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Research

Regulatory strategy for filing NDA/ANDA

Miryala Aishwarya*, Unnam Subamoorthy[1]

Department Of Regulatory Affairs, Sree Dattha Institute Of Pharmacy, Nagarjuna Sagar Road Sheriguda, Ibrahimpatnam Rangareddy - 501510.

*Author for Correspondence: Miryala Aishwarya
Email: aishwaryamiryala1999@gmail.com

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Abstract

In Pharmaceutical Industry, Regulatory Affairs Department makes an interface between the regulatory authorities and pharmaceutical industry. The Regulatory Affairs department is an important part of the organizational structure of pharmaceutical companies. Internally it liaises at the inter phase of drug development, manufacturing, marketing and clinical research. Externally it is the key interface between the company and the regulatory authorities. Regulatory Affairs is involved in the development of new medicinal products from early on, by integrating regulatory principles and by preparing and submitting the relevant regulatory dossiers to health authorities. Regulatory Affairs is actively involved in every stage of development of a new medicine and in the post-marketing activities with authorized medicinal products. This professional can play a key role in guiding drug development strategy in an increasingly global environment and has an important role for submitting the newly discovered drug products approval documents to the US FDA regulatory authorities and to carry out all the practices required for obtaining the drug products approval. This article mainly focuses on the US FDA drug approval strategies. These strategies playing core job in the pharmaceutical industry. These strategies having all the guidelines which are indispensable part of the IND, NDA and ANDA drug approval applications. It plays a significant role in sequence for registration of newly exposed products and also providing the guidelines which is helpful preparing the registration documents to regulatory authorities.

Keywords: IND, NDA, ANDA, CDER,\

INTRODUCTION

The Center for Drug Evaluation and Research (CDER, pronounced "see'-der") is a division of the U.S. Food and Drug Administration (FDA) that monitors most drugs as defined in the Food, Drug, and Cosmetic Act. Some biological products are also legally considered drugs, but they are covered by the Center for Biologics Evaluation and Research. The center reviews applications for brand name, generic, and over the counter pharmaceuticals, manages US current Good Manufacturing Practice (cGMP) regulations for pharmaceutical manufacturing, determines which medications require a medical prescription, monitors advertising of approved medications, and collects and analyzes safety data about pharmaceuticals that are already on the market.

CDER reviews New Drug Applications to ensure that the drugs are safe and effective. Its primary objective is to ensure that all prescription and over-the-counter (OTC) medications are safe and effective when used as directed.

The FDA requires a four phased series of clinical trials for testing drugs. Phase I involves testing new drugs on healthy volunteers in small groups to determine the maximum safe dosage. Phase II trials involve patients with the condition the drug is intended to treat to test for safety and minimal efficacy in a somewhat larger group of people. Phase III trials involve one to five thousand patients to determine whether the drug is effective in treating the condition it is intended to be used for. After this stage, a new drug application is submitted. If the drug is approved, stage IV trials are conducted after marketing to ensure there are no adverse effects or long term effects of the drug that were not previously discovered.

