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How FDA Approves Drugs and Regulates Their Safety and Effectiveness

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Summary

The Food and Drug Administration (FDA), a regulatory agency within the Department of Health and Human Services, regulates the safety and effectiveness of drugs sold in the United States. FDA divides that responsibility into two phases. In the *preapproval* (premarket) phase, FDA reviews manufacturers' applications to market drugs in the United States; a drug may not be sold unless it has FDA approval. Once a drug is on the market, FDA continues its oversight of drug safety and effectiveness. That *postapproval* (postmarket) phase lasts as long as the drug is on the market. Beginning with the Food and Drugs Act of 1906, Congress and the President have incrementally refined and expanded FDA's responsibilities regarding drug approval and regulation.

The progression to drug approval begins before FDA involvement. First, basic scientists work in the laboratory and with animals; second, a drug or biotechnology company develops a prototype drug. That company must seek and receive FDA approval, by way of an investigational new drug (IND) application, to test the product with human subjects. It carries out those tests, called clinical trials, sequentially in Phase I, II, and III studies, which involve increasing numbers of subjects. The manufacturer then compiles the resulting data and analysis in a new drug application (NDA).

At that point, FDA reviews the NDA with three major concerns: (1) safety and effectiveness in the drug's proposed use; (2) appropriateness of the proposed labeling; and (3) adequacy of manufacturing methods to assure the drug's identity, strength, quality, and purity. The Federal Food, Drug, and Cosmetic Act (FFDCA) and associated regulations detail the requirements for each step. FDA uses a few special mechanisms to expedite drug development and the review process when a drug might address an unmet need or a serious disease or condition. Those mechanisms include accelerated approval, animal efficacy approval, fast track designation, breakthrough therapy designation, and priority review.

Once FDA has approved an NDA, the drug may enter the U.S. market, but FDA continues to address drug production, distribution, and use. Its activities, based on ensuring drug safety and effectiveness, address product integrity, labeling, reporting of research and adverse events, surveillance, drug studies, risk management, information dissemination, off-label use, and direct-to-consumer advertising, all topics in which Congress has traditionally been interested.

FDA seeks to ensure product integrity through product and facility registration; inspections; chain-of-custody documentation; and technologies to protect against counterfeit, diverted, subpotent, adulterated, misbranded, and expired drugs. FDA's approval of an NDA includes the drug's labeling; the agency may require changes once a drug is on the market based on new information. It also prohibits manufacturer promotion of uses that are not specified in the labeling. The FFDCA requires that manufacturers report to FDA adverse events related to its drugs; clinicians and other members of the public may report adverse events to FDA. The agency's surveillance of drug-related problems, which had primarily focused on analyses of various adverse-event databases, is now expanding to more active uses of evolving computer technology and links to other public and private information sources.

The FFDCA allows FDA to require a manufacturer to conduct postapproval studies of drugs. The law specifies when FDA must attach that requirement to the NDA approval and when FDA may issue the requirement after a drug is on the market. To manage exceptional risks of drugs, FDA may also require patient or clinician guides and restrictions on distribution. The agency publicly disseminates information about drug safety and effectiveness; and regulates the industry promotion of products to clinicians and the public.

Contents

Legislative History of Drug Regulation 1
How FDA Approves New Drugs 3
The Standard Process of Drug Approval 4
Investigational New Drug (IND) Application 5
Clinical Trials 5
New Drug Application (NDA) 5
FDA Review 6
Abbreviated New Drug Application (ANDA) 8
Special Mechanisms to Expedite the Development and Review Process 9
How FDA Regulates Approved Drugs 14
FDA Entities Responsible for Drug Postapproval Regulation 14
FDA Drug-Regulation Activities 15
Product Integrity 15
Reporting and Surveillance 17
Drug Studies 18
Risk Management 20
Information Dissemination 21
Labeling 22
Off-Label Use 25
Direct-to-Consumer (DTC) Advertising 26

Figures

Figure 1. Drug Development Path 4

Tables

Table 1. Examples of Drug Laws that Amended the FFDCA 3
Table 2. Comparison of FDA's Expedited Programs for Serious Conditions 11

Appendixes

Appendix. Abbreviations and Acronyms 28

Contacts

Author Information 29

The Food and Drug Administration (FDA) oversees the approval and regulation of drugs entering the U.S. market. The agency, part of the Department of Health and Human Services (HHS), is led by the Commissioner of Food and Drugs,[1] who executes the agency's responsibilities on behalf of the HHS Secretary. Two regulatory frameworks support the FDA's review of prescription drugs. First, FDA reviews the safety and effectiveness of new drugs that manufacturers[2] wish to market in the United States; this process is called *premarket approval* or *preapproval review*. Second, once a drug has passed that threshold and is FDA-approved, FDA acts through its *postmarket* or *postapproval* regulatory procedures.

This report is a primer on drug approval and regulation: it describes (1) how drugs are approved and come to market, including FDA's role in that process and (2) FDA and industry roles once drugs are on the pharmacy shelves.

Legislative History of Drug Regulation

The regulation of drugs by the federal government began with the Pure Food and Drug Act of 1906, which prohibited the interstate commerce of adulterated and misbranded drugs.[3] The law did not require drug manufacturers to demonstrate safety or effectiveness prior to marketing.

Over the next half-century, Congress and the President enacted two major pieces of legislation expanding FDA's authority. The Federal Food, Drug, and Cosmetic Act (FFDCA)[4] was enacted in 1938, requiring that drugs be proven safe before manufacturers may sell them in interstate commerce. Then, in 1962, in the wake of deaths and birth defects from the tranquilizer thalidomide marketed in Europe, the Kefauver-Harris Drug Amendments to the FFDCA was

[1] The Commissioner of Food and Drugs, often called the FDA Commissioner, is "appointed by the President by and with the advice and consent of the Secretary" (FFDCA §1003(d) [21 USC 393]).

[2] The Federal Food, Drug, and Cosmetic Act (FFDCA) refers to the sponsor of an application or the holder of an approved application. Because that entity is often the product's manufacturer or its employee, this report uses the term manufacturer throughout. Note that the manufacturer may also be the responsible person, for purposes of enforcement.

[3] The Pure Food and Drug Act of 1906, also referred to as the Federal Food and Drug Act (the F&DA) or the Wiley Act, P.L. 59-384. FFDCA §501 describes when a drug "shall be deemed to be adulterated." The conditions include being "filthy, putrid, or decomposed"; unsanitary conditions of facility that could allow injurious contamination; facility not operated according to current good manufacturing practice; various dangers involving the container or color additives; having different strength or lower quality or purity than the standard for the product; mixture or packing of ingredients that reduces quality or strength; substitution of ingredients; and when it comes from a facility whose operator has refused, delayed, or limited inspection.

FFDCA §502 describes when a drug "shall be deemed to be misbranded." The conditions include false or misleading labeling; a package without specified identifying information including quantity and manufacturer's name and place of business; required labeling element "not prominently placed thereon with such conspicuousness ... and in such terms to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use"; labeling that does not include product and ingredient (active and inactive) names, required information regarding quantity, or other required items; labeling without adequate directions for use and adequate warnings against certain kinds of use; not packaged and labeled as set forth in standards; a drug that imitates another drug or uses another drug's name; if distributed without "all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor ... the established name ... formula ... brief summary relating to side effects, contraindications, and effectiveness, ..."; and other items. Recent additions to the misbranding definition include noncompliance with a REMS, required postmarket studies, or required labeling changes; and nonpayment of PDUFA fees.

[4] Federal Food, Drug, and Cosmetic Act (FFDCA), P.L. 75-717, 1938. The FFDCA included a provision to repeal the F&DA.

enacted,[5] increasing safety provisions and requiring that manufacturers show drugs to be effective as well.[6]

The FFDCA has been amended many times, leading to FDA's current mission of assuring Americans that the medicines they use do no harm and actually work—that they are, in other words, *safe and effective*. In recent decades Congress and the President have enacted additional laws to boost pharmaceutical research and development and to speed the approval of new medicines. (See **Table 1** for examples.) The history of FDA law, regulation, and practice reflects the tension between making drugs available to the public and ensuring that those drugs be safe and effective. Advocates of industry, public health, consumers, and patients with specific diseases urge FDA (and Congress) to act—sometimes to speed up and sometimes to slow down the approval process. As science evolves and public values change, finding an appropriate balance between access and safety and effectiveness is an ongoing challenge.

Since the 1992 Prescription Drug User Fee Act (PDUFA), the budget for FDA's human drugs program has had two funding streams: budget authority (annual discretionary appropriations from the General Fund of the Treasury) and user fees. The user fee supplementation of the program's budget initially went to a narrowly defined set of activities to eliminate the backlog of new drug applications pending FDA review and to maintain an increased staff effort on incoming applications. With each five-year reauthorization, Congress and the President have expanded the range of activities the fees may cover.[7] The 2012 reauthorization added similar fee collection authority for the review of generic drug applications.[8]

While not the focus of this report, FDA also regulates products other than drugs—for example, biological products,[9] medical devices, dietary supplements, foods, cosmetics, animal drugs, and tobacco products.[10] Sometimes the agency addresses issues that straddle two or more product types that the law treats differently.

[5] Kefauver-Harris Drug Amendments to the FFDCA, P.L. 87-781, 1962.

