

4 | U.S. Food and Drug Administration

Overview

The **U.S. Food and Drug Administration (FDA)** is one of the 11 [operating divisions](#) within the United States Department of Health and Human Services (HHS). It ensures “the safety and efficacy of human and veterinary drugs, biologic products, and medical devices,” along with ensuring the safety of the food supply chain, cosmetics, and devices that emit radiation, that are [marketed or sold](#) in the U.S. The FDA also has responsibility for the regulation of tobacco products. It carries out this authority by reviewing manufacturers’ applications to sell these items in the

United States. The FDA does not consider price in its approval process, nor is the agency involved in setting prices for any medical product on the market. However, FDA approvals come with market exclusivity periods which are closely tied with how drugs are priced (you can learn more about drug pricing in this Handbook’s Chapter 5).

The FDA balances pressures from multiple constituencies – to make products available in a timely manner, but also to ensure that they are safe and

efficacious if used as indicated. The agency is under constant pressure to ensure that critical innovations (such as COVID-19 vaccines) are available to the public as expeditiously as possible. Of course, it is impossible to know whether an innovation is important before subjecting it to the very testing that can delay its availability. To carry out its work of determining whether products are safe and efficacious for the public, the agency relies, to a significant extent, on [funding](#) provided in the form of [user fees](#) paid by those products' producers.

Background

The federal role in regulating food and drugs dates back to the [nineteenth century](#). The predecessor to the Food and Drug Administration was the Bureau of Chemistry, created within the Department of Agriculture in [1862](#). The bureau was given its first modern regulatory functions over the pharmaceutical market in the 1902 Biologics Control Act and the 1906 Pure Food and Drugs Act. In 1927, the bureau

Table 4.1: Definitions of Drugs, Including Biological Therapeutics

Type of Drug or Therapy	Definition
Innovator or Originator Drugs	The first drug with a specific set of active ingredients to receive FDA approval and can be granted fixed-term exclusivity, which delays or prohibits approval of competitor drugs.
Generic Drugs	A drug that is comparable to an innovator drug in dose, strength, route of administration, quality, performance, and intended use. More >>
Biologic	A large or complex molecule drug that is made in a living system and can contain proteins, glycoproteins, nucleic acids, cells, or tissues. More >>
Biosimilar	A biologic that is highly similar to a previously licensed innovator biologic; sometimes referred to as a follow-on biologic. More >>
Gene Therapies	A subset of biologics that involves inserting DNA into a cell to correct a mutation that causes disease. More >>
Cell Therapies	Live cells that originate from a patient or a donor are transferred into a patient – a biologics subset. More >>
Specialty Drugs	Drugs that treat complex diseases (such as hepatitis C, cancer, and multiple sclerosis) – often requiring specific handling or administration and frequently, with a high price tag. More >>

was reorganized and its regulatory entity became the Food and Drug Administration. The Food, Drug, and Cosmetic Act of 1938, for the first time, required drug manufacturers to submit safety data to the FDA for evaluation. The agency started evaluating for efficacy in 1962. Currently, the agency is organized into seven centers and 13 offices.

The term “drug” encompasses a wide range of substances used to diagnose, cure, mitigate, treat, or prevent disease. The term includes small molecule drugs and therapeutic biological products, which payers may cover under different benefits. Different types of drugs have different approval processes, distinct market characteristics, and face different pricing and cost challenges. Table 4.1 provides some basic definitions for various drugs and therapeutic biological products.

Four Stages of a New Drug Review Process

The FDA reviews every drug and device that is marketed in America. The process for an innovator (or new) drug requires the manufacturer to go through

four stages to prove the drug’s safety and efficacy (See Fig. 4.1).

In the first stage of the drug approval process, a drug sponsor develops a new molecular entity and then begins pre-clinical development. The process is likely to include initial testing on animals. The sponsor must then submit to the FDA an *Investigational New Drug* (IND) application before it can move to clinical trials on humans. The IND proposes a plan for evaluating the drug and a summary of the preclinical data collected to that point. Human clinical testing can start 30 days after IND submission unless the FDA objects and imposes a clinical hold.

In the second stage, the sponsor engages in clinical trials. In the first phase of clinical trials, the sponsor will work with a small group of individuals, often a dozen or so healthy volunteers, to test how the drug is absorbed, metabolized, and affects the body (i.e., pharmacokinetics and pharmacodynamics). In the second phase, the sponsor works with a larger group of volunteers, perhaps up to a hundred or so patients with the disease in question, to test the drug for safety and perhaps provide the first hint of efficacy. In the third phase, which is not mandatory, the sponsor will expand to an even larger group of patients, hundreds or even thousands of individuals, to test the drug’s efficacy compared to a placebo or other standards of care. The sponsor continues to gather safety data as well.

