation. It is well recognized that “[l]egal outcomes frequently depend on the analytical framework selected; therefore, the critical need to identify and apply the appropriate framework in future cases drives this search for the current Supreme Court model used to analyze whether agency interpretations of statutes will stand or fall.”

Administrative discretion becomes particularly important when disputes arise over an agency’s interpretation of a statute or regulation, or its authority to implement the law. With federal agencies, these disputes often start with review under the APA, and the greater the discretion given to an agency, the less likely a court is to find the agency’s action improper. In this context, the FDA’s power to regulate the food and drug industries was recently enhanced when the U.S. Court of Appeals for the District of Columbia Circuit in *Holistic Candlers & Consumers Ass’n v. Food & Drug Administration* determined that “warning letters” do not constitute “final agency action” subject to judicial review under the APA.

The *Holistic Candlers* case started in February 2010, when the FDA issued warning letters to 15 manufacturers of ear candles. Ear candles are hollow tubes made of fabric soaked in beeswax or paraffin that a user places in his or her ear and sets on fire with an open flame. Manufacturers of ear candles have made claims that they mitigate or treat allergies, headaches, colds, flu, and sinus congestion, and may also relieve vision disorders, depression, or attention-deficit disorder. In the warning letters, the FDA stated that because of the claims, it appeared to the FDA that the ear candles were medical devices that had received neither premarket approval nor clearance. After meeting with the FDA to discuss the warning letters, several manufacturers sued, contending that by issuing the warning letters the FDA had determined that the ear candles are “unapproved medical devices.” The FDA moved to dismiss, *inter alia*, on the basis that the warning letters were not final agency action. The appellate court agreed and stated, “a warning letter communicates the agency’s position on a matter” but is “informal and advisory” and does not commit the FDA to taking any enforcement action. The court also determined that simply because an entity receiving a warning letter may, at some point, have to defend itself in an enforcement action based on the warning letter, it did not convert the warning letter into final agency action for purposes of suit under the APA.

**VII. Conclusion**

The FDA has statutorily defined oversight responsibility for overseeing the process of drug development, marketing and sales, and postmarketing surveillance. The FDA must reconcile competing priorities; the need to ensure public

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690664 F.3d 940 (D.C. Cir. 2012).
691*Id.* at 944.
692*Id.* at 943 n.4.
health and safety must be balanced against the goal of facilitating the expedient availability of medically necessary therapeutics; the need for access to vital pharmaceuticals must be balanced against economic protections under the patent statute; scientific progress must be balanced against risk. Science creates new possibilities, and the oversight for those possibilities must be grounded in the public good. There is little doubt that advances in genomics, proteomics, combination products, vaccines, and other new treatment modalities, as well as controversies in clinical research funding, importation, reimportation, patient-level marketing efforts, and treatment guideline development will continue to challenge the existing regulatory and legal framework.