[6] FDA staff and expert advisors worked to establish the effectiveness of those drugs that had been on the market before the 1962 effectiveness requirement. In 2006, the agency launched its Unapproved Drugs Initiative to remove unapproved drugs from the market through a risk-based enforcement program, see FDA, "Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100: Marketed New Drugs Without Approved NDAs or ANDAs," September 19, 2011, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf.

[7] CRS Report R44864, *Prescription Drug User Fee Act (PDUFA): 2017 Reauthorization as PDUFA VI*.

[8] The prescription drug and generic drug user fees were most recently reauthorized by the FDA Reauthorization Act of 2017 (FDARA; P.L. 115-52). See CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*, and CRS Report R44961, *FDA Reauthorization Act of 2017 (FDARA, P.L. 115-52)*.

[9] Whereas the FFDCA authorizes FDA to approve and regulate drugs, the Public Health Service Act (PHSA) authorizes FDA to license biological products (e.g., vaccines). Many of the FDA procedures described in this report also apply to the agency's regulation of biological products.

[10] See CRS reports on other FDA activities, such as CRS Report R42130, *FDA Regulation of Medical Devices*; CRS Report R43062, *Regulation of Dietary Supplements*; CRS Report R42885, *Food Safety Issues for the 114th Congress*; and CRS Report R41304, *FDA Final Rule Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco* (out of print; available to congressional clients upon request).

Table 1. Examples of Drug Laws that Amended the FFDCA

1983 *Orphan Drug Act* (P.L. 97-414) provided incentives for pharmaceutical manufacturers to develop drugs, biotechnology products, and medical devices for the treatment of rare diseases and conditions.
1984 *Hatch-Waxman Act* (Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417) was a compromise balancing greater patent protection of manufacturers with quicker public access to lower-priced generic drugs.
1992 *Prescription Drug User Fee Act* (PDUFA, P.L. 102-571) ushered in user fees and performance goals for faster drug approvals.
1998 *Food and Drug Administration Modernization Act* (FDAMA, P.L. 105-115) relaxed clinical testing requirements, eased access to experimental therapies, and awarded drugmakers six more months of marketing protection for testing drugs in pediatric patients.
2002 *Best Pharmaceuticals for Children Act* (BPCA, P.L. 107-109) reauthorized the FDAMA pediatric testing provision.
2002 *Public Health Security and Bioterrorism Preparedness and Response Act* (P.L. 107-188) extended the drug user fee law for five more years.
2003 *Pediatric Research Equity Act* (PREA, P.L. 108-155) required manufacturers to include pediatric assessments in new drug applications.
2007 *Food and Drug Administration Amendments Act* (FDAAA, P.L. 110-85) went beyond the anticipated reauthorization of PDUFA, BPCA, and PREA (among other provisions) by also expanding FDA authority to regulate drug safety.
2012 *Food and Drug Administration Safety and Innovation Act* (FDASIA, P.L. 112-144) reauthorized PDUFA, permanently authorized BPCA and PREA, authorized a new *Generic Drug User Fee Act* (GDUFA), amended drug-related sections of the FFDCA regarding drug shortages, supply chain security, and drug development incentives, and included other provisions regarding other FDA-regulated products.
2013 *Drug Quality and Security Act* (DQSA, P.L. 113-54) created a new category of compounding entities called *outsourcing facilities*, which engage in activities that go beyond what the FFDCA allows pharmacies to do under state regulation. The DQSA also created new track and trace requirements for drug manufacturers, wholesale distributors, repackagers, and dispensers.
2016 *21st Century Cures Act* (Division A of P.L. 114-255) modified the drug approval pathways at the FDA to support innovation, included provisions that support patient-focused drug development, and streamlined and clarified pathways to approval for drugs, combination products, antimicrobials, drugs for rare disease, and regenerative therapies.
2017 *FDA Reauthorization Act* (FDARA; P.L. 115-52) reauthorized PDUFA and GDUFA, amended FFDCA provisions to facilitate the development and approval of drugs for pediatric populations, modified the generic drug regulatory process to increase competition, and made various other changes regarding drug supply chain security, pediatric labeling, and expanded access, among other things.

How FDA Approves New Drugs

To market a prescription drug in the United States, a manufacturer needs FDA approval.[11] To get that approval, the manufacturer must demonstrate the drug's safety and effectiveness according to criteria specified in law and agency regulations, ensure that its manufacturing plant passes FDA inspection, and obtain FDA approval for the drug's labeling—a term that covers all written

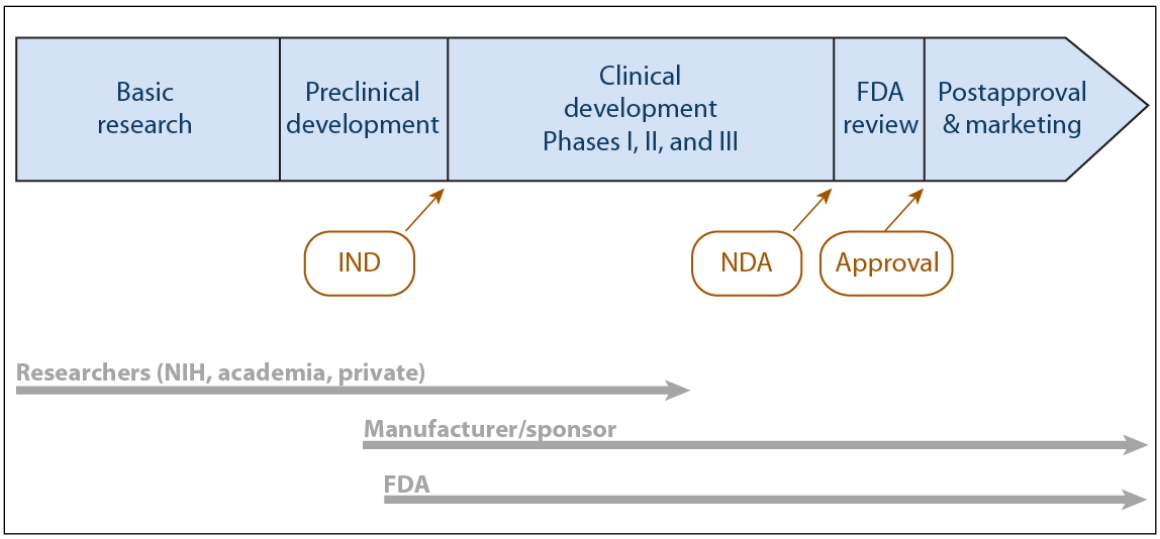
[11] FDA-approved drugs are designated by law into only two categories: prescription and nonprescription (also referred to as over-the-counter). No drug was prescription-only until the 1951 Humphrey-Durham amendments [P.L. 82-215, the Food, Drug, and Cosmetics Act Amendments Act, 1951], which stated, "A drug intended for use by man which ... because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (FFDCA §503(b)(1)). See CRS In Focus IF10463, *Regulation of Over-the-Counter (OTC) Drugs*.

material about the drug, including, for example, packaging, prescribing information for physicians, and patient brochures.

The drug development process begins before the law requires FDA involvement. **Figure 1** illustrates a product's timeline both before and during FDA involvement.

The research and development process for a finished drug usually begins in the laboratory—often with basic research conducted or funded by the federal government.[12] When basic research yields an idea that someone identifies as a possible drug component, government or private research groups focus attention on a prototype design. At some point, private industry (either a large, established company or a newer, smaller, start-up company) continues to develop the idea, eventually testing the drug in animals. When the drug is ready for testing in humans, the FDA must get involved.

Figure 1. Drug Development Path



Source: Created by CRS.

Note: FDA = Food and Drug Administration. IND = investigational new drug application. NDA = new drug application. NIH = National Institutes of Health.

The Standard Process of Drug Approval

This section outlines key activities leading to FDA's approval of a *new drug* for marketing in the United States. The law also provides for an abbreviated process for a *generic drug*—one chemically and therapeutically identical to an already approved drug.[13]

[12] CRS Report R41705, *The National Institutes of Health (NIH): Background and Congressional Issues*, provides a definition ("basic research is research in the fundamental medical sciences, sometimes called lab or bench research, while clinical research involves patients") and a discussion of its relationship to drug development and clinical research.

[13] CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

Investigational New Drug (IND) Application

Except under very limited circumstances, FDA requires data from clinical trials—formally designed, conducted, and analyzed studies of human subjects—to provide evidence of a drug's safety and effectiveness. Before testing in humans—called *clinical testing*—the drug's sponsor (usually its manufacturer) must file an investigational new drug (IND) application with FDA.[14] The IND application includes information about the proposed clinical study design, completed animal test data, and the lead investigator's qualifications. It must also include the written approval of an Institutional Review Board,[15] which has determined that the study participants will be made aware of the drug's investigative status and that any risk of harm will be necessary, explained, and minimized. The application must include an "Indication for Use" section that describes what the drug does and the clinical condition and population for which the manufacturer intends its use. Trial subjects should be representative of that population. The FDA has 30 days to review an IND application. Unless FDA objects, a manufacturer may then begin clinical testing.

