

OVERVIEW OF DRUG APPROVAL PROCESS IN THE UNITED STATES

Explore the journey a new drug takes from lab to pharmacy



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Abstract

The United States Food and Drug Administration (FDA) serves as the principal regulatory authority overseeing the safety, efficacy, and labeling of diverse products, including pharmaceuticals, medical devices, and biopharmaceuticals. This whitepaper explores the multifaceted role of the FDA in safeguarding public health while fostering innovation within the pharmaceutical industry. Key focus areas include an overview of the FDA's regulatory functions, drug approval pathways, and considerations for successfully obtaining market authorization in the United States.

Through a comprehensive examination of regulatory strategies, preclinical research, clinical trials, New Drug Application (NDA) submission, and post-approval commitments, this whitepaper provides valuable insights into the complexities of navigating the FDA approval process. Additionally, it delves into the intricacies of FDA approval fees and the challenges encountered in submitting Investigational New Drug (IND) or New Drug Application (NDA) applications. By identifying regulatory compliance, data requirements, communication strategies, and resource allocation as key challenges, this whitepaper offers practical recommendations for overcoming obstacles and achieving successful market entry.

Ultimately, this whitepaper underscores the critical importance of strategic planning, adherence to regulatory guidelines, and collaborative engagement with regulatory authorities in facilitating the successful introduction of new drugs to the U.S. market. Through a concerted effort to address these considerations, pharmaceutical companies can enhance patient access to innovative therapies and contribute to improved public health outcomes.



Introduction to the U.S. FDA - Regulatory Authority of the United States

The United States Food and Drug Administration (FDA) is a federal agency within the Department of Health and Human Services responsible for protecting and promoting public health. The FDA oversees the regulation of various products, including food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.

The FDA's primary functions and responsibilities are as follows.

1. Regulatory Oversight



The FDA regulates products that account for about 20% of the U.S. consumer spending, ensuring that these products are safe, effective, and accurately labeled.

3. Inspections and Compliance



The FDA conducts inspections of facilities involved in the manufacturing, processing, packing, or holding of FDA-regulated products to ensure regulatory compliance.

2. Product Approval



Before products like drugs, medical devices, and vaccines can be marketed in the U.S., they undergo rigorous testing to demonstrate their safety and efficacy. The FDA reviews data submitted by manufacturers to ensure these products meet the required standards.

4. Enforcement Actions



The FDA enforces regulations by taking actions against companies that violate them, including issuing warning letters, recalls, seizures, injunctions, and criminal prosecution when necessary to protect public health.



5. Public Health Education



The FDA provides healthcare professionals, industry stakeholders, and the public with information on drug safety, nutrition, and emerging health threats.

6. Research and Innovation



The FDA supports its regulatory mission by conducting research and fostering innovation, offering guidance to developers of new medical products.

7. Emergency Response



The FDA plays a critical role in responding to public health emergencies, such as foodborne illness outbreaks, natural disasters, and emerging infectious diseases. It closely collaborates with other federal agencies, state and local governments, and international partners to coordinate responses and mitigate health risks.

The FDA's primary goal is to protect and promote public health by ensuring the safety, efficacy, and quality of products within its regulatory purview impacting nearly every aspect of healthcare and consumer products in the United States.



Drug Approval Pathways

Several pathways exist for the approval of new drugs or new indications for existing medications through the FDA. These pathways involve various processes for submitting drug product applications. Two common routes are the 505(b)(2) and the Abbreviated New Drug Application (ANDA). Additionally, FDA regulations in Title 21 CFR Parts 312 and 314 cover the Investigational New Drug Application (IND) and the Application for FDA Approval to Market a New Drug (NDA), respectively. These pathways play a crucial role in expediting drug development and regulatory approval, helping safe and effective drugs reach the market efficiently.

FDA Standard Approval Process

Drugs can follow multiple approval pathways through the FDA, typically beginning with an Investigational New Drug (IND) application based on pre-clinical data. There are three types of IND applications: **Investigator IND**, **Emergency Use IND**, and **Treatment IND**. All require information regarding animal pharmacology and toxicology, manufacturing information on composition and stability, and proposed clinical indications.