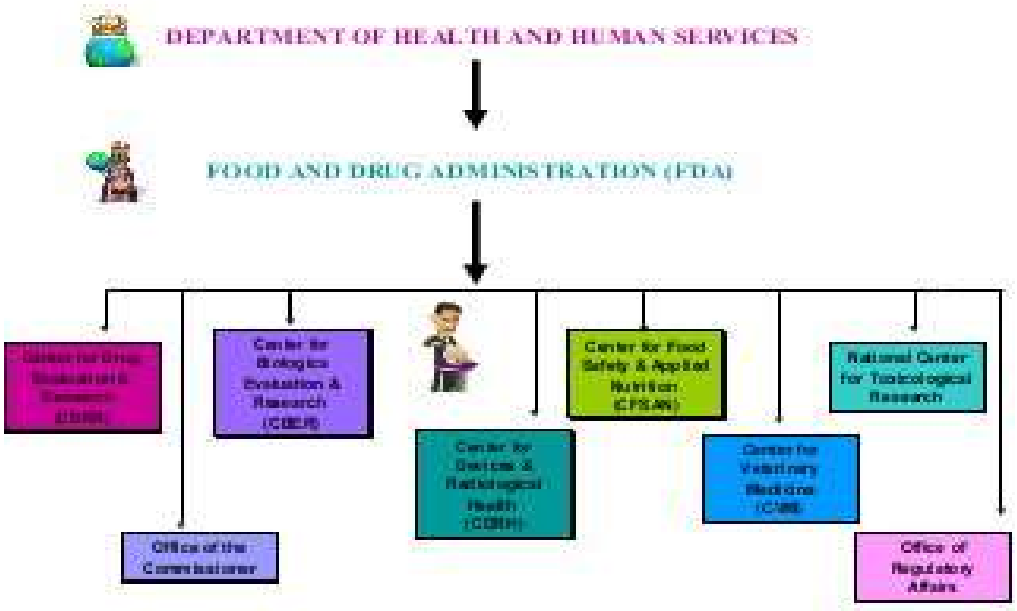

Fig 1: CDER

With the rapid advancement of biologically-derived treatments, the FDA has stated that it is working to modernize the process of approval for new drugs. In 2017, Commissioner Scott Gottlieb estimated that they have more than 600 active applications for gene and cell based therapies.[1]

The Center for Drug Evaluation and Research (CDER) performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States. As part of the U.S. Food and Drug Administration (FDA), CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. This work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered drugs.[2] The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness. It has responsibility for both prescription and nonprescription or over-the-counter (OTC) drugs. Some companies submit a new drug application (NDA) to introduce a new drug product into the U.S. Market. It is the responsibility of the company seeking to market a drug to test it and submit evidence that it is safe and effective. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the sponsor's NDA containing the data and proposed labeling.

AIM AND OBJECTIVES

- New Drug Application (NDA) is the application process through which pharmaceutical drugs for human use are approved by the United States Food and Drug Administration (US FDA).
- All ANDA submissions MUST be in eCTD format. eCTD submission sizes 10 GB or less must use the FDA Electronic Submission Gateway (ESG). If an eCTD submission is greater than 10 GB, it may be submitted via physical media (DVD/USB Drive) to the CDER Document Room or via ESG.
- Filing review is conducted to determine whether the application is sufficiently complete to permit a substantive review and these strategies plays a significant role in sequence for registration of newly exposed

products and also providing the guidelines which is helpful preparing the registration documents to regulatory authorities.

Types of Applications[3]

- Investigational New Drug (IND)
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Over-the-Counter Drugs (OTC)
- Biologic License Application (BLA)