Clinical Trials

With IND status, researchers test in a small number of human volunteers the safety they had demonstrated in animals. These trials, called *Phase I clinical trials*, attempt, in FDA's words, "to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects." If the sponsor considers the product still worthy of investment, it continues with *Phase II and Phase III clinical trials*. Those trials gather evidence of the drug's efficacy and effectiveness in larger groups of individuals with the particular characteristic, condition, or disease of interest, while continuing to monitor safety.[16]

Safety, Efficacy, and Effectiveness

Safety is often measured by toxicity testing to determine the highest tolerable dose or the optimal dose of a drug needed to achieve the desired benefit. Studies that look at safety also seek to identify any potential adverse effects that may result from exposure to the drug. *Efficacy* refers to whether a drug demonstrates a health benefit over a placebo or other intervention when tested in an ideal situation, such as a tightly controlled clinical trial. *Effectiveness* describes how the drug works in a real-world situation. Effectiveness is often lower than efficacy because of, for example, interactions with other medications or health conditions of the patient, or a sufficient dose or duration of use was not prescribed by the physician or followed by the patient.[17]

New Drug Application (NDA)

Once a manufacturer completes clinical trials, it submits a new drug application (NDA) to FDA's Center for Drug Evaluation and Research (CDER). In addition to the clinical trial results, the NDA contains information about the manufacturing process and facilities, including quality control and assurance procedures. Other mandatory information: a product description (chemical formula, specifications, pharmacodynamics, and pharmacokinetics)[18]; the indication (specifying

[14] FFDCA §505(1) and 21 C.F.R. Part 312—Investigational New Drug Application.

[15] 21 C.F.R. Part 56—Institutional Review Boards.

[16] FDA, "Inside Clinical Trials: Testing Medical Products in People; What Is a Clinical Trial?" Information for Consumers, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm.

[17] A resource for epidemiologic terms is *A Dictionary of Epidemiology, Fifth Edition*, Miquel Porta, editor, Oxford University Press, 2008.

[18] Pharmacokinetic [PK] studies provide information on what the body does to a drug (e.g., how a drug is absorbed,

one or more diseases or conditions for which the drug would be used and the population who would use it); labeling; and a proposed Risk Evaluation and Mitigation Strategy (REMS), if appropriate.[19]

There are generally two types of NDAs that a manufacturer may submit, named for their locations in the FFDCA

- A 505(b)(1) NDA is an application that contains full reports of investigations of safety and effectiveness conducted by or for the applicant or for which the applicant has a right of reference or use.
- A 505(b)(2) NDA is an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature, FDA's finding of safety and/or effectiveness for a listed drug).[20]

During the NDA review, CDER officials evaluate the drug's safety and effectiveness data, analyze samples, inspect the facilities where the finished product will be made, and check the proposed labeling for accuracy.

FDA Review

FDA considers three overall questions in its review of an NDA[21]

- Whether the drug is safe and effective in its proposed use, and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used to manufacture the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

FDA scientific and regulatory personnel consider the NDA and prepare written assessments in several categories, including Medical, Chemistry, Pharmacology, Statistical, Clinical, Pharmacology, Biopharmaceutics, Risk Assessment and Risk Mitigation, Proprietary Name, and Label and Labeling.[22]

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distributed, metabolized and eliminated by the body) while pharmacodynamic [PD] studies provide information on what a drug does to the body (e.g., how a drug works in the body, the amount needed to provide an effect). See presentation by G. Gieser, Office of Clinical Pharmacology, FDA presentation "Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development," https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf.

[19] NDA content and format requirements are specified in 21 C.F.R. 314.50.

[20] FDA, DRAFT Guidance for Industry, "Determining Whether to Submit an ANDA or a 505(b)(2) Application," October 2017, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf.

[21] FDA, "New Drug Application (NDA): Introduction," http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm.

[22] The listed categories are the sections of drug approval packages posted by FDA; for example, see the December 2012 files regarding Eliquis (apixaban), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000TOC.cfm.

The FFDCA requires "substantial evidence" of drug safety and effectiveness.[23] FDA has interpreted this term to mean that the manufacturer must provide at least two adequate and well-controlled Phase III clinical studies, each providing convincing evidence of effectiveness.[24] The agency, however, exercises flexibility in what it requires as evidence.[25] As its regulations describe in detail, FDA can assess safety and effectiveness in a variety of ways, relying on combinations of studies by the manufacturer and reports of other studies in the medical literature.[26] For some NDAs, FDA convenes advisory panels of outside experts to review the clinical data.[27] While not bound by their recommendations regarding approval, FDA usually follows advisory panel recommendations.

FDA approves an NDA based on its review of the clinical and nonclinical research evidence of safety and effectiveness, manufacturing controls and facility inspection, and labeling. An approval may include specific conditions, such as required postapproval studies (or postapproval clinical trials, sometimes referred to as *Phase IV clinical trials*) that the sponsor must conduct after marketing begins. An approval may also include restrictions on distribution, required labeling disclosures, or other elements of REMS, which are described below in the section titled "How FDA Regulates Approved Drugs."

The statute requires FDA to approve an NDA within 180 days after the filing of an application, or an additional period agreed upon by FDA and the applicant.[28] In 1992, pursuant to PDUFA, FDA agreed to specific goals and created a two-tiered system of review times: Standard Review and Priority Review. Compared with the amount of time standard review generally takes (approximately 10 months), a Priority Review designation means FDA's goal is to take action on an application within 6 months.[29] If FDA finds deficiencies, such as missing information, the clock stops until the manufacturer submits the additional information. If the manufacturer cannot respond to FDA's request (e.g., if it has not done a required study, making it impossible to evaluate safety or effectiveness), the manufacturer may voluntarily withdraw the application. If and when the manufacturer can provide the information, the clock resumes and FDA continues the review.

When FDA makes a final determination to approve an NDA, the agency sends the applicant an approval letter or a tentative approval letter if the NDA meets requirements for approval but cannot be approved due to a patent or exclusivity period for the listed drug.[30] If FDA determines that an NDA does not meet the requirements for approval, the agency sends a "complete response letter" describing the specific deficiencies the agency identified and recommending ways to make

[23] FFDCA (P.L. 75-717, 1938), §505(c) and (d).

[24] The requirements for adequate and well-controlled studies are given in 21 C.F.R. 314.126.

[25] See FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, CDER and CBER, May 1998, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf.

[26] The requirements for adequate and well-controlled studies are given in 21 C.F.R. 314.126.

[27] FDA has established various advisory committees whose members advise the agency. The names of most committees relate to an area of medicine (such as the Cardiovascular and Renal Drugs Advisory Committee) and some reflect cross-cutting issues (such as the Drug Safety and Risk Management Advisory Committee); see FDA, "Committees & Meeting Materials," http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm.

[28] FFDCA §505(c)(1).

[29] FDA, "Priority Review," https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm.

[30] 21 C.F.R. 314.105.

the application viable.[31] An unsuccessful applicant may request a hearing. Regulations identify the reasons for which FDA can reject an NDA, which include problems with clinical evidence of safety and effectiveness for its proposed use, manufacturing facilities and controls, labeling, access to facilities or testing samples, human subject protections, and patent information.[32]

Supplemental NDA. In order to make a change to an approved NDA—for example, to change the labeling, manufacturing process, or dosing, or to add a new indication (i.e., new use)—the manufacturer must submit a supplement (also referred to as a supplemental NDA). Agency regulations describe the required contents of those applications. Regarding clinical data, the applicant must submit descriptions and analysis of controlled and uncontrolled clinical studies, as well as "a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers."[33] The 21st Century Cures Act amended these requirements to allow reliance upon qualified data summaries to support approval of a supplemental application for a qualified use of a drug. Data summaries may be used only if existing safety data are available and acceptable to FDA, and all data used to develop the qualified data summaries are submitted as part of the supplemental application.[34] The 21st Century Cures Act also required the establishment of a program at FDA to evaluate the potential use of *real world evidence* (RWE) to support a new indication for an approved drug.[35] The law defines RWE to mean "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."[36]

Abbreviated New Drug Application (ANDA)

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act," P.L. 98-417) established an abbreviated approval pathway for generic drugs, allowing a manufacturer to submit to FDA an abbreviated NDA (ANDA), rather than a full NDA, demonstrating that the generic product is the same as the brand drug (i.e., the reference listed drug [RLD]).[37] Rather than replicate and submit data from animal, clinical, and bioavailability studies, the generic drug applicant relies on FDA's previous findings of safety and effectiveness

[31] 21 C.F.R. 314.110. Complete response letter to the applicant. Until July 2008, FDA responded to applicants with a letter indicating whether the application was "approved," "approvable" (pending specified additions, such as more testing, made to the application), or "unapprovable." In July 2008, FDA issued the rules regarding the "complete response letter" (FDA, 21 C.F.R. Parts 312, 314, 600, and 601 [Docket No. FDA–2004–N–0510] (formerly Docket No. 2004N–0267), "Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications; Final rule," *Federal Register*, v. 73, no. 133, July 10, 2008, pp. 39588- 39611). See FDA, "Action Packages for NDAs and Efficacy Supplements," MAPP 6020.8, Manual of Policies and Procedures, Office of New Drugs, Center for Drug Evaluation and Research, Effective Date: June 13, 2016, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM082010.pdf.

[32] 21 C.F.R. 314.125. Refusal to approve an application.

[33] 21 C.F.R. 314.50(d)(5)(iv).

[34] FFDCA §505(c)(5)(A), as amended by Section 3031 of P.L. 114-255. See also the FDA Proposed FDA Work Plan for 21st Century Cures Act Innovation Account Activities, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM556618.pdf.

[35] FFDCA §505F, as established by Section 3022 of P.L. 114-255.

[36] Ibid.

