IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW : PHARMACOVIGILANCE

Dnyanada R. Janjire[1], Hrutik A. Hole[2], Siddhesh L. Chavan[3], Sanket B. Jagatap[4]

Mahadev Kanchan College Of Pharmaceutical Education And Research,Uruli Kanchan, Pune MH, India-412202.

Address for correspondence,

Dnyanada Rohidas Janjire.

A/P patas railway station, Kangaon, Daund, Pune MH, India-412219.

Abstract :

Clinical research is an important part of the drug discovery process to ensure the safety and efficacy of any new drug. In today's global scientific era, clinical trials are the compulsory for bringing newer and better drugs to market. Clinical trials test potential treatments in human volunteers (subjects) to see whether they should be approved for wider use in the general population. India stood as a global hub for clinical trials in past years due to various factors. In this paper we discuss about clinical trials and clinical trials in India. We also discussed about types of clinical trials, Functions of DCGI and CDSCO, general introduction of Regulatory Applications such as NDA, INDA and ANDA.

Keywords : Clinical Trials, phases, Regulatory Application, Protocols for clinical trial

Introduction :

As the name implies, clinical trials are a series of observations and experiments conducted on human participants for clinical research. They are carried out in search of new treatments, interventions or tests as a means to prevent, detect, treat or manage various diseases, medical conditions. Clinical Trials helps in determining if a new intervention works, its safety & efficacy, and is it better than already available treatments [1].

According to WHO, clinical trial is defined as : **Any scientific investigation in which human subjects or human groups are prospectively assigned to one or more health-related interventions in order to assess the impact on health outcomes [1].**

The primary goal of drug discovery research is to provide humanity with better, safer, and more effective medications. A new medication must pass numerous stages of rigorous testing, first on animals and then on human beings, before it is released onto the market. They play a crucial and deciding role in the introduction of new drugs to the market. Without clinical trials, scientists are unable to accurately assess the efficacy and safety of novel medications created in the lab or using animal models, as well as the appropriate functioning of diagnostic tests in a clinical context [1].

Clinical Trials

History :

Clinical research has had a lengthy and fascinating history of development. Clinical trials have a history that dates back to the 500 BC descriptions found in books. From dietary therapy—legumes and legumes—to medication, the path progresses [2].

Clinical trials have faced a wide range of difficulties throughout history, including ethical, legal, and scientific ones. The earliest known trial of legumes was conducted in biblical times, while the first randomised controlled trial of streptomycin took place in 1946. The majority of the components of a controlled trial were present in James Lind's well-known scurvy trial from 1747. The first double blind controlled trial took place in 1943 when the UK Medical Research Council (MRC) tested patulin for the common cold. This made it possible for the MRC of the UK to conduct the first randomised control trial of streptomycin in pulmonary tuberculosis in 1946. Clinical Trials Day is observed on May 20th globally to commemorate James Lind's first controlled clinical experiment, which was carried out in May 1747. Lind was able to discover a treatment for scurvy in sailors through his clinical studies. Since its establishment in 2005, Clinical Trials Day has been observed as a national holiday [2].

Definition and phases of clinical trials :

Definition : Research on novel diagnostic procedures and therapeutic approaches that assess their impact on human health outcomes is known as clinical trials [1].

In order to evaluate medications, stem cells, and other biological products, surgical techniques, radiological techniques, equipment, behavioural therapies, and preventive care, people volunteer to participate in clinical trials. Clinical trials must first be approved. They must then be meticulously planned, examined, and finished. Clinical trials are open to participants of all ages, including minors [1].

Participants in clinical trials typically come from multiple medical or research facilities, as well as multiple nations. In an effort to provide a single point of access and clear trial identification, WHO's International Clinical Trials Registry Platform (ICTRP) connects clinical trials registers worldwide. The goal is to improve information access for patients, families, patient groups, and other stakeholders. An international project called the ICTRP seeks to provide the public with access to data regarding all human clinical trials [1].

Types of Clinical Trials :

Clinical trials can be classified into different ways.

A. One way is to classify clinical trials on basis of mode of study-

1) **Interventional Study:** Researchers track the patients' changes in health in this study. The research participants are administered a certain medication, and the outcomes are compared between the treated group and the control group. This kind of study is a comparative one [1].

2) **Clinical observational study:** In this study, the researchers examine the participants who are given new medication and track their results [1].

B. Another way is to classify trials is by their purpose-

1) **Prevention trials:** In order to prevent an illness from spreading to others who have never experienced it or to stop an illness from coming back. These methods could involve taking medications, vitamins, minerals, immunisations, or altering one's lifestyle [1].

2) **Screening trials:** examine the most effective methods for identifying specific illnesses or medical conditions [1].

3) **Diagnostic trials:** are carried out to develop more accurate methods or tests for identifying a specific illness or condition [1].

4) **Treatment trials:** test new drug combinations, surgical techniques, radiation therapy regimens, or experimental treatments [1].

5) **Quality of life trials**(Supportive Care Trials) look at ways to make people with chronic illnesses more comfortable and enhance their quality of life [1].

6) **Compassionate use trials** or greater access trials offer a certain amount of testing. unapproved medications to a small number of patients who have no other feasible options. This pertains to an illness for which there is currently no recognised treatment, or it concerns a patient whose health is too poor to be eligible for randomised clinical trials, or who has already exhausted all conventional therapies [1].

It also aims to : [3]

• enhance the accuracy, completeness, and depth of registered clinical trial data;

• Explain and make people aware of the necessity of registering clinical trials;

• Assure that registered data is accessible;

• Increase the ability to register clinical trials;

• Assure the ICTRP's viability; and

• Promote the use of registered data.

Phases of clinical trials :

Pre-clinical studies

Pre-clinical research includes experiments conducted on animal populations as well as in vitro (i.e., in a test tube or laboratory). The study drug is administered at varying dosages to the animal subjects or an in-vitro substrate to gather preliminary data on pharmacokinetics, toxicity, and efficacy. This information helps pharmaceutical companies determine whether to proceed with more testing or not [4].

It offers details on dosage and levels of toxicity. Preclinical research takes many years to test and evaluate medications [4].