Once clinical trial data shows efficacy on standard endpoints in a disease state, the sponsor (individual, corporation, or manufacturer responsible for drug development) submits a New Drug Application (NDA). However, not all drugs that file for an IND progress to an NDA, as they must demonstrate clinical benefit to continue. There are three types of NDAs below.

505(b)(1): Traditional pathway

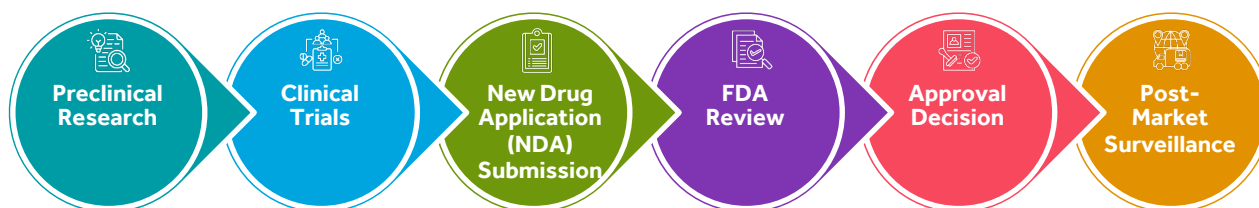
505(b)(2): Drugs with similar active ingredients to a previously approved drug

505(j): Abbreviated New Drug Application (ANDA): Bioequivalent drugs (generics)



Overview of Obtaining Drug Approval in the U.S.

Obtaining approval from the FDA for pharmaceuticals involves several steps, as illustrated below:



Preclinical Research (for Pharmaceuticals):

- Before human testing, preclinical research involves laboratory and animal studies to gather initial data on the product's safety and efficacy.
- Researchers submit an Investigational New Drug (IND) application to the FDA, outlining their proposed clinical trial plans and supporting data.

Clinical Trials:

- **Phase 1:** Small-scale studies in healthy volunteers to assess safety, dosage, and side effects.
- **Phase 2:** Larger studies in patients to evaluate efficacy and further assess safety.
- **Phase 3:** Large-scale, randomized, controlled trials to confirm efficacy, monitor side effects, and gather additional safety data.

New Drug Application (NDA) or Biologics License Application (BLA):

- After successful completion of clinical trials, a sponsor submits an NDA or BLA to the FDA to request marketing approval.
- The application includes comprehensive data from preclinical and clinical studies, as along with information on manufacturing, labeling, and proposed marketing plans.

FDA Review:

- The FDA reviews the submitted application to ensure the product's safety, efficacy, and quality.
- Review timelines vary based on product complexity and resources availability.



FDA Approval or Complete Response Letter (CRL):

- If the FDA determines that the product meets regulatory standards, it approves the application.
- If additional information or clarification is needed, the FDA issues a CRL outlining deficiencies or concerns that must be addressed before approval.

Post-Approval Commitments and Requirements:

- After approval, the sponsor may be required to fulfill post-marketing commitments, such as conducting additional studies or monitoring for adverse events.

- Manufacturers must also comply with ongoing FDA regulations and quality standards.

FDA Inspections:

- The FDA inspects manufacturing facilities to ensure compliance with Good Manufacturing Practices (GMP) and other regulatory requirements.

Throughout this process, communication between the sponsor and the FDA is critical, with opportunities for dialogue during pre-submission meetings, application review, and post-approval discussions. Compliance with FDA regulations and guidelines is essential for successful approval and ongoing marketing of the product.



Overview of Different Submission Routes

505(b)(1) Application

A 505(b)(1) is an NDA application that requires full reports of investigations of safety and effectiveness investigations conducted by or for the applicant, or for which the applicant has a right of reference. Known as “stand-alone” NDAs, are submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act .

505(b)(2) Application

A 505(b)(2) application is an NDA that includes full reports on safety and effectiveness, where some information for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference . This may include, the FDA’s prior findings on a listed drug’s safety or effectiveness or published literature.

505(j)/Abbreviated New Drug Application (ANDA)

An ANDA, submitted and approved under section 505(j) of the FD&C Act, is used for a drug product that is a duplicate of a previously approved drug. It relies on the FDA’s finding that the reference listed drug (RLD) is safe and effective, and cannot be submitted if clinical investigations are required to establish safety and effectiveness. An ANDA must show that the proposed generic product is the same as the RLD in active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and is bioequivalent to the RLD.