[37] The brand product is called the reference listed drug (RLD) because the generic product ANDA refers to the clinical data in the brand-name drug's NDA.

of the approved brand drug. To obtain premarket approval of the generic, the sponsor submits an ANDA demonstrating that the generic product is pharmaceutically equivalent (e.g., has the same active ingredient[s], strength, dosage form, route of administration) and bioequivalent[38] to the brand-name product. It also must meet other requirements (e.g., reviews of chemistry, manufacturing, controls, labeling, and testing). The generic and brand drugs may differ in certain characteristics (e.g., shape, excipients, packaging).[39]

Special Mechanisms to Expedite the Development and Review Process

Not all reviews and applications follow the standard procedures. For drugs that address unmet needs or serious conditions, have potential to offer better outcomes or fewer side effects, or meet other criteria associated with improved public health, FDA uses several formal mechanisms to expedite the development or review processes[40]

- *Fast track* and *breakthrough product* designations affect the administrative processes for the development of a drug and review of an application, for example, by providing for more frequent drug development-related meetings and interactions between the sponsor and FDA. Such designation does not alter the types of evidence required to demonstrate safety and effectiveness.
- *Accelerated approval* and *animal efficacy approval* change what is needed in an application. For accelerated approval, rather than requiring evidence of effectiveness on the final clinical endpoint, approval may be based on effectiveness on a surrogate or intermediate clinical outcome.[41] Under the Animal Rule, when human efficacy trials are not ethical or feasible, approval may be based on adequate and well-controlled animal efficacy studies.[42]

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[38] Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient/moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See 21 C.F.R. 320.1(e).

[39] For additional information about generic drugs, see CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

[40] FDA, "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, May 2014, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf; and FDA, "Review Designation Policy: Priority (P) and Standard (S)," MAPP 6020.3 Rev. 2, Manual of Policies and Procedures, Center for Drug Evaluation and Research, Office of New Drugs, June 25, 2013, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM082000.pdf.

[41] A clinical endpoint "is a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility) or survives." "A *surrogate endpoint* "is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit." An *intermediate clinical endpoint* is a "clinical endpoint ... that can be measured earlier than an effect on irreversible morbidity or mortality [IMM]" and is a "measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM" (FDA, "DRAFT Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics," CDER and CBER, June 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf).

[42] 21 C.F.R. 314.600. Use of the Animal Rule for approval is intended for drugs developed to treat or prevent serious or life-threatening conditions caused by chemical, biological, radiological, or nuclear substances, provided that human efficacy studies are not ethical or feasible, see FDA Guidance for Industry, "Product Development Under the Animal Rule," October 2015, https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf.

- *Priority review* designation affects the timing of the review, not the process (neither content nor timing) leading to submission of an application.

Table 2 compares these mechanisms across several development and review characteristics.

In addition to the five mechanisms described above, various laws have provided FDA with other tools aimed at bringing products to the public. Through statutory authorities and regulatory actions, FDA provides incentives to those who would develop certain categories of drugs. The main set of incentives is the granting of market exclusivity, while a newer incentive is providing priority review vouchers. The FFDCA has provisions to grant regulatory exclusivity for statutorily defined time periods (in months or years) to the holder[43] of the NDA for a product that is, for example, the first generic version of a drug to come to market, a drug used in the treatment of a rare disease or condition,[44] certain pediatric uses of approved drugs, and new qualified infectious disease products.[45] During the period of exclusivity, FDA does not grant marketing approval to another manufacturer's product. FDA may award a priority review voucher (shortening the time from an application's submission to FDA's approval decision) to the manufacturer with a successful NDA for a drug used for certain tropical diseases, rare pediatric diseases, or agents that present national security threats.[46] The manufacturer may use the voucher (or sell it to another manufacturer) to get priority review of a subsequent NDA.

Other options fit limited situations and support shorter times from idea to approved public use. For example, the Project BioShield Act of 2004 and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) allow the HHS Secretary to authorize in certain circumstances the *emergency use* of products or uses that do not yet have FDA approval.[47]

[43] The NDA holder is usually the manufacturer.

[44] FFDCA §§525-527 [21 USC 360aa,bb,cc].

[45] CRS Report R42890, *The Role of Patents and Regulatory Exclusivities in Pharmaceutical Innovation*.

[46] FFDCA §524, §529, and §565A.

[47] FFDCA §564 [21 USC 360bbb-3]. See CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

Table 2. Comparison of FDA's Expedited Programs for Serious Conditions

Attribute	Fast Track	Breakthrough Therapy	Accelerated Approval	Animal Efficacy	Priority Review
Nature of program	Product designation	Product designation	Process alteration	Process alteration	Product designation
Authority	FFDCA §506(b)	FFDCA §506(a)	21 C.F.R. 314 Subpart H FFDCA §506(c)	21 C.F.R. 314 Subpart I	CDER MAPP 6020.3 CBER SOPP 8405
Establishing vehicle	FDAMA, FDASIA	FDASIA	rules, FDASIA	rules	policy, PDUFA[a]
Qualifying criteria	Would treat a serious condition (variously defined)				
	AND nonclinical or clinical data demonstrate the potential to address unmet medical need	AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	AND generally provides meaningful advantage over available therapies AND demonstrates an effect on a **surrogate endpoint** that is reasonably likely to predict clinical benefit or on an **intermediate clinical endpoint**	AND human efficacy studies cannot be ethically or feasibly conducted AND safety has been established AND "adequate and well-controlled **animal studies** ... establish that the drug product is reasonably likely to produce clinical benefit in humans"	AND if approved, would provide a significant improvement in safety or effectiveness
Alternate qualifying criteria	• designated qualified infectious disease product (QIDP)[b]				• proposed labeling change pursuant to a report on a pediatric study under 505A[c] • designated QIDP[b] • priority review voucher[d]

Attribute	Fast Track	Breakthrough Therapy	Accelerated Approval	Animal Efficacy	Priority Review
Benefits	• actions to expedite development and review • rolling review	• all fast track features • intensive guidance on efficient drug development during IND • organizational commitment involving senior managers	• approval based on an effect on a surrogate or intermediate clinical endpoint	• approval based on animal efficacy studies	• shorter clock for review of marketing application (6 months compared to the 10-month standard review)
Postmarket requirements			• submission of copies of promotional materials for review • conduct of any required postapproval trials to verify and describe the anticipated clinical benefit or effect on irreversible morbidity or mortality	• conduct of postmarketing studies when feasible • subject to distribution restrictions to ensure safe use • labeling for patients that explains nature (animal studies) of the approval	

Sources: FFDCA §506; 21 C.F.R. 314 Subparts H and I; and table from FDA, "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics," CDER and CBER, May 2014, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

Notes:

BLA=biologics license application. CBER=Center for Biologics Evaluation and Research. CDER=Center for Drug Evaluation and Research. FDAMA=FDA Modernization Act. FDASIA=FDA Safety and Innovation Act. FFDCA=Federal Food, Drug, and Cosmetic Act. IND=investigational new drug application. MAPP=CDER Manual of Policies and Procedures. NDA=new drug application. PDUFA=Prescription Drug User Fee Act. SOPP=CBER Standard Operating Procedures and Policies.

a. Although priority review is not explicitly required by law, FDA has established it in practice. Various statutes, such as the Prescription Drug User Fee Act (PDUFA), refer to and sometimes require it.

b. Title VIII of FDASIA entitled "Generating Antibiotic Incentives Now (GAIN)" provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP) if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review. However, QIDP designation is beyond the scope of this guidance.

c. Any supplement to an application under FFDCA §505 that proposes a labeling change pursuant to a report on a pediatric study under this section shall be considered to be a priority review supplement per FFDCA §505A as amended by Section 5(b) of the Best Pharmaceuticals for Children Act.

d. Any application or supplement that is submitted with a priority review voucher will be assigned a priority review. Priority review vouchers will be granted to applicants of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in FFDCA §524(a)(3) and (4); for treatment of rare pediatric diseases, as defined in FFDCA §529(a)(3); or for treatments for agents that present national security threats, as defined in FFDCA §565A.

How FDA Regulates Approved Drugs

FDA's role in making sure a drug is safe and effective continues after the drug is approved and it appears on the market. FDA acts through its *postmarket regulatory procedures* after a manufacturer has sufficiently demonstrated a drug's safety and effectiveness for a defined population and specified conditions and the drug is *FDA-approved*. Manufacturers *must* report all serious and unexpected adverse reactions to FDA, and clinicians and patients *may* do so. FDA oversees surveillance, studies, labeling changes, and information dissemination, among other tasks, as long as the drug is sold.

FDA Entities Responsible for Drug Postapproval Regulation

Offices throughout FDA, mostly in the Center for Drug Evaluation and Research, address the safety of the drug supply. The primary focus of activity is the Office of Surveillance and Epidemiology (OSE). OSE uses reports of adverse events that consumers, clinicians, or manufacturers believe might be drug-related to "identify drug safety concerns and recommend actions to improve product safety and protect the public health."[48] FDA activities regarding drug safety once a drug is on the market (postmarket or postapproval period) are diverse. FDA staff

- look for "signals" of safety problems of marketed drugs by reviewing adverse event reports through the MedWatch program;
- review studies conducted by manufacturers when required as a condition of approval;
- monitor relevant published literature;
- conduct studies using computerized databases;
- review errors related to similarly named drugs;
- conduct communication research on how to provide balanced benefit and risk information to clinicians and consumers; and
- remain in contact with international regulatory bodies.