Fig 4.1 Drug Development and FDA Marketing Approval Process Steps



Source: “FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue.” Dicken, J., Crosse, M., Copeland, R., et al. U.S. Government Accountability Office. November 2018. Available at <http://allh.us/f6vy>.

KEY FDA ISSUES IN 2021

- Preparing for [reauthorization](#) of user fee programs in 2022.
- Increased scrutiny on regulatory efficiency and availability of new therapies given faster than normal COVID-19 vaccine development.
- Uses of [real-world evidence](#) apart from post-market surveillance.
- Scope of products the agency is regulating, such as diagnostic tests, digital health, and nicotine/e-cigarettes.
- Continued [implementation](#) of the [21st Century Cures Act](#) (which, among many other things, aims to streamline the drug, biologics, and device approval process) and potential discussion of “[Cures 2.0](#)” legislation.

In the third stage, the drug sponsor submits a *New Drug Application* (NDA) to the FDA. The NDA is the sponsor’s formal request to have the FDA approve the drug for marketing and distribution in the United States. FDA scientists review the NDA inclusive of all the data collected by the sponsor from its use anywhere in the world, and approve the drug’s manufacturer-written labeling that summarizes all of that data. The FDA also inspects the facilities where the drug will be manufactured. When all of these separate steps have been concluded to the FDA’s satisfaction, the drug is approved for sale in the U.S. market for a particular disease or indication.

In the fourth stage, the FDA continues to work with the drug sponsor to [monitor](#) the drug for side effects that may occur while on the market (also known as post-market surveillance). Prescribers and consumers can bring any [adverse events](#) that occur with the use of the drug to the FDA’s attention. If evidence emerges that an approved drug is safe and effective for additional clinical uses, manufacturers can submit a streamlined application (“[efficacy supplements](#)”).

This streamlined approval is not to be confused with [off-label uses](#), i.e., unapproved uses for an approved drug.

Generic Drug Review Process

Generic drugs do not have to go through the extensive efficacy and safety trials expected of the innovator drug. A generic drug goes through an [Abbreviated New Drug Application](#) process in which the generic sponsor is required to prove that the generic drug is bioequivalent to the innovator drug. If the generic sponsor can meet that benchmark, it does not have to conduct costly and duplicative clinical trials to establish the generic drug’s safety and efficacy. This abbreviated process allows generic drugs to come to the market faster. Generic drugs are usually cheaper because there are typically multiple generic manufacturers, and FDA-approved generic drugs are generally automatically interchangeable at the pharmacy level for their brand-name drugs (see chapter 5 of the Handbook for more details).

Biologic and Biosimilar Drug Review Process

Unlike chemically synthesized drugs, **biologic** drugs are complex combinations of sugars, proteins, or nucleic acids that are usually produced by living cells and tissues. Innovator biologics require an approval process called [Biologics License Application](#) (BLA) that mirrors the NDA process. **Biosimilar** drugs are meant to replicate an existing biologic drug’s clinical outcome and therefore go through a more [extensive review process](#) than generic drugs. The goal of the approval process is to show that the biosimilar drug has a similar structure to a reference innovator drug and can be expected to have no clinical differences.

Device Review Process

The FDA has broad authority over any **device** used in the care of a person or animal. While a popsicle stick and a tongue depressor may look like similar pieces of wood, only a tongue depressor is considered a device under the FDA's authority because it is intended to be used for clinical purposes.

The FDA divides medical devices into [three classes](#) and the approval process for each varies depending on the assigned class of the device in question.

Class I devices (tongue depressors) pose the lowest risk to the patient and are simply registered with the FDA without any formal review. **Class II** devices pose a moderate risk and require clearance from the FDA. Most Class II devices reach the market by submitting a 510(k) application that shows they are substantially equivalent to another already legally marketed device. **Class III** devices have the greatest potential risk to the patient, and new Class III devices require premarket approval from the FDA, going through a process similar to those for new drugs or biologics.

New technologies have made the device field even more complex in recent years, especially when a device is used in combination with a drug or biologic. Software, for example, has historically been excluded from the FDA's approval process as a medical device. However, software that is diagnostic and is

connected to a hardware medical device is subject to the approval process. As artificial intelligence and machine learning advance, the FDA's challenge in determining what is and is not a medical device will only grow more complicated.