Need for 505(b)(2) and 505(b)(j) pathways

The development of the 505(b)(2) and 505(b)(j) pathways was driven by challenges in the pharmaceutical industry, including patent expirations, cost and time concerns in traditional drug development, regulatory hurdles, and the need for innovation. The Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Amendments) added sections 505(b)(2) and 505(j) to the Federal Food, Drug, and Cosmetic Act (FD&C Act), establishing abbreviated routes for NDAs and ANDAs approvals. The 505(b)(2) pathway provided a regulatory framework for approving modified or repurposed drugs, leveraging existing safety and efficacy data for the active ingredient. The 505(b)(j) pathway facilitated the approval of generic versions of drugs, addressing specific regulatory considerations. Overall, these pathways aimed to streamline drug development, encourage innovation, and improve access to medications.

General Content Comparison of Applications

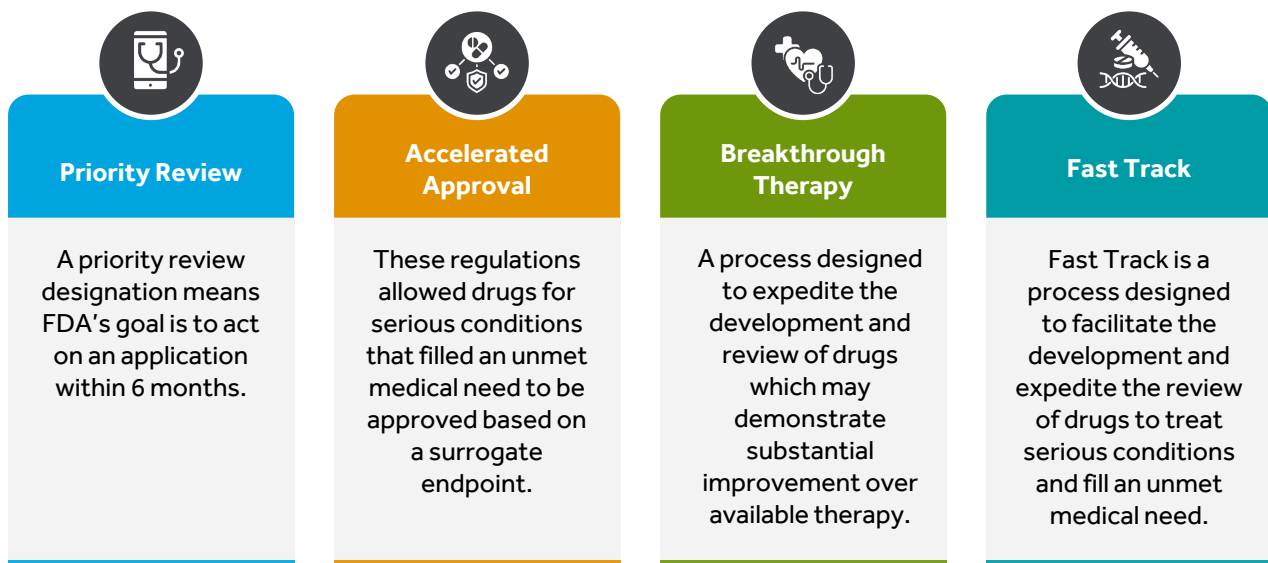
505(b)(1) NDA	505(b)(2) NDA	505(j)
Preclinical	Preclinical	-
Clinical	Clinical	-
Chemistry, Manufacturing, Controls (CMC)	CMC	CMC
Pharmacokinetics (PK) & Bioavailability	PK, Bioavailability, Comparative Bioavailability	Bioequivalence
Labeling	Labeling	Labeling
Patent Information	Patent Information	-
	Patent Certification (if applicable)	Patent Certification
Exclusivity Request	Exclusivity Request	-
-	Exclusivity Statement	Exclusivity Statement

(Source: Abbreviated Approval Pathways for Drug Product: 505(b)(2) or ANDA, 2019)



FDA “Alternative” Approval Processes

The FDA currently uses four “alternative” approval processes, each with unique eligibility criteria and specific benefits for sponsors. Except for the Breakthrough Therapy designation, these processes are applied at the New Drug Application (NDA) stage.