Other CDER units evaluating safety issues include the Office of Prescription Drug Promotion; the Division of Drug Information; and the Office of Compliance, which has offices addressing drug security, manufacturing quality, and unapproved drugs and labeling. Outside of CDER, the Office of Regulatory Affairs (ORA) performs field activities, including domestic and foreign inspections. The FDA human drugs program budget includes funding for CDER and the CDER-related activities of ORA.

Among the many advisory groups that work with FDA, two focus specifically on drug safety. The *Drug Safety and Risk Management Advisory Committee* met for the first time with this name in July 2002.[49] Members, appointed by the commissioner, are nonfederal and represent areas of expertise in science, risk communication, and risk management. One member may be designated to represent consumer concerns; one nonvoting member may represent industry concerns. The

[48] FDA, "Office of Surveillance and Epidemiology (OSE)," CDER, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm106491.htm.

[49] A predecessor group was the Drug Abuse Advisory Committee (http://www.fda.gov/OHRMS/DOCKETS/98fr/071102f.htm).

group "advises the Commissioner or designee in discharging responsibilities as they relate to helping to ensure safe and effective drugs for human use."[50]

FDA created the *Drug Safety Oversight Board* as part of its 2005 Drug Safety Initiative and later required by FDAAA in 2007.[51] Its members include both FDA personnel and representatives of the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Department of Defense, the Indian Health Service, the National Institutes of Health, and the Department of Veterans Affairs. Its roles are to advise the CDER director "on the handling and communicating of important and often emerging drug safety issues" and to provide "a forum for discussion and input about how to address potential drug safety issues."[52]

FDA Drug-Regulation Activities

FDA postmarket drug safety and effectiveness activities address aspects of drug production, distribution, and use. This section highlights nine activities that have traditionally interested Congress in relation to drug safety and effectiveness: product integrity, labeling, reporting, surveillance, drug studies, risk management, information dissemination, off-label use, and direct-to-consumer advertising.

Product Integrity

Ensuring product integrity[53] was the key task of FDA's predecessors in the early 1900s. Protecting the supply chain from counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs remains an essential concern of the agency. But as drug production has shifted to a global supply chain, FDA has broadened the scope of the way it monitors manufacturers, processers, packagers, importers, and distributors.[54] The FFDCA dictates requirements that manufacturers must meet, and it allows FDA to regulate manufacturing facilities, warehouses, and transportation plans.[55] For example, among many other requirements, the FFDCA requires (1) annual registration, including a unique facility identifier, of any domestic or foreign establishment "engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs" or their excipients (such as fillers, preservatives, or flavors) for U.S. distribution;[56] (2) registration of importers;[57] (3) submission of lists of products, including

[50] FDA, "Drug Safety and Risk Management Advisory Committee Charter," http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm094886.htm.

[51] FDAAA §901(b) added FFDCA §505-1(j).

[52] FDA, "Drug Safety Oversight Board," http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082129.htm.

[53] FFDCA section titles refer to "adulterated" (§501) and "misbranded" (§502) drugs.

[54] According to the Government Accountability Office (GAO), "FDA estimates that nearly 40 percent of finished drugs and approximately 80 percent of active pharmaceutical ingredients (API) are manufactured in registered establishments in more than 150 countries; yet, the agency is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are produced." For additional information, see the GAO report "FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices," December 2016, https://www.gao.gov/assets/690/681689.pdf.

[55] Although this discussion focuses on U.S. facilities, the FFDCA includes registration and product listing requirements for foreign facilities involved with drugs FDA-approved for sale in the United States.

[56] FFDCA §510(b) and (i) [21 USC 310(b) and (i)] and 21 C.F.R. Part 207.

[57] FFDCA §801.

ingredients and labeling;[58] (4) adherence to current good manufacturing practice (cGMP);[59] (5) various inspection requirements including risk-based facility inspections, inspection of drug lots for packaging and labeling control,[60] and "sampling and testing of in-process materials and drug products;"[61] and (6) numerous reporting requirements, among other actions.

FDA monitors product integrity beyond the drug's initial manufacture. It continues as the drug moves throughout the supply chain from its manufacturer to one or more wholesale distributors to the entity that dispenses it to the patient. Title II of the Drug Quality and Security Act of 2013 (DQSA; P.L. 113-54), the Drug Supply Chain Security Act, established track-and-trace requirements for prescription drugs, to be implemented over a period of 10 years. Among other things, the law requires manufacturers and repackagers to a put a product identifier, including a standardized numerical identifier, on each package and homogenous case.[62] With certain exceptions, exchange of transaction information, histories, and statements is required when a manufacturer, repackager, wholesale distributor, or dispenser transfers or accepts a drug. The law also requires a system of verification and notification when FDA or a trading partner within the supply chain suspects that a product may be suspect or illegitimate,[63] and for the Secretary to establish national standards for the licensing of wholesale distributors and third-party logistics providers.[64]

One area of federal and state interest is the practice of drug compounding. While FDA regulates drug manufacturers, the regulation of pharmacies and pharmacists has generally resided with state boards of pharmacy. The regulation of compounding pharmacies—where a pharmacist compounds (mixes) ingredients to create a product that differs from an FDA-approved drug based on a prescription for a specific patient—is a state function. However, in past years, some businesses licensed as pharmacies have engaged in compounding large amounts of a drug without corresponding patient-specific prescriptions and then selling the drug out of state. In 2012, long-term concern about the practice came to the forefront with an epidemic of fungal meningitis that CDC and FDA have traced back to a compounding business. The following year, Title I of the DQSA, the Compounding Quality Act, created a new category of drug compounders called *outsourcing facilities*, a term that describes entities that compound sterile drugs in circumstances that go beyond what the FFDCA allows pharmacies to do under state regulation (e.g., an

[58] FFDCA §510(j) [21 USC 360(j)] and 21 C.F.R. Part 207.

[59] FFDCA §501(a)(2)(B); 21 C.F.R. Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals; and FDA, "Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs," http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm124740.htm.

[60] 21 C.F.R. 211.134.

[61] 21 C.F.R. 211.110.

[62] FFDCA §582.

[63] FFDCA §581(21) defines *suspect product* to mean "a product for which there is reason to believe that such product—(A) is potentially counterfeit, diverted, or stolen; (B) is potentially intentionally adulterated such that the product would result in serious adverse health consequences or death to humans; (C) is potentially the subject of a fraudulent transaction; or (D) appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans." FFDCA §581(8) defines an *illegitimate product* to mean "a product for which credible evidence shows that the product—(A) is counterfeit, diverted, or stolen; (B) is intentionally adulterated such that the product would result in serious adverse health consequences or death to humans; (C) is the subject of a fraudulent transaction; or (D) appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans." These terms are further explained in the FDA draft guidance "Definitions of Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply Chain Security Act," March 2018, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM598737.pdf.

[64] FFDCA §§582 and 583.

outsourcing facility might compound drugs in bulk for use in hospitals and other facilities).[65] Unlike traditional compounding pharmacies, outsourcing facilities are required to register with FDA and are subject to CGMPs, in addition to other requirements.[66]

Reporting and Surveillance

One way FDA monitors the safety of approved drugs involves gathering information about possible adverse reactions to the products it has approved for U.S. use. Manufacturers *must* report all serious and unexpected adverse events (AEs) to the FDA Adverse Event Reporting System (FAERS) within 15 days of becoming aware of them.[67] Health professionals and patients *may* report adverse events to FDA's reporting system at any time.[68] According to the July 2017 report from the Institute for Safe Medication Practices (ISMP), in CY2016, FDA received 1.2 million new reports of adverse events for prescription and over-the-counter drugs.[69]

The agency collects AE reports through MedWatch and uses the FAERS database[70] to store and analyze them. Not all AEs may be actual drug reactions.[71] Using large surveillance data sets such as FAERS and with an understanding of the pharmacologic and pharmacokinetic functioning of various drugs, FDA scientists review the reported AEs to assess which ones may indicate a drug problem. They then use information gleaned from the surveillance data to determine a course of action. FDA might recommend a change in drug labeling to alert users to a potential problem or, perhaps, require the manufacturer to study the observed association between the drug and the adverse event.

Unlike planned studies with hypotheses to support or refute, for which researchers gather information, most surveillance activities are characterized as *passive*, in that the information is submitted by others.[72] The agency only learns of an adverse event when someone reports it. There are limitations to that approach. The reported event may signal a problem with the drug or be unrelated but have occurred coincident with the dosing. Other actual drug effects may be

[65] FFDCA §503B.

[66] For additional information, see CRS Report R45069, *Drug Compounding: FDA Authority and Possible Issues for Congress*.

[67] 21 C.F.R. 314.80 (for approved drugs) and 21 C.F.R. 310.305 (for drugs without approved NDAs). A manufacturer must also report the results of clinical studies it conducts on its approved products, along with what it knows about others' research and publications (FFDCA §505(k)). For General Instructions for Form FDA 3500A MedWatch (for mandatory reporting), see https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM295636.pdf.

[68] Before 2012, FAERS had been called AERS.

[69] Institute for Safe Medication Practices (ISMP), Quarter Watch, "Monitoring FDA MedWatch Reports," July 12, 2017, http://www.ismp.org/quarterwatch/pdfs/2016Q4.pdf.

[70] FDA, "MedWatch: The FDA Safety Information and Adverse Event Reporting Program," http://www.fda.gov/Safety/MedWatch/default.htm; and FDA, "FDA Adverse Event Reporting System (FAERS) (formerly AERS)," http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm.