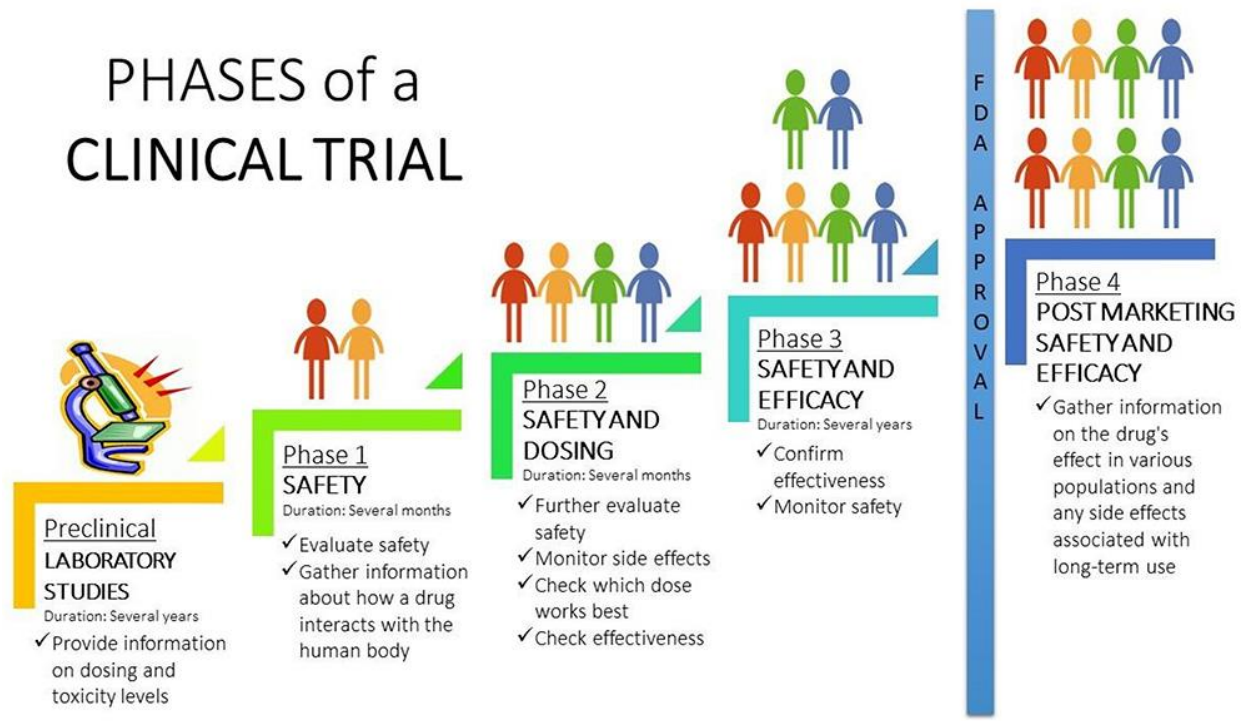


Fig. Phases of Clinical Trials [5]

Phase 0

The U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies designates exploratory, first-in-human trials as phase 0, as of late. Through the early determination of whether a medicine or imaging agent behaves in humans as predicted from preclinical studies, phase 0 trials aim to expedite the development of promising treatments or agents. Phase 0 trials are characterised by the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) in order to collect preliminary data on the pharmacokinetics and pharmacodynamics of the agent (i.e., how the drug functions in the body) [4].

Phase I

The initial phase of testing with human volunteers is known as a phase I trial. Normally, a small (20-80) group of healthy volunteers will be selected. There are trials in this stage. The safety (pharmacovigilance), which is intended to evaluate a drug's pharmacokinetics, pharmacodynamics, and safety tolerability. These studies are frequently carried out in an inpatient clinic where full-time staff members may monitor the participant. The patient is often monitored for a number of the drug's half-lives after administration. Additionally, phase I trials typically involve dose-ranging, or dose escalation, investigations to determine the right dose for therapeutic use. Typically, the tested dose range is a small portion of the dose that harms animals when tested on them. Healthy participants are typically included in phase I trials. Real patients are utilised in specific situations, nevertheless, such as when they are terminally ill and have no other options for therapy. The most common instances of this exception to the rule are in HIV medication trials and oncology (cancer). For their time spent in the volunteer centre, volunteers get an inconvenience fee. Depending on how long a participant stays, pay may vary from a small sum for a brief stay to a larger sum of up to almost £4,000 [4].

There are various types of Phase I trials:

1) **SAD**

Just One Ascending Dose studies are those in which a medicine is administered to small groups of participants once while they are monitored and tested over an extended period of time. The dose is increased and a new set of participants is given a larger dose if they show no unfavourable side effects and the pharmacokinetic data generally aligns with expected safe values. This process is repeated until the medicine reaches the Maximum tolerated dosage (MTD) or until pre-calculated pharmacokinetic safety values are reached or severe side effects begin to manifest [4].

2) **MAD**

Several Ascending To learn more about the pharmacokinetics and pharmacodynamics of the medicine at different dosages, dose studies are carried out [4].

Phase II

Phase II trials are conducted on bigger groups (20–300) and are intended to evaluate the drug's efficacy in addition to carrying out Phase I safety assessments in a wider number of patients and volunteers. Phase I trials confirm the study drug's initial safety. When a novel drug's development process fails, it usually happens during Phase II trials when it is shown to not function as intended or to have harmful side effects [4].

Studies in Phase II are occasionally separated into Phase IIA and Phase IIB. Phase IIA is especially meant to determine dosage needs (how much drug should be administered), whereas Phase IIB is specifically designed to study efficacy (how effectively the drug works at the specified dose(s)). Certain studies integrate Phase I and Phase II and assess both toxicity and efficacy [4].

Phase III

Phase III studies involve large patient groups (300–3,000 or more, depending on the disease/medical condition being examined) in randomised controlled multicenter trials. They are meant to represent the last evaluation of

the medication's efficacy when compared to the "gold Standard" of care as it is now provided. Phase III studies are the most expensive, time-consuming, and challenging to plan and conduct because to their scale and comparatively long duration, particularly when it comes to treatments for long-term medical disorders. It is customary to carry conduct some Phase III trials while the relevant regulatory agency is still processing the regulatory filing. It is generally assumed, though not always necessary, that a medicine must pass at least two successful Phase III trials that show its safety and effectiveness before receiving approval from the relevant regulatory bodies (such as the FDA in the USA, the TGA in Australia, the European Medicines Agency in the EU), etc.) [4].

When a medication has successfully completed Phase III trials, the trial data are typically compiled into a sizable document that includes a thorough explanation of the techniques followed during manufacture, the formulation specifics, shelf life, and the outcomes of both human and animal investigations. The "regulatory submission" is this compilation of data that is sent to the relevant regulatory bodies in various nations for evaluation [4].

The majority of medications entering Phase III clinical trials are eligible for marketing under FDA regulations with the appropriate advice and guidelines; however, the medications must be promptly recalled from distribution if any adverse effects are recorded anywhere. Although the majority of pharmaceutical companies avoid doing this, it is common to find several medications during Phase III clinical trials on the market [4].

Phase IV

A post-marketing surveillance trial is another name for a phase IV trial. Phase IV trials include continuing technical assistance and safety monitoring, or pharmacovigilance, of a medicine after it is approved for sale. Phase IV studies can be mandated by regulatory bodies or carried out by the sponsoring company for competitive (discovering a new market for the drug) or other reasons (e.g., the drug might not have been tested for interactions with other drugs or on specific population groups like pregnant women, who are unlikely to submit themselves to trials). More patients will be included in the safety surveillance, which will allow for the detection of any uncommon or long-term side effects over a longer period of time than was feasible in the Phase I–III clinical studies. If Phase IV trials reveal harmful consequences, a medicine may be pulled off the market or limited to specific uses: Recent examples include rofecoxib (Vioxx), troglitazone (Rezulin), and cerivastatin (brand names Baycol and Lipobay) [4].

Drug Controller General of India (DCGI) : [6]

The Central Drugs Standard Control Organisation is headed by the Drugs Controller General of India (DCGI) (CDSCO). The Ministry of Health and Family Welfare is in charge of this agency (MOHFW). The 1940 Drugs and Cosmetics Act is the source of their authority [6].

In terms of the Indian health sector, this role is crucial. It is crucial to the regulatory approval process in India for medications and vaccines. The DCGI was instrumental in the recent approval of the COVID vaccinations [6].