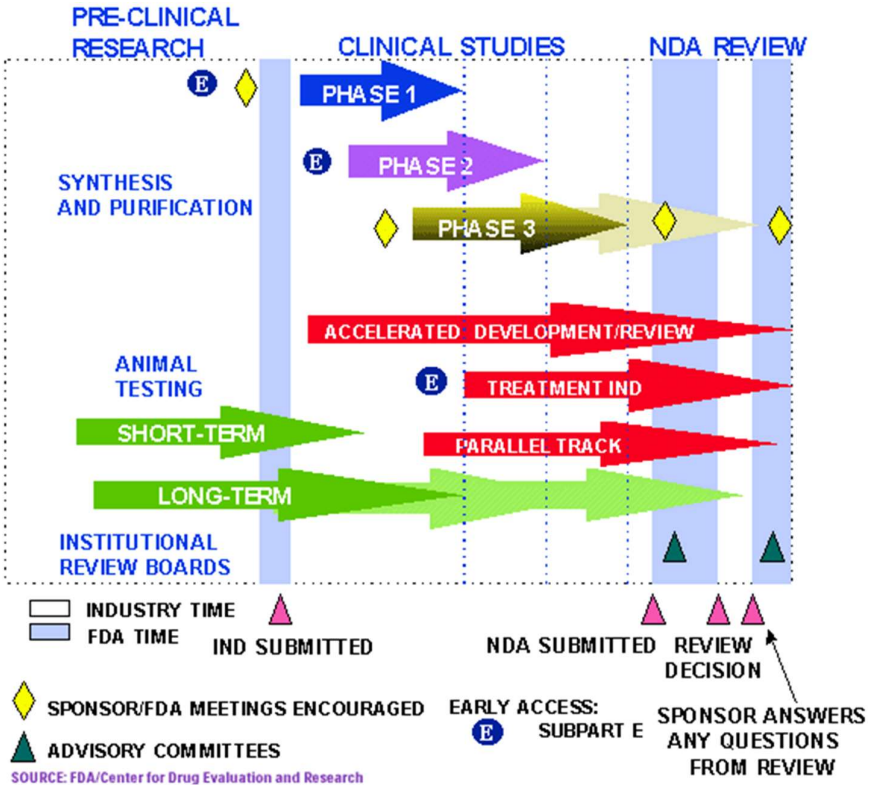

Fig 2: New Drug Approval Process and strategy

Investigational New Drug (IND)[4]

An Investigational New Drug Application (IND) is a request from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Clinical studies are often conducted to collect safety and effectiveness information in support of marketing applications for biologic and drug products. Unless exempted, the sponsor for a clinical study must obtain authorization from FDA for conducting the study by submitting an IND Application. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics Product License Application.

Expanded access to a product in an investigational stage can be granted by FDA as a compassion measure. These INDs are used for patients with serious diseases outside of clinical trials when no comparable or satisfactory alternative therapy options are available and are requested by the treating licensed physicians who determine whether the benefit outweighs the probable risk.

Clinical studies must follow a set of laws and regulations, which are intended to protect the right, safety, and welfare of human subjects participating in human trials, ensure the quality, validity, and integrity of the clinical trial data, and promote the availability of new medical products to the public. These laws and regulations define the roles and responsibilities of entities, such as sponsors, clinical investigators, and institutional review boards. In addition, various guidance documents and standard operating procedures are available to clarify policies and procedures for the IND process.

Laws, Regulations, Policies and Procedures

Code of Federal Regulations (CFR)

The following regulations apply to the IND application process;

21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

Content of an initial IND

1. Cover Sheet (Form FDA 1571)
2. Table of Contents
3. Introductory Statement & General investigational plan
4. Investigator's Brochure
5. Protocols
6. Chemistry, Manufacturing & Control Information
7. Previous Human Experience with the Investigational Drug
8. Additional Information