(Source: Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, 2023)

There are multiple FDA approval processes for pharmacologic therapies and drugs for various conditions. Understanding these processes and their relationship to high drug costs, access to care and treatments, and the use of generics and bioequivalents is a high priority to modify treatments within the evolving therapeutic landscape. Unique situations such as the COVID-19 public health emergency, underscore the importance of patient safety and timely access to breakthrough treatments as science advances. Maintaining a credible drug development system, free from political interference, is crucial to providing safe and accessible drugs to patients.



FDA Advisory Board

The FDA Advisory Board is a group of independent physicians and other clinicians that meets to discuss New Drug Applications (NDAs) with FDA reviewers and the product's manufacturer. This advisory team includes physicians, pharmacists, chemists, pharmacologists, statisticians, and patient representatives. These meetings typically last one or two days.

Following the meeting, the Advisory Board makes a recommendation – usually through a vote - on whether to approve the new drug. While the FDA often follows the Board's advice, it is not obligated to do so.

Cost to Bring a Drug to the Market

Developing a new drug and bringing it to market can cost billions of dollars. A study by the London School of Economics estimated that the median cost to be \$985 million, while other studies have suggested costs up to \$2.6 billion. Therapeutic class can also impact costs; for instance, drugs for cancer and immunomodulators have a median cost up to \$2.7 billion.

Post-Drug Approval

After final approval, the drug becomes available for physicians to prescribe. However, market entry may be delayed due to patents disputes, manufacturing issues, or controlled substance designation from the DEA.

Drug pricing is typically disclosed post-approval. However, unlike in many other countries, the FDA does not consider drug pricing or economic factors as part of its approval process.

MedWatch Safety Program

Once on the market, the drug company continues to report adverse reactions and other clinical data to the FDA. Patients and healthcare providers can also report side effects or other concerns through the FDA's MedWatch Program. If a new risk is identified, the FDA updates the product label to ensure public awareness.



Considerations for Successfully Placing a Drug on the U.S. Market

Successfully bringing a drug to the U.S. market requires navigating regulatory requirements and achieving market authorization. Key considerations include:

1

Regulatory Strategy

Develop a regulatory strategy aligned with FDA guidelines, addressing the drug's therapeutic area, regulatory pathway, and target patient population.



2

Preclinical Research

Conduct thorough preclinical studies, and submit an Investigational New Drug (IND) application to the FDA before initiating clinical trials.



3

Clinical Trials

Design and conduct clinical trials per FDA regulations and Good Clinical Practice (GCP) standards to gather comprehensive safety and efficacy data.



4

New Drug Application (NDA) Submission

Compile a comprehensive NDA dossier with preclinical and clinical study results, manufacturing information, labeling, and proposed marketing plans.



5

FDA Review

Engage in effective communication with the FDA during the review process to ensure the drug's safety, efficacy, and quality.



6

Post-Approval Commitments

Be prepared for post-marketing commitments, such as additional studies or real-world safety monitoring.



7

Pricing and Market Access

Develop a pricing strategy based on drug efficacy, market competition, and healthcare payer reimbursement policies.



8

Marketing and Distribution

Establish strategies for promoting the drug and distributing it widely.



9

Pharmacovigilance

Implement a pharmacovigilance program to monitor and report adverse events post-market.



10

Compliance

Ensure ongoing compliance with FDA standards, including manufacturing, labeling, and post-market surveillance.



By addressing these factors and collaborating closely with regulatory authorities, pharmaceutical companies can enhance their chances of successfully placing a drug on the U.S. market, thereby, improving patient access to innovative therapies.

Application Fees

FDA drug approval fees are significantly high compared to other regulatory fees in the United States:

1. For fiscal year 2022, the fee for new drug applications (NDAs) and biologics license applications (BLAs) requiring clinical data surpassed \$3 million.
2. In comparison, a patent application filing fee at the United States Patent and Trademark Office (USPTO) is \$300.
3. The Environmental Protection Agency (EPA) charges approximately \$65,000 for pesticide registration fees.
4. The Federal Communications Commission (FCC) charges an average of \$1,000 for wireless spectrum license application fees.