Function of DCGI : [6]

The DCGI is in charge of several projects in the medical field. The DCGI also establishes the necessary requirements for drug quality and standards. It has to do with the production, distribution, importation, and sale of pharmaceuticals in India. It also controls pharmaceutical and medical standards. Additionally, the DCGI has appellate jurisdiction over drug quality decisions [6].

• The necessary reference standard for drugs is prepared and maintained by it.

• The Drugs and Cosmetics Act of 1940 is uniformly implemented thanks to the DCGI.

• The DCGI is in charge of this field's training. It provides training for the State Drug Control Laboratories' and associated institutions' drug analysts.

• As survey samples, cosmetics are also analysed by the DCGI. The Central Drugs Standard Control Organisation is the source of it.

• The Medical Device Rules of 2017 designate the DCGI as the primary licencing authority. It deals with the licencing of medical equipment covered by this Act.

• In accordance with the substances and Cosmetics Act, it also authorises the substances.

• Clinical trial conduct is managed by the DCGI. Drug standards are also established by the DCGI.

• The DCGI also guarantees quality control for medications that are imported into the nation.

• It combines the efforts of different state-based drug control agencies.

• It is in charge of foreign manufacturer registration. These manufacturers deal in pharmaceuticals and medical equipment that is imported into India.

• It is in charge of awarding permits for the import of medications. Government hospitals and other medical facilities use it for the benefit of their patients.

• It suggests outlawing dangerous or sub- therapeutic medications. In accordance with Drugs and Cosmetics Act Section 26A, it does so.

The Central Drugs Standard Control Organisation(CDSCO) :

Under Directorate General of Health Services,Ministry of Health & Family Welfare,Government of India is the National Regulatory Authority (NRA) of India. FDA Bhawan, Kotla Road, New Delhi 110002 is home to the organization's headquarters. In addition, the nation is home to nine zonal offices, seven sub zonal offices, eighteen port offices, seven central laboratories, and six mini labs. The pharmaceuticals and Cosmetics Act of 1940 and the Rules of 1945 have assigned central and state regulators a number of duties related to the regulation of pharmaceuticals and cosmetics [7].

Function of CDSCO : [8]

1. Establishing regulations and amending Acts and Rules

2. Laying forth the standards for pharmaceuticals, cosmetics, diagnostics and gadgets.

3. Control over new medication approval for the market.

4. Regulation of clinical research (clinical trials) in India.

5. Approval of medicines.

6. Obtaining a test licence, a personal licence, and NOCs in order to export goods from India

7. Regulation of the standards of and control the quality of imported pharmaceuticals in the India.

8. Co-ordination of the operations of SDCOs.

9. Work connected to the DTAB and DCC.

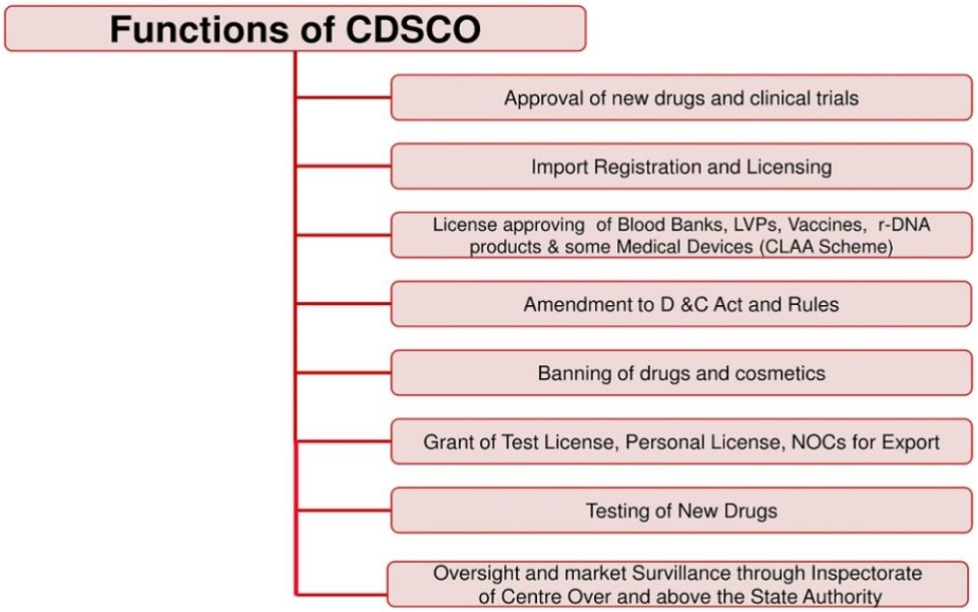


Fig. Functions of CDSCO [9]

Types of Regulatory Applications :

Internatinal New Drug Application (IND) :

The United States Food and Drug Administration's Investigational New Drug (IND) programme is the means by which a pharmaceutical company obtains approval to start human clinical trials and to ship a novel medication across state lines (usually to clinical investigators) before a marketing authorization for the medication has been approved[10].

A medication or biological product that has not received FDA approval for widespread usage is known as an investigational new drug (IND). It is put to use in a clinical trial to look into its effectiveness and safety. Biological products employed in vitro for diagnostic purposes are also included in the phrase [11].

Three types of IND : [11]

Research IND It is intended for a medical professional who orders the drug to be supplied or administered under their direct supervision as well as begins and performs the inquiry. A medical professional might suggest researching [11].

- an unlicensed medication;
- a product that has been approved for a novel indication; or
- among a fresh group of patients.

Emergency Use IND In an emergency where there is not enough time to submit an IND, it enables the FDA to approve the use of an investigational medication. Additionally, it is employed for patients who do not fit the requirements of an approved study protocol or in the absence of one [11].

Treatment IND It is filed for experimental medications that demonstrate potential in clinical trials for severe or immediately fatal illnesses while the last clinical work is completed and the FDA assessment is ongoing [11].

There are two categories of IND : [12]

1) Commercial 2) Research (non-commercial)

IND Commercial Category

An IND application submitted by a pharmaceutical firm or sponsor—such as the National Cancer Institute—is typically regarded as a commercial IND. Their clinical study aims to gather the information required to launch the medication. Clinical research data are needed for the FDA to approve a medication before it can be sold to physicians and patients. The goal of an IND, even submitted by a non-profit research organisation, is to eventually place the medication on the open market. The widespread dissemination of a medicine is regarded as a commercial endeavour even in cases where it is not motivated by financial gain [12].

Compared to a research IND, the commercial IND application can be longer. The testing processes are more complicated because clinical trials are frequently carried out at several locations. This kind of IND frequently involves multiple investigators, all of whom must be listed in the application along with their qualifications [12].

IND Research Category

Applications for INDs submitted by physicians are often regarded as research INDs when they do not aim to sell a novel medication. Alternatively, their clinical trials might aim to demonstrate the effectiveness of an already-approved medication for a novel use. Physicians frequently conduct clinical research to evaluate novel dosages or indications; however, the data they collect is not meant to be utilised in a later application for market clearance. An IND is necessary when clinical research is conducted solely to validate a hypothesis or enhance the application of an already approved medicine. Compared to a commercial IND, the application package for this kind of IND is typically smaller and less complicated. This kind of research involves fewer investigators and is frequently conducted at a single site[12].

Importance of INDA [13]

• Every time I wish to carry out a clinical trial for an unapproved medication, I have to submit an IND.