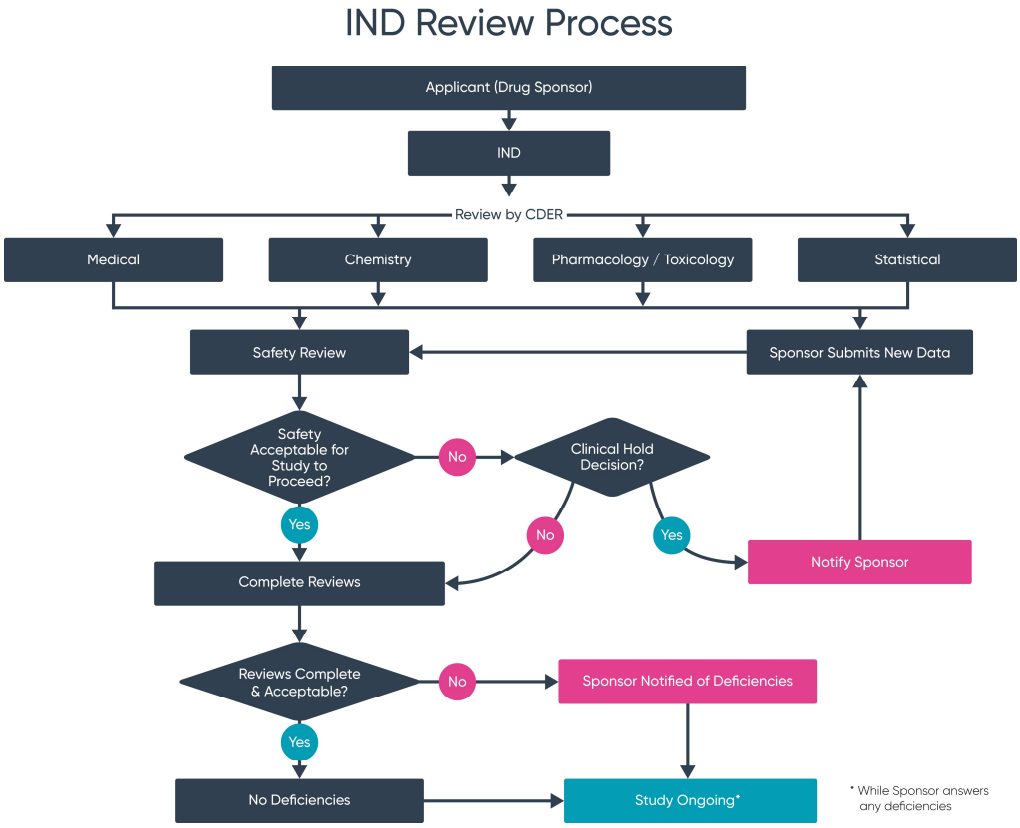

Fig 3: IND Review Process

The drug sponsor formally asks the FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data, the analyses of that data, information about how the drug behaves in the body, and a description of how it is manufactured.

After an NDA is received, the FDA has 60 days to decide whether the application is complete enough to go through formal review. If it is not, the FDA asks the sponsor for more information, and sometimes even more studies. Once the FDA finds the application to be sufficient, an FDA review team is assigned to evaluate the research on the drug's safety and effectiveness. The review timeline varies, depending on several factors:

whether other, similar drugs are already in the market; whether the drug treats a condition that is lacking sufficient treatments; whether the drug is the first of its kind, scientifically; and so forth.[5]