For latest information on fees please refer to the link below -

Prescription Drug User Fee Amendments | FDA

The high FDA drug approval fees are reflecting the complexity and length of the drug evaluation process. The Prescription Drug User Fee Act (PDUFA) allows the FDA to collect fees from pharmaceutical companies to expedite drug approval. While these fees are substantial, they have contributed to faster approvals since the program's inception in 1992. In 2007, the fees covered over 51% of the cost of reviewing and approving new drugs. However, some consumer groups have raised concerns about the potential conflict of interest when a significant portion of the FDA's funding comes from the industry it regulates.



Challenges in Submitting IND/NDA to U.S.-FDA

Submitting Investigational New Drug (IND) or New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) can present numerous challenges due to the complex regulatory landscape and the stringent requirements. Here are some key challenges faced by sponsors during the process:

- 1. Regulatory Compliance:** Meeting extensive regulatory requirements and ensuring compliance with FDA guidelines can be daunting. Any deviations or errors in submissions may lead to delays or rejections.
- 2. Data Requirements:** Sponsors must provide comprehensive data on safety, efficacy, manufacturing, labeling, and marketing. Ensuring the accuracy and completeness of this data is often challenging.
- 3. Communication with FDA:** Effective communication with the FDA throughout the submission process is crucial. Sponsors need to engage in numerous communications, meetings, and teleconferences, which can be time-consuming and require meticulous documentation.
- 4. Timelines and Review Process:** Adhering to required timelines for submissions, responding to FDA queries promptly, and navigating the FDA review process are critical but challenging aspects. Delays at any stage can impact the overall approval timeline.
- 5. Resource Allocation:** IND/NDA submissions demand substantial resources in terms of time, expertise, and financial investment. Ensuring that all necessary resources are allocated effectively can be a significant challenge.
- 6. Foreign Clinical Studies Acceptance:** When sponsors use foreign clinical studies not conducted under an IND, ensuring that the FDA accepts the data and meets standardization requirements can pose additional challenges.

Navigating these challenges requires careful planning, attention to detail, and close collaboration between sponsors and the FDA to facilitate a successful submission and approval process for IND/NDA applications.



Conclusion

The United States Food and Drug Administration (FDA) plays a vital role in safeguarding public health through its regulatory oversight of various products. Key functions include product approval, inspections, enforcement actions, public health education, research, and emergency response. Drug approval pathways, such as 505(b)(2), ANDA, and standard approval processes, are essential for bringing new medications to market. Achieving market clearance in the United States requires careful planning, strict adherence to regulatory requirements, and active engagement with regulatory authorities. Although FDA approval fees are high, they contribute to expediting the drug approval process. Nonetheless, challenges in submitting IND/NDA applications to the FDA persist, including regulatory compliance, data requirements, communication, timelines, resource allocation, and acceptance of foreign clinical studies. Overcoming these challenges requires meticulous planning and close collaboration between sponsors and regulatory authorities.

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<https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>

<https://courseware.cutm.ac.in/wp-content/uploads/2020/06/Concecpt-of-consumer.pdf>

<https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/abbreviated-approval-pathways-drug-product-505b2-or-anda>

About the Author



Prachi Bhatnagar is a medical writer (Regulatory Affairs) specializing in Pharmaceuticals Clinical Affairs and Medical Writing, with over three years of hands-on experience in the industry. She has successfully supported multiple drug submissions for U.S. FDA, showcasing her in-depth understanding of regulatory requirements and submission processes.

Prachi has also conducted thorough medical reviews on Veeva Promo-Mats, ensuring compliance with the ABPI and EFPIA Codes of Practice. She has authored a range of critical regulatory documents, including Clinical and Non-Clinical overviews.

She is skilled in developing and implementing comprehensive regulatory strategies by conducting feasibility analysis, defining regulatory requirements, and efficiently coordinating with cross-functional teams. Her dedication to regulatory excellence and global compliance has made her a key contributor towards successful market entry for various pharmaceutical products.

She has also been a key contributor towards placing personal grooming product which involved thorough knowledge of chemicals consumer goods regulations across globally which comprises of Europe, U.S., APAC region.

About Cyient

Cyient (Estd: 1991, NSE: CYIENT) partners with over 300 customers, including 40% of the top 100 global innovators of 2023, to deliver intelligent engineering and technology solutions for creating a digital, autonomous, and sustainable future. As a company, Cyient is committed to designing a culturally inclusive, socially responsible, and environmentally sustainable Tomorrow Together with our stakeholders.

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