[71] An event may occur after the use of a drug for reasons entirely unrelated to the drug. For example, an individual takes a blood pressure medication just before boarding a commuter train that later crashes leaving the passenger with a broken arm. The broken arm happened immediately after taking the drug but is unrelated. If, however, the train driver had taken the medication and then crashed the train, analysts could, with more information, pursue whether the drug was implicated.

[72] CDC has described four types of surveillance methods, with the passive method's being predominant. "The term *passive* is used to convey the idea that health authorities take no action while waiting for report forms to be submitted" (CDC, "Methods of Surveillance" in "Program Operations Guidelines for STD Prevention: Surveillance and Data Management," http://www.cdc.gov/std/program/Surveillance.pdf).

unrecognized as such and consequently not be reported. In addition, it is difficult to interpret the extent of a problem without knowing how many people took a specific drug.

In 2008, FDA began work on its Sentinel Initiative, both recognizing these limitations and responding to a requirement in FDAAA to create and maintain a Postmarket Risk Identification and Analysis System.[73] With Sentinel, FDA began moving from its predominantly passive surveillance system to an active one. Building on surveillance activities already in place (e.g., MedWatch and FAERS) and using evolving computer technology, Sentinel uses data from public and private sources such as electronic health records and insurance claims and registries to expand its information base while protecting patient confidentiality.[74] In 2016, Sentinel moved out of its pilot phase and began operating on a larger scale. An FDAAA-required independent, third-party interim assessment in 2015 noted that Sentinel had already formed partnerships with 19 data organizations covering 178 million lives, allowing more precise estimates of usage and possible adverse events. The analyses had informed FDA decisions to both take and not take actions.[75] However, a 2017 article presented more mixed opinions. It described several researchers' disappointment in Sentinel's utility, noting "little measureable impact" despite the resources already committed. Other researchers, noting the difficulties in data surveillance, pointed to the value of Sentinel's continued efforts.[76]

Drug Studies

After a drug is on the market, FDA can recommend and ask product sponsors to conduct studies. As described below, the law authorizes FDA to *require* studies in the postapproval period. Two sets of situations—distinguished by when the requirement is set—involve required postapproval studies: when a requirement is attached to the initial approval of the drug and when FDA informs the sponsor of a required study once a drug is on the market.

Postmarket Studies Required upon Drug Approval

Accelerated Approval. When FDA grants accelerated approval, it attaches a postmarket study requirement to that approval.[77] FDA regulations state, "Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."[78]

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[73] FDAAA §905(a) amended FFDCA §505(k) to require the Secretary to, among other things, "use electronic health data for risk identification and analysis; provide standardized reporting of adverse event data; and use federal, private, and other data sources to conduct active adverse event surveillance and identify trends and patterns." A fuller description is in CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Susan Thaul.

[74] FDA, "FDA's Sentinel Initiative—Ongoing Projects," http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm203500.htm; FDA, "The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety," May 2008, http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf; and FDA, "Report to Congress: The Sentinel Initiative—A National Strategy for Monitoring Medical Product Safety," August 19, 2011, http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM274548.pdf.

[75] FDA, "Sentinel Program Interim Assessment (FY 15)," http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM464043.pdf.

[76] S. Kaplan, "Failure to warn: An early warning system for drug risks falls flat," *STAT news*, June 6, 2017, https://www.statnews.com/2017/06/06/sentinel-fda-drug-risks/.

[77] FFDCA §506(c)(2).

[78] 21 C.F.R. 314.510.

Animal Efficacy. When FDA grants approval based on its animal efficacy rule, it attaches a postmarket study requirement to that approval. The Animal Efficacy Rule allows manufacturers to submit effectiveness data from animal studies as evidence to support applications of certain new products "when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible."[79] The regulations state,

> The applicant must conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises.… Applicants must include as part of their application a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.[80]

Pediatric Assessments. When FDA approves a drug for which it has deferred the required pediatric assessment, it attaches a postmarket pediatric assessment requirement to that approval. The Pediatric Research Equity Act (PREA, first authorized in P.L. 108-155) required that manufacturers submit a pediatric assessment with each submission of an application to market a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.[81] The law specified situations in which the Secretary might defer or waive the pediatric assessment requirement. For a deferral, an applicant must include a timeline for completion of studies. The Secretary must review each approved deferral annually, for which the applicant must submit evidence of documentation of study progress.

When Otherwise Required by the Secretary. The FDA Amendments Act of 2007 (P.L. 110-85) added another opportunity for a postmarket requirement at the time of approval. The Secretary may include in a drug's approval the requirement for specific postapproval studies or clinical trials.[82]

Postmarket Studies Required After Drug Approval

Pediatric Assessment. In addition to the pediatric assessment required as part of a drug's approval, PREA allows the Secretary, in certain circumstances, to require a pediatric assessment of a drug already on the market.[83]

Based on New Information Available to Secretary. The Secretary, under specified conditions after a drug is on the market, may *require* a study or a clinical trial.[84] The Secretary may determine the need for such a study or trial based on newly acquired information. To require a postapproval study or trial, the Secretary must determine that (1) other reports or surveillance would not be adequate and (2) the study or trial would assess a known serious risk or signals of

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[79] 21 C.F.R. 314 Subpart I and 21 C.F.R. 601 Subpart H. For example, FDA approved a supplemental NDA for the use of Levaquin (levofloxacin), a drug already marketed with FDA approval for other indications, for treatment and prevention of plague in individuals over the age of six months under the animal efficacy rule (http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020634s061,020635s067,021721s028ltr.pdf).

[80] 21 C.F.R. 314.610.

[81] PREA provisions are generally codified in FFDCA §505B [21 USC 355c] Research Into Pediatric Uses for Drugs and Biological Products. See CRS Report RL33986, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective*, for a description of the law's requirements and a discussion of the issues.

[82] FFDCA §505(o) [21 USC 355(o)].

[83] FFDCA §505B(b) [21 USC 355c(b)].

[84] These provisions are in FFDCA §505(o) [21 USC 355(o)] New Drugs; Postmarket studies and clinical trials; labeling.

serious risk, or identify a serious risk. The law directs the Secretary regarding dispute resolution procedures.

Risk Management

With authority under the FFDCA or by its own practices, FDA has long implemented various tools in its attempt to ensure that the drugs it has approved for marketing in the United States are safe and effective for their intended and approved uses. In addition to the actions the agency requires of the manufacturers of all approved drugs, it may deem additional actions appropriate for specific drugs or specific circumstances surrounding a drug's use. Some of those additional actions are risk-management processes to identify and minimize risk to patients. The FDA *Manual of Policies and Procedures* notes that risk management attempts to "minimize [a drug's] risks while preserving its benefits."[85] In that 2005 document, FDA described its approach to risk management as "an iterative process" that includes both risk assessment and risk minimization.

The FDAAA named the risk-management process risk evaluation and mitigation strategies (REMS) and expanded the risk-management authority of FDA.[86] FDA practice had long included most of the elements that a REMS may include, but FDAAA gave FDA, through the REMS process, the authority for structured follow-through, dispute resolution, and enforcement.

FDA may require a REMS under specified conditions—including if it determines such a strategy is necessary to ensure that the benefits of a drug outweigh its risks. It may make the requirement when a manufacturer submits a new drug application, after initial approval or licensing, when a manufacturer presents a new indication or other change, or when the agency becomes aware of new information and determines a REMS is necessary.

As part of a REMS, the Secretary may require instructions to patients and clinicians, and restrictions on distribution or use (and a system to monitor their implementation). A REMS may include the following components:

Patient information. The manufacturer must develop material "for distribution to each patient when the drug is dispensed."[87] This could be a Medication Guide, "as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations),"[88] or a patient package insert.[89]

Health care provider information. The manufacturer must create a communication plan, which could include sending letters to health care providers; disseminate information to providers about REMS elements to encourage implementation or explain safety protocols; disseminate information through professional societies about any serious risks of the drug and any protocol to

[85] FDA, "Review Management: Risk Management Plan Activities in OND and ODS," *Manual of Policies and Procedures*, MAPP 6700.1, CDER (Originator: Office of New Drugs), effective September 8, 2005, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082058.pdf.

[86] The REMS authority is in FFDCA §505-1 [21 USC §355-1]. See CRS Report R44810, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development*.

[87] FFDCA §505-1(e)(2).

[88] FFDCA §505-1(e)(2)(A).

[89] When FDA began using the REMS procedures, as outlined in FDAAA, it approved many REMS that included only a Medication Guide requirement. It later released (ended) many of those REMS, while maintaining the Medication Guide requirement under its other drug safety authorities (FDA, "Guidance: Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, November 2011, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf).

assure safe use; or disseminate to health care providers information about drug formulations or properties, including the limitations of those properties and how they may be related to serious adverse events.[90]

Elements to assure safe use (ETASU). An ETASU is a restriction on distribution or use that is intended to (1) allow access to those who could benefit from the drug while minimizing their risk of adverse events and (2) block access to those for whom the potential harm would outweigh potential benefit. By including these restrictions, FDA can approve a drug that it otherwise would have to keep off the market because of the risk it would pose. FFDCA Section 505-1(f)(3) lists the types of restrictions FDA could require as

- health care providers who prescribe must have particular training or experience, or be specially certified;
- pharmacies, practitioners, or health care settings that dispense must be specially certified;
- the drug must be dispensed to patients only in certain health care settings, such as hospitals;
- the drug must be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results;
- each patient using the drug must be subject to certain monitoring; and
- each patient using the drug must be enrolled in a registry.