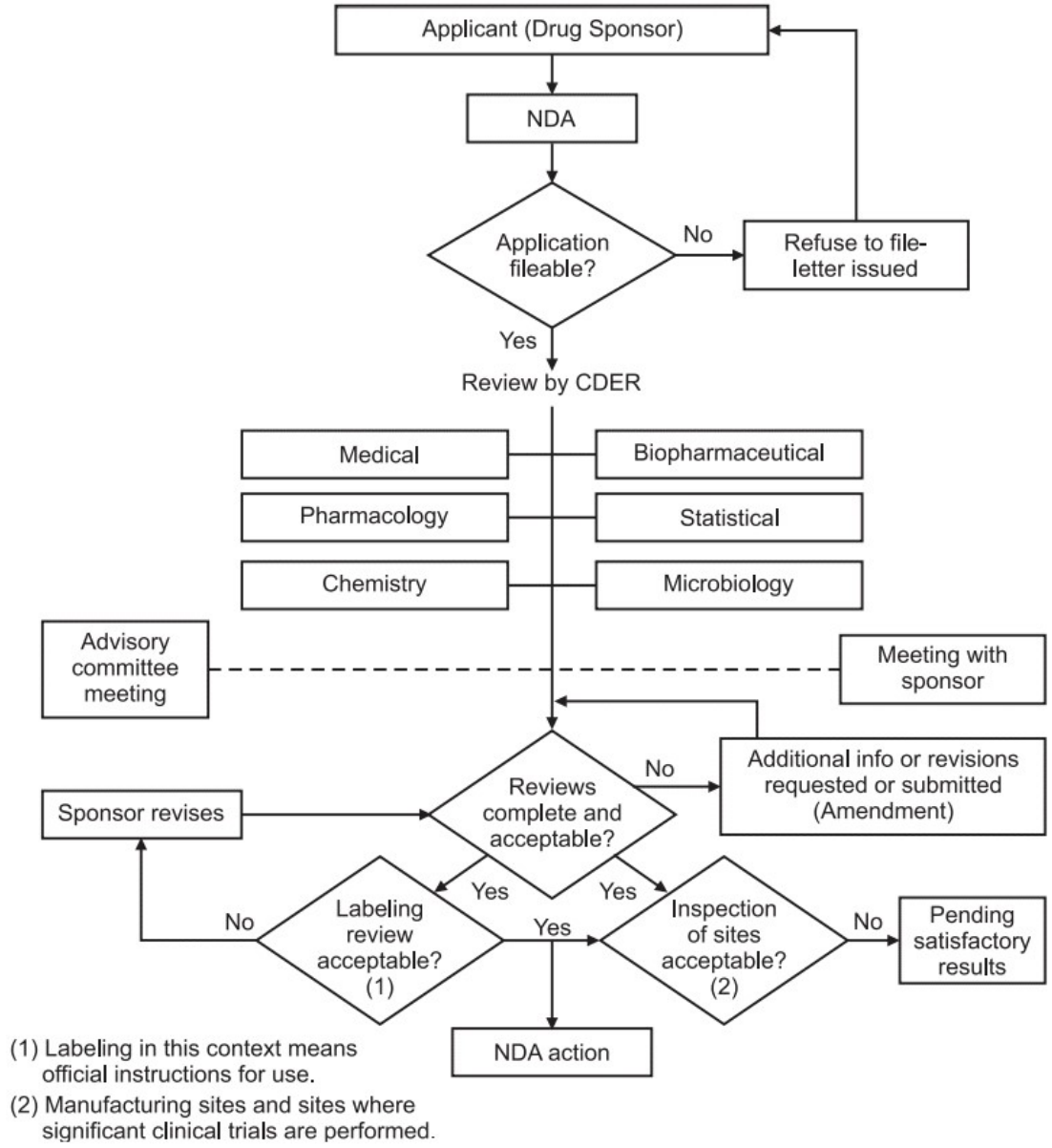

Fig 4: NDA Review Process

The NDA is the vehicle through which drug sponsors (pharmacy companies) formally propose that the FDA approve a new pharmaceutical for sale and marketing inthe U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

In simple terms "It is an application filed with USFDA to get approval for marketing a new pharmaceutical for sale in the U.S." Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Is the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Is the drug's proposed labeling (package insert) is appropriate, and what it should contain?

- Are the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity

Resources for NDA Submissions

The following resources have been gathered to provide you with the legal requirements of a new drug application, assistance from CDER to help you meet those requirements, and internal NDA review principles, policies and procedures.

Guidance Documents for NDAs

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

For the complete list of CDER guidances, please see the Guidance Index. For information on a specific guidance document, please contact the originating office.

Guidance documents to help prepare NDAs

- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs and General Considerations
- Changes to an Approved NDA or ANDA
- Changes to an Approved NDA or ANDA: Questions and Answers
- Container Closure Systems for Packaging Human Drugs and Biologics
- Format and Content of the Microbiology Section of an Application,
- Format and Content of the Clinical and Statistical Sections of an Application
- Summary for New Drug and Antibiotic Applications--Format and Content of the Summary for New Drug and Antibiotic Applications
- Formatting, Assembling and Submitting New Drug and Antibiotic Applications,
- Guideline For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Products
- NDAs: Impurities in Drug Substances
- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application
- Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- Drug Master Files: Guidelines
- FDA IND, NDA, ANDA, or Drug Master File Binders
- PET Drug Applications - Content and Format for NDAs and ANDAs — 2011

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code Of Federal Regulations (CFR)

The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* and related statutes. Section 21 of the *CFR* contains all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

- 21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

CONCLUSION

A regulatory strategy is a science-driven assessment of a product's development options, key consider-actions and likely regulatory outcome. It should span the earliest development stages through further modifications planned post authorization.

Regulatory Strategies describes how the pharmaceutical companies communicate about the approval for drug products. It is necessary to understand the various steps for drug approval. Deciding on a suitable regulatory strategy plays a vital role in gaining time on the market authorization of a drug product.

Pharmaceutical regulations, or medicines regulations, have been defined as the combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information.

The drug regulatory authority is "the agency that develops and implements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information. This is done by making certain that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specified standards. Several of these functions also contribute to efforts to promote rational drug use.

ACKNOWLEDGEMENT

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