Expedited Approval and Emergency Use Authorizations

The FDA has the authority to [expedite](#) the development and review process for drugs, biologics, and devices deemed to fill an unmet medical need or offer better health outcomes. There are [four mechanisms](#) that alter the process – fast track and breakthrough product designations change the administrative procedures of the review, accelerated approval designation modifies the clinical evidence needed in an application, and priority review designation accelerates the FDA application review start date. Additionally, in public health emergency situations, the Secretary of Health and Human Services and FDA may utilize **Emergency Use Authorization (EUA)** to permit the use of unapproved medical products or unapproved uses of approved medical products to provide medical countermeasures. Recent issuances of EUAs were in December 2020 and February 2021 to allow use of vaccines against COVID-19.

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Dietary Supplements

The FDA oversees dietary supplements like it does foods; however, there is no approval process requiring dietary supplements to show efficacy or safety. One of the FDA's roles is to ensure that a dietary supplement's intended effect is not misrepresented to the public.

What the FDA Does Not Do

The FDA is statutorily charged with approving products under its jurisdiction if they are (1) safe and efficacious when used as indicated and (2) if their benefits outweigh their risks. The FDA does not engage in any effort to evaluate comparative effectiveness between any two drugs or devices. The FDA does not have the authority to require product sponsors to show comparative effectiveness with other products that treat the same condition. However, most clinical trials treat their control group with the current standard of care. The agency also does not oversee the practice of medicine and pharmacy – which are state-based and govern how medicines are used in practice.

The FDA also does not consider the pricing of any drug or device as part of its review process, and subsequently most products going through FDA review do not have a price attached as they are yet to be approved for marketing in the U.S.

The FDA does not determine whether a drug or device will be covered by insurance or other payers. The FDA approves a drug or device for use by the public for a specific indication, although physicians may prescribe off-label for additional disease or conditions as they are covered by state-based medical licenses and the practice of medicine. Payers determine whether to cover a drug or device within the terms of their insurance programs. While FDA approval makes coverage highly likely for private insurers, it is not a certainty, and coverage can vary depending on the availability of multiple

GLOSSARY OF TERMS

Patent: Granted by the U.S. Patent and Trademark Office and provides for the protection of property rights, for example, in the active ingredient of a drug. The term of the patent is 20 years from the date of application.

Exclusivity: Prohibits the approval of competitor drugs by the FDA. All new drugs get five years of exclusivity from their FDA approval date. However, different types of exclusivities are intended to provide additional incentives for the production of certain types of drugs.

Safety: “Often measured by toxicity testing to determine the highest tolerable dose or the optimal dose of a drug needed to achieve the desired benefit.” A safe drug does not mean that there are no side effects, but benefits outweigh the potential risks of side effects and that the drug is not toxic. Safety trials may also identify adverse events (injury resulting from medical intervention).

Efficacy: Performance of an intervention under ideal and controlled circumstances.

Effectiveness: Performance of an intervention under real-world conditions.

medicines, including generics, for any given condition. However, FDA approval generally guarantees coverage by Medicaid (if manufacturers choose to participate), and specific categories of drugs are also required to be covered by Medicare Part D plans. For drugs not subject to guaranteed Medicare coverage, Part D plans have their own review processes for determining if an approved drug or device should be covered.

User Fee Acts

In 1992, Congress passed the first Prescription Drug User Fee Act (PDUFA), in part, as a response to drug manufacturer and patient advocate complaints about delays in the FDA approval process. The act's solution was to require manufacturers to pay a [user fee](#) at the time of the NDA submission, which the FDA then used to increase staffing to address pending applications.

The User Fee Act's purview for originator drugs has since been expanded to include user fees for animal drugs, generic drugs, biosimilars, and medical devices. The whole Act (and its amendments for other drug/device types) is subject to renewal every five years. The process of writing the legislation to extend the act is carefully negotiated between the industry and the FDA, with results presented to Congress for approval. Through the negotiations, each of the parties, as well as stakeholder groups like patient advocates, are trying to achieve improvements they see as being in their interests.

Patents v. Exclusivity and the Hatch Waxman Act

[Patents and exclusivity](#) are similar in concept in that they relate to how long a new drug can be on the market before the drug can be replicated and sold by competitors. Still, they are distinct and governed by different statutes and parts of the government. A **patent** is granted by the U.S. Patent and Trademark Office and provides for the protection of property rights, for example, the active ingredient of a drug. The term of the patent is 20 years from the date of application, regardless of the drug's FDA approval status.