• If the medication is a new chemical entity and is not licenced for the indication under research in a new dosage form, an IND would be needed to undertake clinical trials.

• Being given at an increased dosage.

• In conjunction with another medicine and the combination is not approved.

•An IND is necessary for every clinical study involving the administration of a novel drug to human participants, regardless of whether the medicine will be commercially produced.

IND application : [14]

A request for FDA approval to deliver an experimental medication or biological product to humans is known as an IND application [14].

Content of INDA : [14]

The IND application must contain information in three primary sectors:

1. Animal Pharmacology and Toxicology Studies
2. Manufacturing Information
3. Clinical Protocols and Investigator Information

1. **Animal Pharmacology and Toxicology Studies -** Preclinical data that allow evaluation of the product's suitability for early human testing. Any prior human drug usage history (often from overseas use) is also provided [14].
2. **Manufacturing Information -** Details on the drug substance and drug product's composition, manufacturer, stability, and manufacturing controls. To make sure the business can sufficiently produce and distribute consistent batches of the medication, this information is evaluated [14].
3. **Clinical Protocols and Investigator Information -** Comprehensive procedures to evaluate whether the first-phase trials will put participants at undue risk are included in the proposed clinical research. In order to determine whether a professional is qualified to carry out the responsibilities of a clinical trial,

it is also necessary to obtain information on the qualifications of clinical investigators, who are usually doctors and who supervise the administration of the experimental compound. Lastly, pledges to follow the investigational new medication legislation, get institutional review board (IRB) review of the study, and secure informed permission from the research subjects [14].

New Drug Application (NDA) :

The New Drug Application (NDA) has served as the cornerstone for decades of American drug regulation and oversight. Since 1938, when a medicine is commercialised in the United States, it must first get approval through an NDA. Drug sponsors formally request FDA approval of a new medicine for sale and marketing in the United States through the NDA application [15].

An NDA provides a comprehensive description of a medicine. Its goal is to prove, for the population under study, that a medicine is both safe and effective when used as prescribed. All information pertaining to a medicine, including preclinical and Phase 3 trial data, must be included in a new drug application (NDA). Reports on all investigations, data, and analysis must be included by developers. In addition to clinical outcomes, developers need to provide: suggested labelling updates on safety, information on drug abuse, details about patents, Usage instructions [16].

A pharmaceutical producer or its agent can apply for a licence to market a medicine for one or more specific indications from the U.S. Food and medicine Administration (FDA) by submitting a new drug application (NDA). An NDA must include information about the drug's chemistry and pharmacology as well as the outcomes of clinical trials done in relation to the indication for which a licence is sought [17].

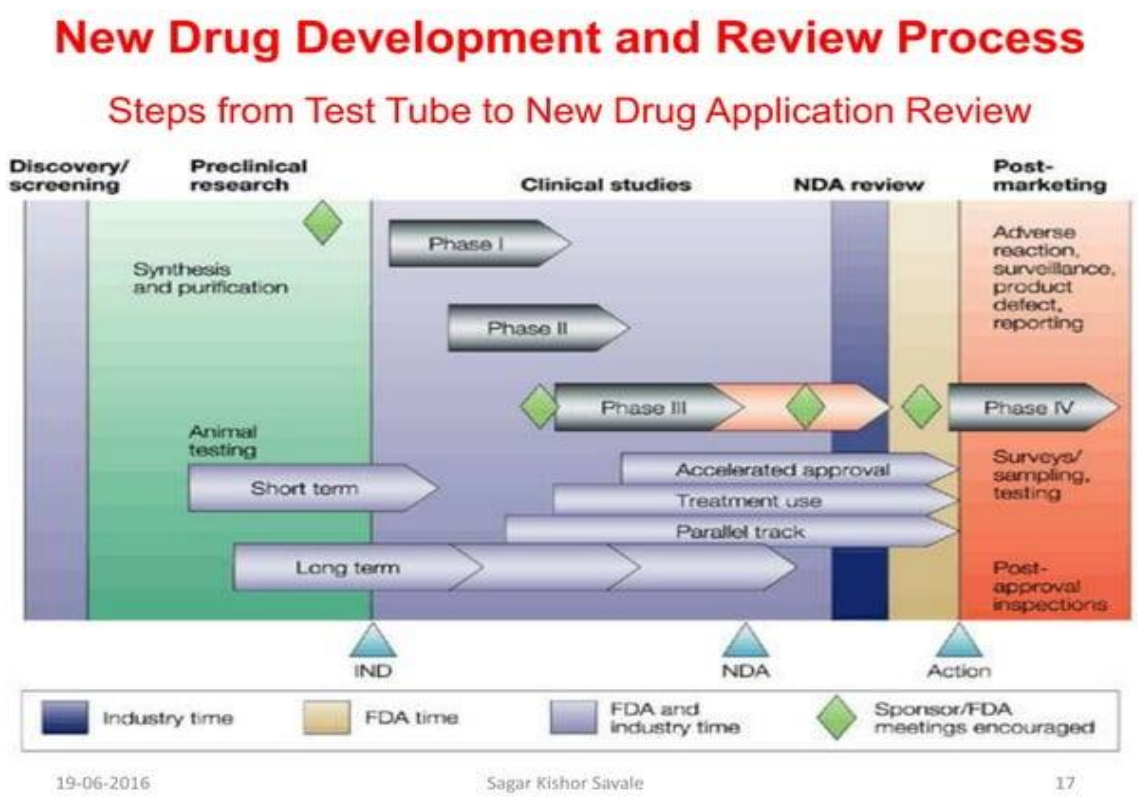


Fig. Schematic representation of new drug development and review [18]

NDA application : [18]

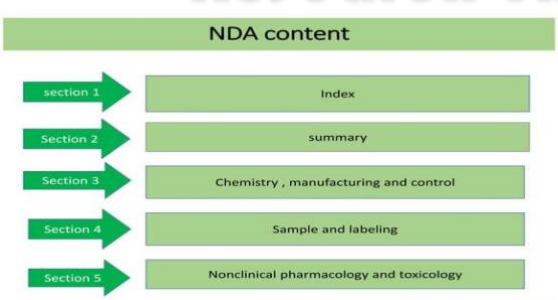
An NDA application must provide the full history of the medication and contain information that the FDA can use to assess the medication's safety when used as prescribed by humans [18].