Any approved REMS must include a timetable of when the manufacturer will provide reports to allow FDA to assess the effectiveness of the REMS components.[91]

Information Dissemination

FDA maintains several communications channels through which it distributes information on drug safety and effectiveness to clinicians, consumers, pharmacists, and the general public. An FDA web page titled "Postmarket Drug Safety Information for Patients and Providers" includes links to drug-specific information, potential signals of serious risks and summary statistics from FAERS,[92] *Drug Safety Communications*, and *FDA Drug Safety Podcasts*.[93] Other channels include *FDA Drug Info Rounds*[94] and *FDA Drug Information on Twitter*.[95]

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[90] FFDCA §505-1(e)(3), as amended by Section 606 of FDARA (P.L. 115-52).

[91] See CRS Report R44810, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development*.

[92] FDA presents quarterly summaries of FAERS data on its website (FDA, "FDA Adverse Event Reporting System (FAERS) Statistics," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm). The agency also makes raw adverse event data available to the public, although it notes that "[U]sers of these files need to be familiar with creation of relational databases using applications such as ORACLE®, Microsoft Office Access, MySQL® and IBM DB2 or the use of ASCII files with SAS® analytic tools. ... A simple search of AERS/FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases" (FDA, "FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files," http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm).

[93] FDA, "Postmarket Drug Safety Information for Patients and Providers," http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm.

[94] FDA, "FDA Drug Info Rounds," http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm211957.htm.

[95] FDA, "FDA Drug Information (FDA_Drug_Info) on Twitter," https://twitter.com/FDA_Drug_Info.

FDA has been required by law to take various actions regarding how it informs the public, expert committees, and others about agency actions and plans and information the agency has developed or gathered about drug safety and effectiveness. Examples include directing FDA to establish advisory committees (e.g., an Advisory Committee on Risk Communication to "advise the Commissioner on methods to effectively communicate risks associated with" FDA-regulated products);[96] to report certain information to Congress (e.g., annual fiscal and performance reports related to user fees);[97] to hold public meetings with stakeholders (e.g., public meeting with patients, health care providers, and others to discuss clinical trial inclusion and exclusion criteria);[98] and to make certain information available on the agency's website (e.g., publication of action packages for product approval or licensure, including certain reviews).[99]

Labeling

What Is Labeling?

A drug's labeling is more than the sticker the pharmacy places on the amber vial it dispenses to a customer. FFDCA Section 201(m) defines labeling to include "... all labels and other written, printed, or graphic matter ... accompanying" the drug. FDA regulations on labeling[100] dictate the material the labeling must provide along with required formatting.[101] FDA included the following description when it issued its 2006 final rule on labeling:[102]

> A prescription drug product's FDA approved labeling (also known as "professional labeling," "package insert," "direction circular," or "package circular") is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use. It is written for the health care practitioner audience, because prescription drugs require

[96] FDAAA §917. The Risk Communication Advisory Committee was established on June 5, 2007, according to the FDAAA Implementation Chart, https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FDAAAImplementationChart/default.htm.

[97] FFDCA §736B, as amended by FDARA §103.

[98] FDARA §610.

[99] FFDCA §505(l), as amended by FDAAA §916. FDA describes an action package as "a compilation of (1) FDA-generated documents related to review of an NDA or efficacy supplement (i.e., from submission to final action), (2) documents (e.g., meeting minutes, pharmacology reviews) pertaining to the format and content of the application generated during drug development (investigational new drug [IND]), and (3) labeling submitted by the applicant." (FDA, "Action Packages for NDAs and Efficacy Supplements," MAPP 6020.8, CDER Manual of Policies and Procedures, November 13, 2002, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm082010.pdf.)

[100] 21 C.F.R. Part 201—Labeling.

[101] FDA, "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, February 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf. "PLR" refers to the 2006 "physician labeling rule" (FDA, "[Docket No. 2000N–1269] (formerly Docket No. 00N–1269) RIN 0910–AA94, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, *Federal Register*, vol. 71, no. 15, January 24, 2006, pp. 3922-3997, http://www.gpo.gov/fdsys/pkg/FR-2006-01-24/pdf/06-545.pdf).

[102] FDA, "[Docket No. 2000N–1269] (formerly Docket No. 00N–1269) RIN 0910–AA94, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," *Federal Register*, vol. 71, no. 15, January 24, 2006, pp. 3922-3997, http://www.gpo.gov/fdsys/pkg/FR-2006-01-24/pdf/06-545.pdf.

> "professional supervision of a practitioner licensed by law to administer such drug" (section 503(b) of the act (21 U.S.C. 353(b))).

FDA regulations on prescription drug advertising refer to examples of labeling:[103]

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the FD&C Act.

FDA requires that labeling begin with a highlights section that includes, if appropriate, black-box warnings, so called because they are bordered in black to signify their importance.[104] The regulations list the required elements of labeling: indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions, use in specific populations, drug abuse and dependence, overdosage, clinical pharmacology, nonclinical toxicology, clinical studies, references, how supplied/storage and handling, and patient counseling information.[105]

How Is Labeling Used?

Labeling plays a major role in the presentation of safety and effectiveness information. It is a primary source of prescribing information used by clinicians. The manufacturer submits labeling for publication in the widely used *Physician's Desk Reference* and is the basis of several patient-focused information sheets that manufacturers, pharmacy vendors, and many Web-based drug information sites produce.[106] When FDA determines that additional information is necessary for safe use, it may require the manufacturer to produce a Medication Guide.[107] The agency, through its Office of Prescription Drug Promotion (OPDP), conducts and supports research on risk and benefit communication to both professionals and consumers.[108] OPDP looks for ways to present information to consumers that is accessible, accurate, and up-to-date. FDA-approved labeling is relevant to discussions of insurance or benefits coverage, market exclusivity periods, and liability.[109]

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[103] 21 C.F.R. 202.1(l)(2)). 21 C.F.R. Part 202—Prescription Drug Advertising.

[104] "Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box" (21 C.F.R. 201.57(c)(1)).

[105] 21 C.F.R. 201.56(d). For older drugs, labeling content requirements are listed in 21 C.F.R. 201.56(e).

[106] PDR Network, http://www.pdr.net/about-pdr-network/. Examples of consumer medication information materials include those by Wolters Kluwer Health, Inc. (used, for example, with Target dispensing, http://www.consumerreports.org/health/best-buy-drugs/prescription-labels/patient-instructions/index.htm); First Databank, Inc. (provides FDA Medication Guides, http://www.fdbhealth.com/solutions/retail-pharmacy-dispensing/); and American Society of Health-System Pharmacists Consumer Medication Information (http://www.ahfsdruginformation.com/products_services/ahfs_cmi.aspx).

[107] 21 C.F.R. Part 208—Medication Guides for Prescription Drug Products. Regulations also require patient package inserts for oral contraceptives (21 C.F.R. 310.501) and drug products containing estrogen (21 C.F.R. 310.515).

[108] FDA, "Office of Prescription Drug Promotion (OPDP) Research," http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm.

[109] For a discussion about the legal implications of drug labeling, see CRS Report R43218, *Preemption of Drug and Medical Device Claims: A Legal Overview*, by Andrew Nolan and Jennifer A. Staman (out of print; available to congressional clients upon request).

When and How May Labeling Be Changed?

Adverse events sometimes warrant regulatory actions such as labeling changes, letters to health professionals, or, once in a great while, a drug's withdrawal from the market. The regulations refer to required labeling revisions as soon as there is reasonable evidence—not proof—of a causal association with a clinically significant hazard.[110]

FDA can request labeling changes based on information it gathers from mandatory industry reports to FAERS, manufacturer-submitted postmarket studies, and voluntary adverse event reports from clinicians and patients.[111] The agency may, upon learning of new relevant safety information, require a labeling change.[112]

When a manufacturer of an innovator (brand-name) drug believes data from original or published studies support a new use for a drug, a manufacturer itself can initiate a label change to support a new marketing claim.[113] The manufacturer can submit to FDA the new data in a supplement to the original NDA and request that FDA allow it to modify the labeling. In addition, if a manufacturer of an innovator drug submits a supplement to strengthen warning labeling, regulations describe when the change can be made prior to FDA approval.[114]

The FFDCA requires that a generic drug have the same labeling as the innovator drug on which its application draws, with some exceptions.[115] For example, a generic drug may omit from its labeling certain patent- and exclusivity-protected information concerning the pediatric use of the brand-name drug, and may be required to include a disclaimer with respect to the omitted information.[116] This sameness requirement has implications when an injured party seeks to sue the generic manufacturer, and when new safety information becomes available when only generic products remain on the market.[117]

In November 2013, FDA issued a proposed rule to allow ANDA holders to voluntarily update drug labeling to reflect certain types of newly acquired information related to drug safety even if that labeling differs from that of the brand reference drug.[118] Specifically, the ANDA holder would be allowed to distribute the revised product labeling with respect to the safety-related change, on a temporary basis, upon submission to FDA of a "changes being effected" supplement. The safety-related change(s) proposed in the supplement would be made publicly

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[110] 21 C.F.R. 201.57(c)(6). Other regulations affect whether the manufacturer must get approval from FDA before making a labeling change (e.g., 21 C.F.R. 314.70).