Exclusivity prohibits the approval of competitor drugs by the FDA. All new drugs get five years exclusivity from their date of approval by the FDA. However, there are different types of exclusivities intended to provide supplemental incentives for the production of certain types of drugs. For instance, drugs for rare diseases (sometimes called orphan drugs) receive an exclusivity of seven years, and drugs tested in children receive an

additional six months added to their existing exclusivity. Additional exclusivities may be limited to an [individual indication](#) rather than the entire product.

The first generic drug to the marketplace can earn a 180-day period of exclusivity from other generic entrants, which encourages generic manufacturers to challenge brand-name manufacturers' patents so they may be the first to bring competition to the market. Patent terms and exclusivity periods may or may not co-occur.

Many of these provisions were initially established in the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the [Hatch-Waxman Act](#), which intended to preserve the incentives that bring innovator drugs to the market while allowing a streamlined process for the approval of generic drugs. The Act provided for patent extensions to account for clinical testing and regulatory review periods and minimum competition-free periods for drugs without patents. In addition, a streamlined process was formalized to bring generic competition to the market after the exclusivity period. The FDA publishes a compendium of approved drugs with therapeutic equivalents (generics), commonly referred to as the Orange Book (for the orange cover from its original printing). The Orange Book lists key patent and exclusivity information for drugs approved by the FDA.

In theory, patent terms and exclusivity periods reward innovators for bringing new drugs to the market by allowing them to charge monopoly prices while preventing competitors from immediately copying their products. When the exclusivity period expires, competition from generic drugs benefits consumers by bringing down the cost of prescription drugs. [Patent-related protection](#) from generic competition can often extend past 20 years because brand-name manufacturers may obtain numerous patents on multiple aspects of their drug, including its formulation, salt forms, and uses (method patents).

Chapter 5 of this Handbook goes into more detail about the many facets and actors that impact the final cost and price of prescription drugs, as well as the various financing challenges and opportunities.

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RESOURCES

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FDA User Fee Programs. <http://allh.us/Yafe>

BACKGROUND

When and Why Was FDA formed? <http://allh.us/79wk>
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FOUR STAGES OF A NEW DRUG REVIEW PROCESS

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. <http://allh.us/7mDA>
How FDA Approves Drugs and Regulates Their Safety and Effectiveness. <http://allh.us/7DfG>
The Sentinel System – An Overview of FDA's Tools For Assessing Medical Product Safety And Gathering Real-World Evidence. <http://allh.us/UWDt>
What is a Serious Adverse Event? <http://allh.us/vjhu>
New and Expanded Uses of Already FDA-Approved Drugs. <http://allh.us/PaDc>
Understanding Unapproved Use of Approved Drugs “Off Label”. <http://allh.us/gM9m>

GENERIC DRUG REVIEW PROCESS

Abbreviated New Drug Application (ANDA). <http://allh.us/TB8q>

BIOLOGIC AND BIOSIMILAR DRUG REVIEW PROCESS

Development & Approval Process (CBER). <http://allh.us/qc7D>
Biologics and Biosimilars: Background and Key Issues. <http://allh.us/XGj3>

DEVICE REVIEW PROCESS

Overview of Device Regulation. <http://allh.us/KRHx>

EXPEDITED APPROVAL AND EMERGENCY USE AUTHORIZATIONS

Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. <http://allh.us/EypF>

How FDA Approves Drugs and Regulates Their Safety and Effectiveness. <http://allh.us/yu6v>
Emergency Use Authorization. <http://allh.us/Kn9g>

USER FEE ACTS

FDA User Fee Programs. <http://allh.us/Yafe>

PATENTS V. EXCLUSIVITY AND THE HATCH WAXMAN ACT

How Can I Better Understand Patents and Exclusivity? <http://allh.us/3rhP>
Repurposing Existing Drugs for New Uses: A Cohort Study of the Frequency of FDA-Granted New Indication Exclusivities Since 1997. <http://allh.us/Pv9e>
The Hatch-Waxman Act: A Primer. <http://allh.us/nbMC>
Drug Pricing and Pharmaceutical Patenting Practices. <http://allh.us/nQef>

Table 4.1

Drugs@FDA Glossary of Terms. <http://allh.us/fPF7>
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Biosimilars. <http://allh.us/9QYA>
Cellular & Gene Therapy Products. <http://allh.us/kdyx>
Congressional Research Service: Specialty Drugs – Background and Policy Concerns. <http://allh.us/7MNH>

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The 21st Century Cures Act (Division A of P.L. 114-255). <http://allh.us/URcY>
Building Upon the Promise of 21st Century Cures: The Cures 2.0 Concept Paper. <http://allh.us/PdTm>

Box: Glossary of Terms

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