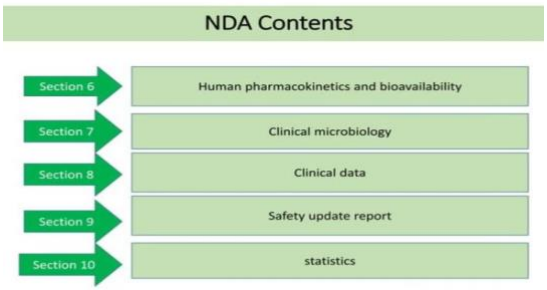
Sponsors must include a vast array of necessary data, including:

- A cover letter that offers an overview of the information in the application and summarises the NDA [18].
- Administrative details, such as the corporate name, address, and phone number, concerning the medication's sponsor [18].
- Results of preclinical research and laboratory testing, providing details on the medication's effectiveness and safety in animal models [18].
- Results of clinical trials, providing details regarding the drug's safety and effectiveness in human subjects, the study's methodology, and the patient population [18].
- Information regarding the statistical significance of the findings from the clinical trial data's statistical analysis [18].
- Details on the drug, such as its ingredients, production methods, and suggested labelling This can be the final package insert, the annotated package insert, or the target product profile [18].
- Details about the manufacturing process, including the plants and methods utilised to make the medication. This is done to assess the quality of the medication and make sure that good manufacturing practices are being followed in its production [18].
- Details on patents, such as the status of patents pertaining to the new medication, the claims contained in the patents, licencing arrangements, and details about any associated legal actions. This aids the FDA in evaluating the medication's suitability for approval and identifying any unresolved legal or patent-related concerns [18].
- Information on clinical trial protocols, ethical approvals, patient safety, and monitoring processes, as well as information about Institutional Review Board (IRB) compliance In order to ensure that clinical trials were carried out in a way that safeguards patient safety and upholds patient rights, this aids the FDA in evaluating the new drug's safety and effectiveness [18].
- The FDA can assess whether a new drug will be safe and effective for its intended use and whether the instructions are easy to understand and straightforward for patients and healthcare providers by looking at the directions for use, which include information on the recommended dose, administration, storage, handling, and labelling of the drug [18].
- FDA correspondence pertaining to regulations, including requests for further details or explanation, from the medication manufacturer [18].
- Reports, journals, and other information sources are among the references listed in the NDA [18].
- These details are combined to show that the product is safe for the intended use and target market, that its advantages outweigh the known risks, that it can be produced in a way that guarantees a high-quality product, and that it can be sold to and used by patients and consumers in a safe manner [18].

NDA Contents :

The NDA have 15 different section in addition to the Form FDA 356h itself. The nature of the drug product and the information available at the time the application was submitted will determine the precise content of the NDA [18]





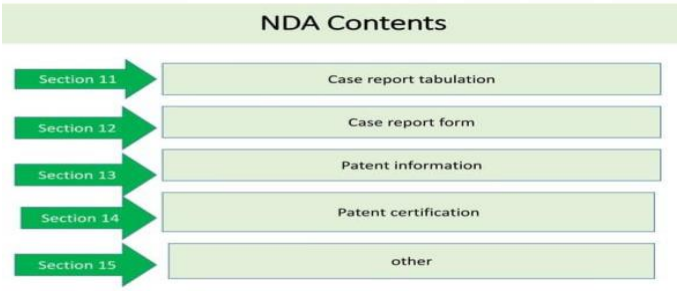


Fig. Contents of NDA [18]

Goals of the NDA :

The NDA's objectives are to give FDA reviewers enough details to enable them to fully understand the proposed drug's history [19].

Among facts needed for the application are:

- Informational on patents and manufacturers [19].
- The Institutional Review Board's reports on the planning, execution, and outcomes of finished clinical studies [19].
- Drug abuse susceptibility [19].
- Suggested labelling (package insert) and usage instructions [19].
- Whether the medication is beneficial and safe for the intended use(s) and whether the risks are outweighed by the advantages [15].
- Whether the suggested labelling for the medication (package insert) is appropriate and what information it should include [15].
- To what extent the drug's identity, strength, quality, and purity can be preserved depends on the manufacturing processes and quality control measures employed [15].

NDA approval process : [20]

The NDA application includes the safety and efficacy data gathered throughout the IND procedure from both human and animal experiments. The NDA must be filed correctly, completely, and with all necessary facts [20].

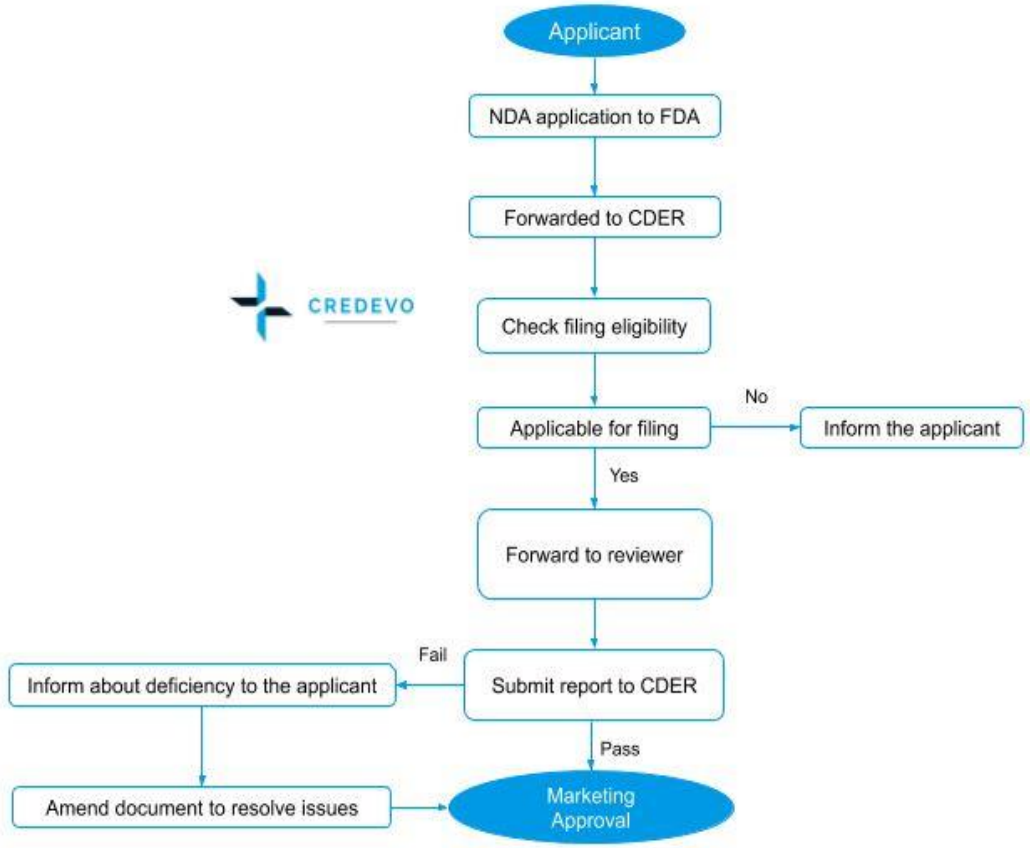


Fig. NDA review process [20]

Review Process : [20]

The Food and Drug Administration Modernization Act allows for either standard categorization or priority consideration of a filed NDA, depending on the potential therapeutic or diagnostic usefulness of the document [20].

There are no regulations or recommendations requiring the FDA and sponsor to communicate openly during the NDA process [20].

1. Priority review: If authorised, the medication product would significantly improve on commercially available options for illness treatment, diagnosis, or prevention [20].

2. Customary evaluation Any application that is not prioritised will be regarded as a normal submission. i.e., applications for medications that are comparable to those sold are accepted as normal [20].

