

From Application to Approval: Exploring the FDA's Review Process

Kiran Bonda, Roche/Syneos, NC, USA

ABSTRACT

Regulatory agencies are the cornerstone of public health, ensuring that pharmaceutical products are safe, effective, and of high quality before they reach the market. Among these agencies, the U.S. Food and Drug Administration (FDA) stands out as a global leader in drug regulation. This paper provides sponsors with a thorough overview of the FDA's review process, highlighting the importance of accurate data capture and validation. The FDA conducts both basic and eCTD validations for every submission and sends acknowledgments to sponsors, confirming whether the submission has been successfully processed or has encountered issues. The paper highlights the essential stages that each undergoes, including receiving, validation, categorization, routing, and filing review. Understanding the FDA's validation process helps sponsors meet the required data quality standards, aligning with the agency's data-driven regulatory decision-making. FDA regularly enhances its analytics capabilities to more efficiently analyze both structured and unstructured data from submissions, so it is crucial for sponsors to adapt accordingly to minimize delays and secure faster regulatory approvals.

INTRODUCTION

Regulatory agencies, such as the FDA, are responsible for overseeing the development, approval, and post-market surveillance of pharmaceutical products. The drug development process is complex and requires adherence to stringent regulatory standards to ensure patient safety and product efficacy. This paper provides an in-depth analysis of the FDA's review process, focusing on the requirements for drug application submissions and the challenges associated with ensuring compliance.

REGULATORY FRAMEWORK AND DRUG DEVELOPMENT PROCESS

The drug development process is a lengthy and resource-intensive journey that begins with preclinical research and progresses through clinical trials, regulatory submission, and post-market surveillance. Regulatory agencies like the FDA are tasked with evaluating the data generated during these stages to determine whether a drug is safe and effective for its intended use.

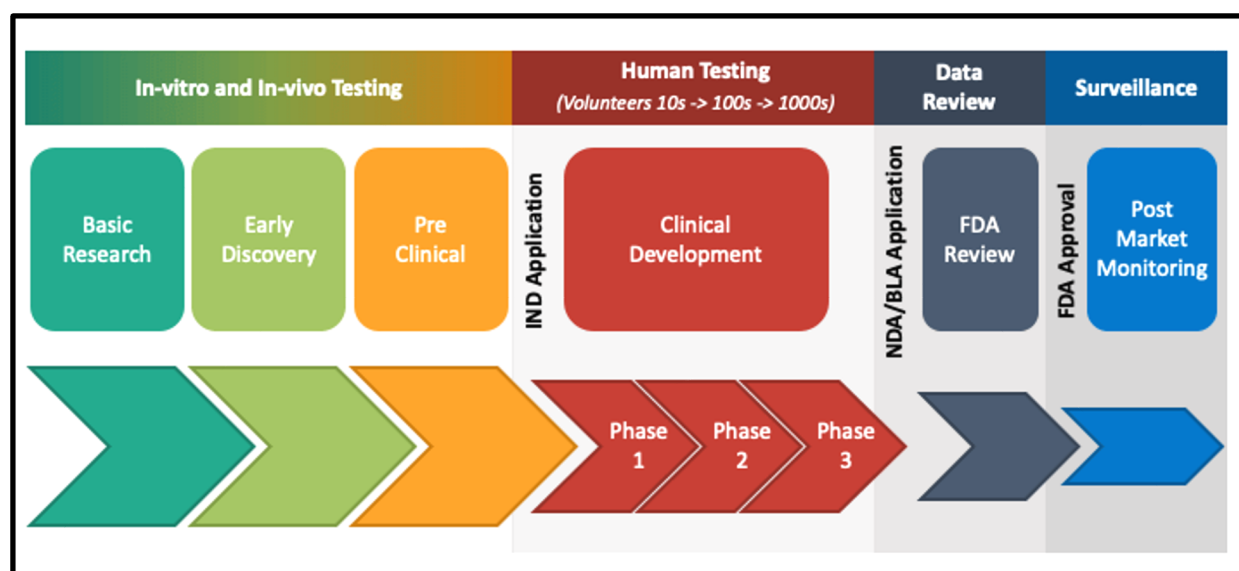


Figure 1. Drug Development Process

The FDA's regulatory framework is governed by the Federal Food, Drug, and Cosmetic (FD&C) Act, which outlines the legal requirements for drug approval. Section 745A(a) of the FD&C Act mandates that drug application sponsors use the standards defined in the FDA Data Standards Catalog. These standards ensure consistency and facilitate the

efficient review of submissions. Over the years, the FDA has implemented several key standards, including the Electronic Common Technical Document (eCTD) format, which has become the global standard for regulatory submissions.