[111] FDA, "Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, July 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf. See Appendix of the draft guidance for examples of safety information sources.

[112] FFDCA §505(o), added by FDAAA, allows the Secretary, upon learning of new relevant safety information, to require that the sponsor submit a supplement for a labeling change. It includes procedures, including time limits, for notification, review, dispute resolution, and violation; it also authorizes the Secretary to accelerate timelines if the Secretary concludes that the labeling change is necessary to protect the public health.

[113] FDA, "Guidance for Industry: Changes to an Approved NDA or ANDA, CDER, April 2004, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf.

[114] 21 C.F.R. 314.70(c)(6)(iii).

[115] FFDCA §505(j)(2)(A)(v); and 21 C.F.R. 314.94(a)(8).

[116] FFDCA §505A(o).

[117] FDA Law Blog "FDA Proposes a Rule that would Undercut Generic Drug Preemption," November 12, 2013, http://www.fdalawblog.net/2013/11/fda-proposes-a-rule-that-would-undercut-generic-preemption/.

[118] *Federal Register*, vol. 78, no. 219, November 13, 2013.

available to prescribers and the public on the agency's website while FDA reviews the supplement. The ANDA supplement for that safety-related labeling change would be approved upon approval of the same labeling change for the RLD (i.e., the brand-name or innovator drug). This proposed change has been met with some opposition, including from the generic drug industry, which has claimed that the rule would expose generic companies to new legal liability.[119] A final rule has not been promulgated.

Off-Label Use

As described earlier, FDA approves a drug for U.S. sale based on its manufacturer's new drug application, which contains evidence of safety and effectiveness in its intended use, manufacturing requirements, and labeling. Despite the indications for use in the approved labeling, a licensed physician may—except in highly regulated circumstances[120]—prescribe the approved drug without restriction. A prescription to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling is called *off-label use* and is accepted medical practice.[121] The FFDCA prohibits a manufacturer from selling a misbranded product, and deems a drug to be misbranded if its labeling is false or misleading.[122] FDA has interpreted the FFDCA, therefore, to prohibit a manufacturer from promoting or advertising a drug for any use not listed in the FDA-approved labeling, which contains those claims for which FDA has reviewed safety and effectiveness evidence.[123] However, FDA's interpretation has been challenged and is in dispute.[124]

Examples of Off-Label Use

- A drug tested for the treatment of one disease may be prescribed in an attempt to prevent or treat another.
- If a drug was tested at one dose, it may be used at higher or lower doses.
- A drug tested in adults may be prescribed to children.
- A drug that was tested in an eight-week trial may be prescribed for long-term use.

Off-label use presents an evaluation problem to FDA safety reviewers. Using drugs in new ways for which researchers have not yet demonstrated safety and effectiveness can create problems that premarket studies did not address. Manufacturers rarely design studies to establish the safety and

[119] Regulatory Affairs Professionals Society (RAPS), "FDA's Punt on Finalizing the Generic Drug Labeling Rule: Experts Debate," *Regulatory Focus*, May 19, 2016, https://www.raps.org/news-articles/news-articles/2016/5/fda%E2%80%99s-punt-on-finalizing-the-generic-drug-labeling-rule-experts-debate.

[120] FDA may place restrictions on prescribing or dispensing as "elements to assure safe use" (ETASU) as part of a REMS that the agency may require (see FFDCA §505-1(f)).

[121] The FFDCA does not give FDA authority to regulate the practice of medicine; that responsibility generally rests with the states and medical professional associations.

[122] FFDCA §502(a).

[123] Materials from FDA's Bad Ad Program describe elements of false or misleading ads. These include promotion of an unapproved use. See FDA, "Truthful Prescription Drug Advertising and Promotion," Page Last Updated: 2/13/2018, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm#ExamplesofViolations. See also FFDCA §§301 and 502(a).

[124] A December 2012 Court of Appeals decision (*United States v. Caronia*) "reversed the criminal conviction of a pharmaceutical representative who had promoted an off-label use of a drug on First Amendment grounds," according to a CRS product that is no longer available, by Andrew Nolan, "Is There a Constitutional Right to Promote an Unapproved Use for a Drug?" Legal Sidebar, Congressional Research Service, April 2, 2013.

effectiveness of their drugs in off-label uses, and individuals and groups wanting to conduct such studies face difficulties finding funding.

Drug and device companies have argued that current regulations prevent them from distributing important information to physicians about unapproved, off-label uses of their products.[125] In November 2016, FDA held a two-day public meeting to obtain input from various groups regarding off-label uses of approved or cleared medical products.[126] In January 2017, FDA issued draft guidance explaining the agency's policy about medical product communications that include data and information that are not contained in FDA-approved labeling, but that concern the approved uses of their products.[127] The draft guidance is in a question and answer format and addresses frequently asked questions. Among other things, the draft guidance provides examples of the kinds of information that the agency considers consistent with FDA-required labeling for a product (e.g., information that provides additional context about adverse reactions associated with a drug's approved use[s] as reflected in the FDA-required labeling), as well as the kinds of information that are not consistent with FDA-required labeling for a product (e.g., if a drug is approved for treatment of only one disease, and the company's communication provides information about using the product to treat a different disease).

Direct-to-Consumer (DTC) Advertising

FDA regulates the advertising of prescription drugs.[128] Although the Federal Trade Commission regulates nonprescription drug advertising, the FDA regulates the product labeling that the nonprescription drug ads must reflect. While the law generally prohibits FDA from requiring preapproval of an ad, manufacturers are required to submit their ads to the agency upon release.[129]

FDAAA expanded and strengthened FDA's enforcement tools regarding advertising, including by authorizing the agency to require submission of a television advertisement for review not later than 45 days before its dissemination.[130] In conducting a review of a television advertisement, the Secretary may make recommendations with respect to information included in the label of the drug on (1) changes that are necessary to protect the consumer good and well-being, or that are consistent with prescribing information for the product under review, and (2) "statements for inclusion in the advertisement to address the specific efficacy of the drug as it relates to specific population groups, including elderly populations, children, and racial and ethnic minorities," if appropriate and if such information exists. The law allows the agency to recommend, but not require, changes in the ad. The law also allows FDA to require that an ad include certain disclosures without which it determines that the ad would be false or misleading. These disclosures could include the date of drug's approval, as well as information about a serious risk listed in a drug's labeling. In 2012, FDA issued draft guidance addressing for which categories of

[125] STAT, "FDA to hold long-awaited meeting to review off-label marketing," August 31, 2016, https://www.statnews.com/pharmalot/2016/05/27/fda-hhs-free-speech-patient-safety/.

[126] FDA, Docket No. FDA-2016-N-1149, https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-21062.pdf.

[127] FDA, DRAFT GUIDANCE, "Medical Product Communications That Are Consistent With the Food and Drug Administration-Required Labeling—Questions and Answers," January 2017, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf.

[128] FFDCA §502(n). For an in-depth discussion of this issue, see archived CRS Report R40590, *Direct-to-Consumer Advertising of Prescription Drugs*.

[129] 21 C.F.R. 314.81(b)(3)(i).

[130] FFDCA §503C, as amended by FDAAA §901(d)(2).

TV ads the agency generally intends to enforce the pre-dissemination review requirement.[131] This guidance has not been finalized.

Television and radio ads must present the required information on side effects and contraindications in a "clear, conspicuous, and neutral manner."[132] Civil penalties are authorized for the dissemination of a false or misleading DTC advertisement. Any published DTC advertisement must include the following statement printed in conspicuous text: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/medwatch, or call 1-800-FDA-1088."[133]

[131] FDA, DRAFT GUIDANCE, "Guidance for Industry Direct-to-Consumer Television Advertisements—FDAAA DTC Television Ad Pre-Dissemination Review Program," OPDP, March 2012, https://www.fda.gov/downloads/Drugs/... /Guidances/UCM295554.pdf.

[132] FFDCA §502(n) as amended by FDAAA §901(d)(3).

[133] FFDCA §502(n) as amended by FDAAA §906(a).

Appendix. Abbreviations and Acronyms

AERS	Adverse Event Reporting System, now FAERS
ANDA	abbreviated new drug application
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
C.F.R.	Code of Federal Regulations
DTC	direct-to-consumer, as in advertising
ETASU	elements to assure safe use, as in REMS
FAERS	FDA Adverse Event Reporting System, formerly AERS
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act, 2007
FDAMA	Food and Drug Administration Modernization Act, 1998
FDASIA	Food and Drug Administration Safety and Innovation Act, 2012
FDARA	FDA Reauthorization Act, 2017
FFDCA	Federal Food, Drug, and Cosmetic Act
GAIN	Generating Antibiotic Incentives Now Act
GDUFA	Generic Drug User Fee Amendments
IND	investigational new drug
MAPP	Manual of Policies and Procedures
NDA	new drug application
NIH	National Institutes of Health
OPDP	Office of Prescription Drug Promotion
ORA	Office of Regulatory Affairs
OSE	Office of Surveillance and Epidemiology, formerly Office of Drug Safety
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act
PDUFA	Prescription Drug User Fee Act or Amendments
PREA	Pediatric Research Equity Act
QIDP	qualified infectious disease product
REMS	risk evaluation and mitigation strategy
SOPP	Standard Operating Procedures and Policies
USC	United States Code

Author Information

Agata Dabrowska
Analyst in Health Policy

Susan Thaul
Specialist in Drug Safety and Effectiveness

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