NDA review process :

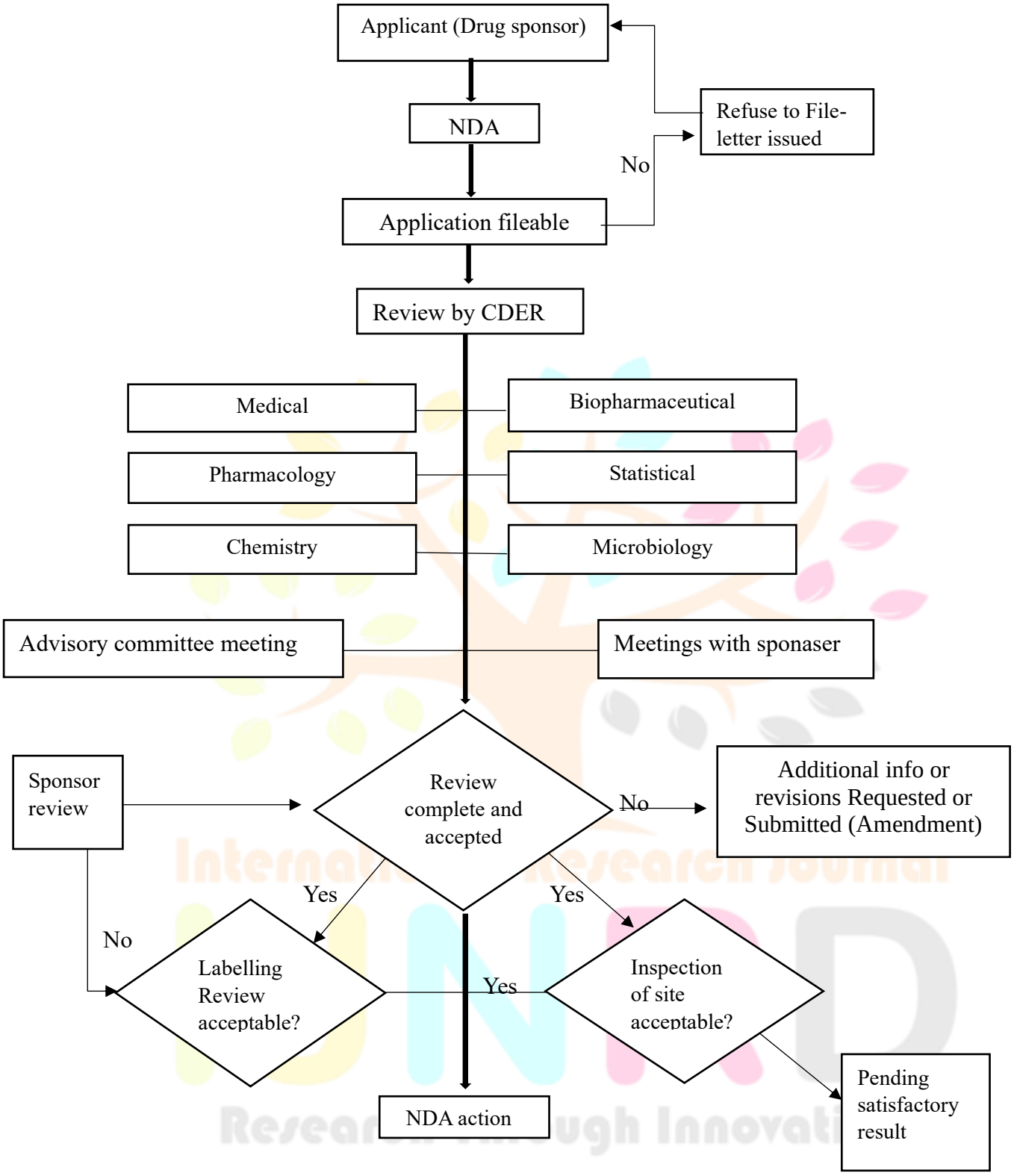


Fig. NDA review process [20]

Abrivated New Drug Application :

Application for approval of a U.S. generic drug for an already-licensed or approved drug is called an Abbreviated New Drug Application (ANDA) [21].

Data is included in an accelerated new drug application (ANDA), which is submitted to the FDA for consideration and possible approval of a generic medication product. Applications for generic drugs are referred to as "abbreviated" because, in most cases, preclinical (animal) and clinical (human) evidence are not needed to demonstrate efficacy and safety. Rather, generic applicants need to provide scientific evidence that their medicine functions similarly to the innovator medication. Measuring how long it takes a generic medication to enter healthy volunteers' bloodstreams is one method used by applicants to show that a generic medicine works in the same way as the innovator drug [22].

The rate of absorption, or bioavailability, of the generic medication is provided by this "bioequivalency" demonstration and can be contrasted with that of the innovator drug. The generic drug must enter a patient's bloodstream with the same quantity of active components in the same amount of time as the original medication in order for the FDA to approve it [22].

ANDAs can be divided into two categories: [23]

ANDA Application: Under section 505(j) of the FD&C Act, this application for a medicine that is identical to one that has already received approval has been filed and authorised. The FDA's earlier finding that the reference listed drug (RLD) is safe and effective is what the ANDA is based on [23].

Petitioned ANDA: This kind of ANDA is for a medication whose dose form, mode of administration, strength, or active component deviates from the RLD. In this instance, the FDA has concluded that further research is not required to prove the safety and efficacy of the suggested medication, in response to a petition filed under section 505(j)(2)© of the FD&C Act. It is anticipated that a petitioned ANDA will function therapeutically similarly to the reference listed medication [23].

Submissions of **ANDAs** are made to the Centre for Drug Evaluation and Research (CDER) of the FDA. To get permission to commercialise a generic drug product, one must contact the Office of Generic Drugs (OGD), which is housed under the CDER under the Office of Pharmaceutical Science. The OGD uses an NDA-like review procedure to guarantee the efficacy and safety of generic medications. [24].

STEPS [24]

1. Filling review
2. Coordination of generic drug review process.
3. Bioequivalence review process.
4. Chemistry review process.
5. Labeling review process.
6. Putting it all together

ANDA Review process : [24]