FDA REVIEW PROCESS AND REQUIREMENTS

The FDA's review process for drug applications is a multi-phase process that ensures submissions are complete, accurate, and compliant with regulatory requirements. The process includes submission validation, categorization, data capture, routing, and filing review. Each phase is critical to the overall efficiency and effectiveness of the review process.

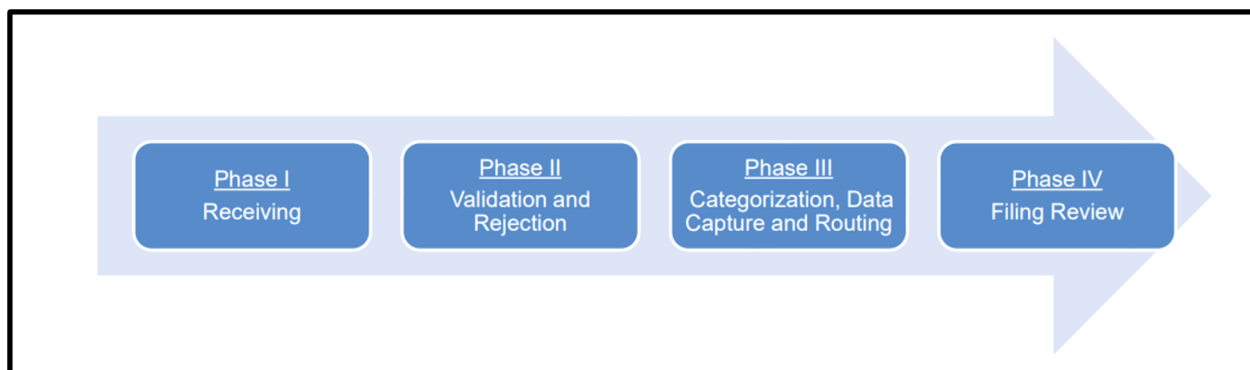


Figure 2 FDA Review Phase's

SUBMISSION VALIDATION

The first step in the FDA review process is the validation of incoming submissions. This involves two main types of validation:

- **Basic Validation:** A preliminary check of the submission to ensure it meets basic requirements, such as file format and completeness.
- **eCTD Validation:** A more detailed validation process that checks the submission against the FDA's eCTD validation criteria. This includes verifying the structure, formatting, and completeness of the submission.

In 2022, the FDA received 248,000 eCTD submissions, with a remarkable 99.7% conformance rate to the eCTD standard. This high conformance rate reflects the industry's commitment to adhering to FDA data standards and highlights the importance of standardized formats in streamlining the review process.

CATEGORIZATION, DATA CAPTURE, AND ROUTING

Once a submission passes validation, the FDA's Document Room and Data Service team capture metadata from the submission. This metadata includes critical information such as:

- **Applicant Information:** The name and contact details of the sponsor.
- **Product Details:** The name, dosage form, and strength of the drug.
- **Indication:** The therapeutic use of the drug.
- **Establishment:** The manufacturing facilities involved in producing the drug.
- **Submission Type:** Whether the submission is an NDA, BLA, ANDA, or another type.
- **Supplement Category:** For supplements, the type of change being proposed (e.g., labeling, manufacturing process).

The FDA has been working to automate the categorization and routing process to expedite the initiation of the review process. However, data discrepancies in eCTD submissions, such as inconsistencies between backbone files and regulatory forms, can hinder full automation. Common issues include underutilization of existing eCTD headings and attributes, failure to identify grouped submissions, and incorrect placement of submission files in eCTD modules or sections.

FILING REVIEW

The filing review phase is a critical step in the FDA's review process. During this phase, FDA reviewers assess whether the submission contains any major deficiencies that could impede a timely and efficient review. If significant issues are identified, the submission may be subject to:

- **Refuse to Receive (RTR):** For ANDA applications, where the submission is rejected due to major deficiencies.
- **Refuse to File (RTF):** For BLA and NDA applications, where the submission is rejected for similar reasons.

In some cases, the FDA may issue a deficiency notice, allowing the applicant to address missing or incomplete information before the submission is rejected. This approach provides sponsors with an opportunity to rectify issues and avoid delays in the review process.

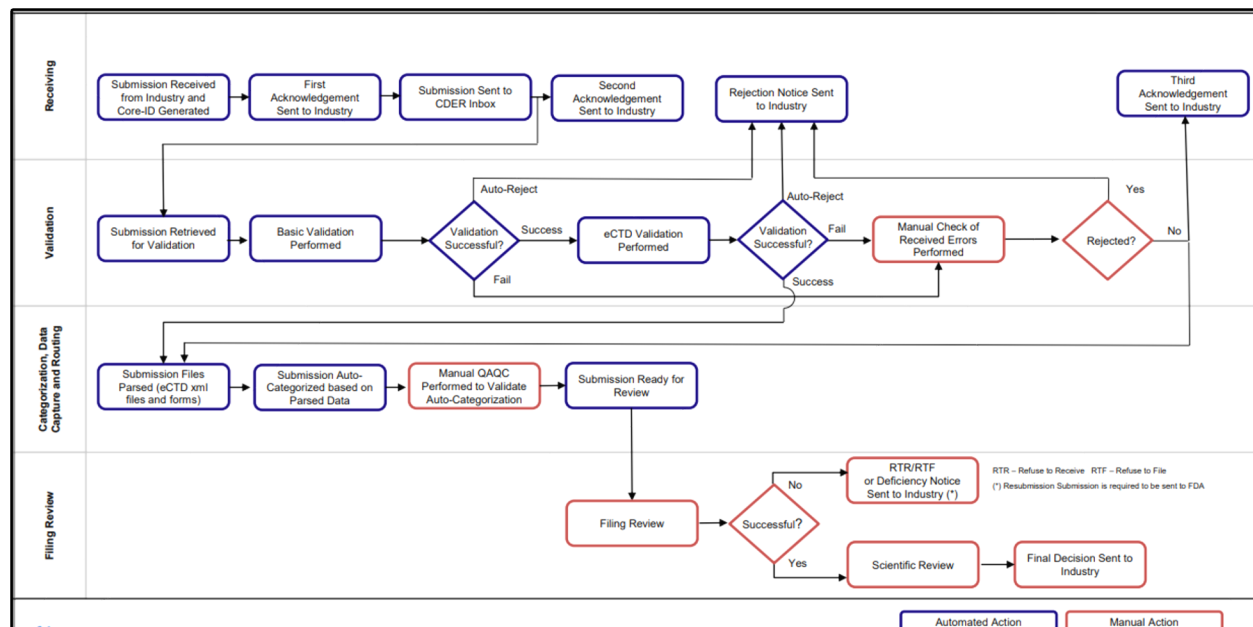


Figure 3. Process Diagram

CHALLENGES IN THE SUBMISSION PROCESS

Despite the high conformance rate to eCTD standards, challenges remain in ensuring the quality and accuracy of submissions. Common issues include:

- **Data Discrepancies:** Inconsistencies between eCTD backbone files and FDA regulatory forms can lead to delays in the review process.
- **Underutilization of eCTD Headings and Attributes:** Sponsors often fail to fully utilize the available eCTD headings and attributes, which can result in incomplete or unclear submissions.
- **Grouped Submissions:** Failure to identify grouped submissions in eCTD backbone files can complicate the review process.
- **Incorrect File Placement:** Submission files placed in eCTD modules or sections that are not relevant to their contents can hinder the review process.

These challenges highlight the importance of data quality in regulatory submissions and underscore the need for sponsors to carefully review their submissions before filing.

FDA'S EFFORTS TO IMPROVE THE REVIEW PROCESS

The FDA is continuously working to enhance its regulatory review process by leveraging advanced analytics and data-driven decision-making. The Center for Drug Evaluation and Research (CDER) is building capabilities to extract and analyze both structured and unstructured data from sponsor submissions. These efforts aim to improve the efficiency and accuracy of the review process, ultimately benefiting both regulators and industry stakeholders. One notable initiative is the FDA's use of advanced analytics to identify patterns and trends in submission data. By analyzing both structured data (e.g., numerical data from clinical trials) and unstructured data (e.g., text from study reports), the FDA can make more informed decisions and identify potential issues earlier in the review process. This approach not only improves the efficiency of the review process but also enhances the agency's ability to ensure the safety and efficacy of pharmaceutical products.

CONCLUSION

Regulatory agencies like the FDA play a vital role in ensuring the safety and efficacy of pharmaceutical products. The FDA's review process is designed to rigorously evaluate submissions while promoting efficiency using standardized data formats and advanced analytics. By adhering to regulatory requirements and maintaining high data quality

standards, sponsors can facilitate a smoother review process and contribute to the timely availability of safe and effective drugs for patients.

As the pharmaceutical industry continues to evolve, the FDA's commitment to innovation and efficiency in its review process will remain critical to its mission of protecting public health. Sponsors must stay informed about regulatory requirements and best practices to navigate the complex landscape of drug development and approval successfully.

REFERENCES

- U.S. Food and Drug Administration. (2022). FDA Data Standards Catalog.
- Federal Food, Drug, and Cosmetic Act, Section 745A(a).
- FDA eCTD Submission Standards and Technical Rejection Criteria.
- Center for Drug Evaluation and Research (CDER). (2022). Advanced Analytics in Regulatory Review.

CONTACT INFORMATION

This paper provides a comprehensive overview of the regulatory review process and highlights the importance of compliance with FDA requirements. If you need further elaboration on any specific section, feel free to ask! Your comments and questions are valued and encouraged. Contact the author at:

Kiran Bonda
Roche/Genentech, NC, USA
Kiran.bonda@roche.com