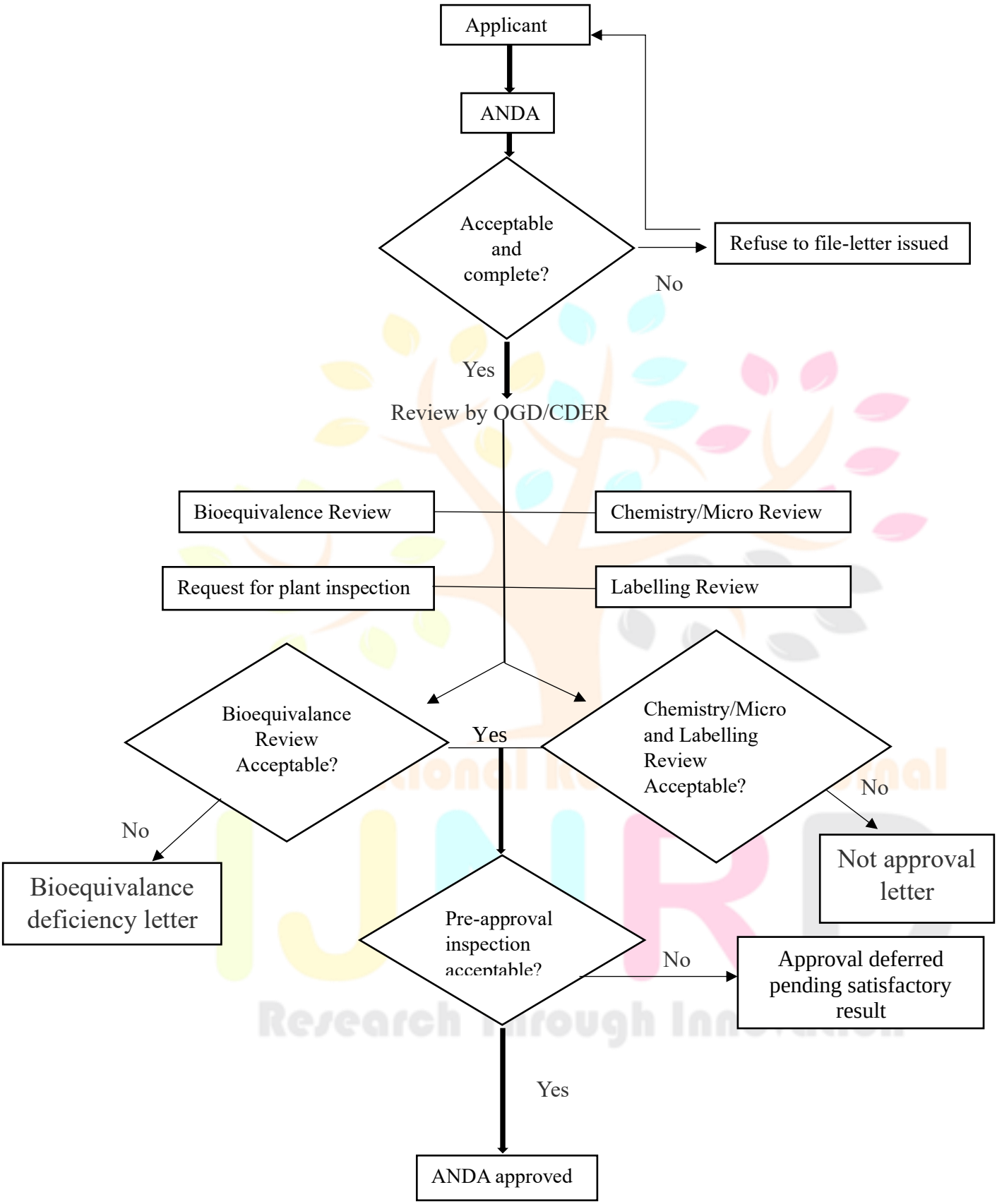


Fig. ANDA review process

Goal of ANDA [25]

- To lower the medication's cost.
- To shorten the development period.
- Boost the medication's absorption in
- Compare with drug references list.

ANDA Requirement : [25]

1) Signed FDA form 356h: This form includes the applicant's name and address, the drug product's name, strength, and administration route; it also includes a list of drug master files cited, suggested indications, and a declaration about whether the product is available over-the-counter or on prescription [25].

2) For every comprehensive and detailed item, an index ought to include the volume and page number [25].

3) Information on the basis for which the ANDA is being submitted -

a) Name of the reference medicine, its dose type & strength.

b) Information on specifically for the listed medicine.

c) A reference to the FDA number assigned to a suitability petition in the event that it is approved [25].

4) Condition for use, including,

a) A description of the ailment for which the medication is intended to be used.
b) b) A reference to the product's annotated label and the label for the mentioned drug product that is currently approved [25].

5) A declaration stating that the active component is the same as it is in the drug of reference. This needs to be displayed for each of the combination product's active ingredients [25].

6) Route of administration, dosage form & strength : It should be stated that these are the same as for the reference medication in this section. Bioequivalency Information proving that the suggested medication is bioequivalent to the specified drug product should be included in this [25].

7) Labeling : A copy of the proposed labelling for the drug being provided for in the ANDA, as well as the existing approved labelling for the listed drug, should be included. It's also essential to compare two sets of labelling side by side [25].

8) Chemistry, Manufacturing & Controls : Provide details about the drug substance's and drug product's manufacturing process, composition, specifications, and analytical methods [25].

9) Human Pharmacokinetics & Bioavailability : Include information concerning-

- The Design
- The Dosing procedure
- The quantity and timing of blood and urine collections, as well as the assay's methodology [25].

10) Samples : The drug material and completed product sample shall be supplied in four independent units, each with adequate quantities to allow the FDA to conduct all the tests specified in the specifications at least three times [25].

11) Analytical method for drug substance & drug product : This section should include the application's specifications, analytical technique, certificates of analysis, method validation, and stability, which should indicate data from the chemical, manufacturing, and control sections [25].

12) Labeling : Included must be 12 samples of the final printed label as well as complete labelling for the pharmaceutical product [25].

13) Case report forms & tabulations : Before submitting the ANDA, the necessary items should be discussed with the relevant division of bioequivalency professionals [25].

Refuse to file letter issued

• A "Refuse to File" letter is provided to the applicant if one or more required components are absent from the application [25].

• Until the applicant submits the necessary information and the application is deemed acceptable and full, it is not reviewed further [25].

Bioequivalence Review:

• Based on evidence that the generic drug's active ingredient absorption rate and extent fall within predetermined limits when compared to the reference listed drug, the Bioequivalence Review process determined that the proposed generic drug is bioequivalent to the listed drug [25].

• For some pharmaceutical medicines, applicants may ask for a waiver from conducting in vivo (human testing) bioequivalency studies if bioavailability can be shown by providing information like:

1) A formulation comparison for goods whose bioavailability is self evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are same.
2) Equivalent dissolution [25].

ANDA Approved

• An applicant receives an acceptance or provisional approval letter once all application components are deemed acceptable [25].

• A tentative approval letter outlining the circumstances surrounding the tentative approval of the generic drug product and any delays is sent to the applicant if the approval takes place before any patents or exclusivities granted to the reference listed drug product expire. approval up until the expiration of any patent and exclusivity issues [25].

• Marketing of the generic medication product is prohibited for the application with a provisional approval [25].

Protocol Designing For Clinical Trial :

A clinical protocol is created at the start of each clinical trial. The protocol serves as a guide that guarantees the safety of the trial participants and the accuracy of the data gathered, outlining the goal(s), design, technique, statistical considerations, and organisational structure of a clinical study. Documents that outline the purpose, rationale, goals, design, technique, statistical considerations, and structure of a clinical research endeavour are called research protocols [26].

A protocol is the set of rules that clinical studies adhere to. A principle investigator (PI) oversees a clinical trial. A protocol describes the following: [27]

- The research's objective
- Who can participate in the Trials?
- safeguards against participation dangers
- Specifics regarding examinations, operations, and therapies
- The anticipated length of the trial
- What data is going to be collected?

The following subjects should be covered in a protocol, under the ICH Good Clinical Practice guidelines: [28]

1. A version identifier (e.g., date) and a descriptive title (e.g., describing the population and research design); if relevant, the registration number (clintrials.gov or ENCEPP register) should be mentioned [28].
2. The list of all cooperating primary institutions and other pertinent study locations, as well as the names, titles, degrees, affiliations, and addresses of all accountable parties, including the principal investigator and co-investigators [28].
3. each sponsor's name and address;
4. A synopsis of the protocol;
5. The suggested study objectives, timetable, and benchmarks;
6. A justification, objectives, and specifics of the research; The knowledge or information to be obtained from the study is described in the research objectives. Key exposures, desired results, and any theories that need to be tested are listed in the specific objectives. A small number of a priori research hypotheses and hypotheses that are developed in light of source data knowledge should be distinguished by the protocol. The justification outlines how achieving the particular goals will advance the goals of the research. Using the PICOT template (population, intervention, comparator, outcome, and time) to formulate the research question [28].
7. A critical analysis of the literature to identify knowledge gaps and relevant information; The precise knowledge gaps that the study aims to fill should be described in the literature review. The examination of the literature may include pertinent studies on humans and animals, clinical trials, important data, and earlier epidemiological research. In addition, the results of related studies and the anticipated contribution of the current study should be cited in the literature review [28].
8. A description of plans for protecting human subjects; This section should contain information about potential situations and safeguards under which identifiable personal information may be provided to entities outside the study, as well as details about whether study subjects will be put at risk as a result of the study and provisions for maintaining confidentiality of information on study subjects. Stopping rules, or the circumstances under which a clinical experiment might end for moral reasons, ought to be specified. The employment of a Data Safety Monitoring Board (DSMB) for clinical trials should be taken into consideration for this purpose, and procedures for monitoring outcomes should be outlined. In compliance with local law, the requirement for informed consent and the necessity of submitting the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) should be taken into account. Since it entails the collecting of anonymous or publicly available data, research employing de-identified data from commercially or publicly available secondary data sources poses the least danger to potential participants. Therefore, if the study complies with existing legal and regulatory standards for the protection of human subjects, it might not be necessary for these studies to undergo IRB review in all jurisdictions [28].
9. An explanation of how study results will be shared and communicated, including whether or not there will be limitations on the scope and timing of publication; It is ethically required to share findings that could be significant to science or public health (such as those regarding the safety of a marketed medication) [28].
10. Bibliographic references;
11. Dated amendments to the protocol. Any major modifications to the population or sample that were made after the study started, together with the reasoning behind them, should be recorded in writing as deviations from the protocol. Any modifications made after the start of data analysis should be noted accordingly and supported by reasoning [28].
12. Archiving or registration of protocol; ISPE supports the possibility of registering and making publicly available hypothesis-driven pharmacoepidemiology research protocols on an appropriate public website, such ClinicalTrials.gov or the ENCePP registry (which is presently serving as the EU PAS Register as well). Should it be selected, the protocol's disclosure and registration should be irreversible, with no way to back out. If at all possible, the researcher should register a protocol with a timeline that has been announced for its eventual publication, as opposed to disclosing the protocol right once when it is registered. In certain situations, such as when gathering data on prior exposures for a case control research, this delay may be scientifically justified in order to minimise the possibility of recall bias or other bias arising from study

participants' knowledge of the study hypothesis. A mechanism for amending previously uploaded protocols ought to be part of the protocol registration procedures. The investigators should disclose in the registration statement the degree to which, at the time the protocol was submitted, they were aware, via preliminary exploratory analyses, of the expected final conclusions of the study [28].

13. Exceptions from overall protocol requirement;
The goal of proactive medical product surveillance is to proactively detect suspected or unexpected adverse events related to medical products. Active surveillance's main objective is to swiftly detect possible safety signs. Although sound design and analytical techniques are typically used in these active surveillance efforts, the analyses are frequently not fully described and protocol-driven. As part of surveillance, safety alarms that are identified are subjected to additional examinations utilising techniques that are customised for certain product-outcome pairs. To the greatest extent feasible, the analysis should adhere to the GPP if a protocol-driven evaluation is thought to be required in order to validate or invalidate the safety signal [28].

Process For Designing Clinical Trials Application :[29]

From start to finish: Clinical trial application under the CTR

1.Preparation

- Transparancy rules
- National or multinational
- Clinical Trials Information System (CTIS)
- Structure research dossier in CTIS
- Section Form and MSC
- Research dossier Part I
- Research dossier Part II

2.Submitting and assessment

- Submission
- Validation phase
- Assessment phase
- Conclusion, decision and appeal

3.Conduct of study

- Notifications
- Modifications
- Intermediate data analysis
- Safety reporting
- Supervision

4.End of study

- Summary of result
- Clinical study report
- Archiving

References :

1. (PDF) Clinical Trials: A General Review - ResearchGate https://www.researchgate.net/publication/349534334_Clinical_Trials_A_General_Review

2. Evolution of Clinical Research: A History Before and Beyond James Lind - NCBI https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149409/
3. Clinical trials - World Health Organization (WHO) https://www.who.int/health-topics/clinical-trials
4. CLINICAL TRIAL: A REVIEW https://www.globalresearchonline.net/volume1issue2/Article%20019.pdf
5. Clinical Research | Stony Brook Medicine https://www.stonybrookmedicine.edu/research/community_education/clinical_trials
6. DCGI Full Form, Responsibilities, Functions & Regulations UPSC https://testbook.com/amp/ias-preparation/drug-controller-general-of-india-dcgi
7. cdsco https://cdsco.gov.in/opencms/opencms/en/Home/
8. Textbook of Industrial pharmacy II (VII sem), Nirali publication by Dr. Ashok A. Hajare, pg.no. 6.10-6.11.
9. functions - cdsco https://cdsco.gov.in/opencms/opencms/en/about-us/Functions/
10. https://en.m.wikipedia.org/wiki/Investigational_New_Drug
11. Investigational New Drug (IND) - University at Buffalo https://www.buffalo.edu/research/research-services/clinical-and-behavioral-research/design-study/investigational-new-drug.html
12. What is the Difference Between Research and Commercial IND Categories? https://blog.td2inc.com/what-is-the-difference-between-research-and-commercial-ind-categories
13. Investigational New drug application [INDA] | PPT - SlideShare https://www.slideshare.net/sagarsavale1/investigational-new-drug-application-inda
14. Investigational New Drug (IND) Application - FDA https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
15. New Drug Application (NDA) | FDA https://www.fda.gov/drugs/types-applications/new-drug-application-nda
16. Step 4: FDA Drug Review https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review
17. New Drug Application – Toolkit https://toolkit.ncats.nih.gov/glossary/new-drug-application/
18. New Drug Application [NDA] | PPT – SlideShare https://www.slideshare.net/sagarsavale1/new-drug-application-nda
19. https://en.m.wikipedia.org/wiki/New_Drug_Application
20. (PDF) New drug application (NDA) – ResearchGate https://www.researchgate.net/publication/369940904_New_drug_application_NDA
21. https://en.m.wikipedia.org/wiki/Abbreviated_New_Drug_Application
22. Abbreviated New Drug Application (ANDA) - FDA https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda
23. What Is an Abbreviated New Drug Application (ANDA)? - Excedr https://www.excedr.com/blog/what-is-abbreviated-new-drug-application
24. ANDA regulatory approval process | PPT - SlideShare https://www.slideshare.net/Rohitkumar2988/anda-regulatory-approval-process
25. ANDA.pdf https://www.chips.ac.in/pages/downloads/PPTs/Pceutics/ANDA.pdf
26. Clinical Trial Protocol Development - Clinical Research Resource HUB https://hub.ucsf.edu/protocol-development
27. The Basics | National Institutes of Health (NIH) https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
28. Guidelines for Good Pharmacoepidemiology Practices ... https://www.pharmacoepi.org/resources/policies/guidelines-08027/
29. Clinical trial application (CTR): from start to finish, investigator- CCMO https://english.ccmo.nl/investigators/clinical-trials-with-medicinal-products-ctr/clinical-trial-application-ctr-from-start-to-finish