Regulatory Approval Process

Approval processes and time-lines involved in

Investigational New Drug (IND)

New Drug Application (NDA)

Abbreviated New Drug Application (ANDA

Changes to an approved NDA / ANDA

Regulatory Approval Process

Background

The drug approval process involves a regulatory pathway through which individuals, organizations, sponsors, or innovators obtain permission to introduce a drug into the market. This process typically includes several stages: applying for clinical trial authorization, conducting clinical trials, applying for marketing authorization, and conducting post-marketing studies. Each country has its own regulatory authority responsible for enforcing rules, issuing guidelines, and overseeing drug marketing regulations.

Investigational Product

An investigational product, as defined by ICH GCP, refers to a pharmaceutical form of an active ingredient or placebo that is being tested or used as a reference in a clinical trial. This can include a marketed product used in a different form than originally approved or used for an unapproved or new indication.

Definition of an Investigational New Drug

According to the Code of Federal Regulations (CFR), an investigational new drug (IND) is defined as a new drug or biological drug used in a clinical investigation. In the United States, an investigational new drug encompasses substances such as drugs, vaccines, or other biological products for which FDA approval is being sought.

Investigational New Drug Application

An Investigational New Drug Application (IND) is a formal request submitted to the Food and Drug Administration (FDA) seeking authorization to administer a new investigational drug or biological product to human subjects. This application is necessary because an investigational new drug, which includes biological products used for diagnostic purposes in vitro, cannot be shipped in interstate commerce without exemption from federal law.

It's important to note that an IND does not constitute an application for marketing authorization of a drug. Instead, it serves as a notification to the FDA that a sponsor, the entity initiating the clinical investigation, intends to conduct studies involving human subjects after completing preclinical research and data collection.

The IND application, also known as the Investigational New Drug Application (INDA or IND), is a mandatory requirement filed with the FDA to obtain permission for administering

a new drug under investigation to human subjects subsequent to the completion of preclinical studies.

	Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File NDA at FDA	Review process / Approval		Additional Post marketing testing required by FDA
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

The IND process provides safeguards for subjects and ensures that the investigational plan is both effective and designed to meet its specified objectives. The sponsor of the drug, who can be an individual (sponsor-investigator), a pharmaceutical company, a governmental agency, an academic institution, or a private or public organization, assumes responsibility for initiating clinical trials.

The Investigational New Drug Application (INDA or IND) is filed with the FDA under Title 21, Code of Federal Regulations Section 312, which outlines guidelines for the preapproval of all clinical testing.

Content of Investigational New Drug Application

1. The requirements for submitting an Investigational New Drug Application (INDA) are outlined in the Code of Federal Regulations and must be accompanied by a cover sheet (Form FDA-1571).
2. The necessary information includes:
   i. Sponsor's name, address, and contact details.
   ii. Name and title of the individual responsible for monitoring the investigation's progress.
   iii. Names and titles of those overseeing drug safety evaluation.
   iv. Name and address of any contracted research organization involved.
   v. Identification of the clinical investigation phase(s).

vi. Overview of the investigational plan, detailing drug name, active ingredients, formulation, administration route, pharmacological class, study objectives, and duration.

vii. Description of the investigational plan specifics.

3. Reasons for selecting the drug or research study, indications to be studied, evaluation approach, study types, estimated participant numbers, and anticipated risks from animal studies.
    i. Concise summary of prior drug experience, including reasons for any prior withdrawals.
    ii. Details on chemistry and manufacturing controls, including physical, chemical, and biological characteristics, as well as product stability throughout the clinical investigation.
    iii. Pharmacological and toxicological information.
    iv. If the drug is a combination of previously studied components, include preclinical and clinical data for these components when administered individually and in combination.
    v. Clinical protocol for the planned study.
    vi. Confirmation that an Institutional Review Board (IRB) has approved the study and will oversee its progress.
    vii. Investigator's brochure.
    viii. Assurance not to initiate clinical investigations until the IND is effective, signed by the sponsor or authorized representative, along with the date of application signature.
4. Following submission to the FDA, the Investigational New Drug (IND) application is reviewed by various divisions within the FDA's Center for Drug Evaluation and Research.
5. The FDA has 30 days from receipt of the IND to determine whether the proposed clinical trial may proceed. If the FDA does not contact the sponsor within this timeframe, the trial may proceed.
6. During review, FDA reviewers have the authority to issue a "Clinical Hold" on proposed clinical trials at any time, preventing human testing of the drug. This action may occur for reasons such as:
    i. Potential threats to the safety of trial subjects, such as illness or injury resulting from treatment.

ii. Insufficient data to assess risks to patients.
iii. Investigators not meeting necessary qualifications.
iv. Misleading or incomplete investigator brochures.

7. If all FDA requirements are met, an IND is granted. Once effective, any proposed changes to the original IND must be submitted as amendments for FDA approval thereafter.

Requirements of IND Application

The FDA places significant regulatory demands on therapeutic drug products, involving extensive laboratory and clinical testing, meticulous sampling procedures, and other resource-intensive processes. Following preclinical testing as per regulations, companies must submit an Investigational New Drug (IND) application to the FDA for approval to proceed with human clinical trials. This application includes a comprehensive plan for studying the drug product and detailed protocols for planned studies. Additionally, the FDA typically requires companies to provide a thorough description of the drug substance, covering its physical, chemical, and biological characteristics, along with details on its preparation method and a list of all components, including inactive ingredients. The IND must detail how the drug substance is composed, manufactured, and controlled, ensuring adequate information on its identification, quality, purity, and strength. Moreover, the IND must include comprehensive pharmacological and toxicological data from animal studies and other tests, demonstrating the sponsor's conclusion that it is reasonably safe to proceed with clinical trials. During clinical trials, sponsors must adhere to strict reporting requirements, including timely progress reports and immediate notification to the FDA and clinical investigators of any unexpected serious side effects or injuries.

Approval processes and time-lines involved in Investigational New Drug (IND)

Current federal law mandates that a drug must have an approved marketing application before it can be transported or distributed across state lines. When sponsors intend to ship an investigational drug to clinical investigators in multiple states, they must seek an exemption from this legal requirement. The Investigational New Drug (IND) application is the mechanism through which sponsors obtain this exemption from the FDA.

During the early preclinical development of a new drug, sponsors primarily aim to establish its initial safety for human use and demonstrate pharmacological activity that justifies further commercial development. Once a product is identified as a viable candidate, sponsors focus

on gathering the necessary data to ensure that its use in limited, early-stage clinical studies does not pose unreasonable risks to humans.

The FDA's involvement in the new drug development process begins when the drug's sponsor—typically the manufacturer or potential marketer—wishes to evaluate its diagnostic or therapeutic potential in humans after screening it for pharmacological activity and acute toxicity in animals. At this stage, the molecule's legal status changes under the Federal Food, Drug, and Cosmetic Act, making it subject to specific regulatory requirements.

An Investigator IND is submitted by a physician who initiates and oversees an investigation, administering or dispensing the investigational drug under their direct supervision. A physician may submit a research IND to propose studying an unapproved drug or an approved product for a new indication or in a different patient population.

An Emergency Use IND allows the FDA to authorize the use of an experimental drug in emergency situations where there is insufficient time to submit a standard IND as per regulations. It is also used for patients who do not qualify for an existing study protocol or when no approved protocol exists.

A Treatment IND is submitted for experimental drugs that show promise in clinical testing for serious or immediately life-threatening conditions while final clinical trials are ongoing and FDA review is underway.

IND categories

Commercial

Research (non-commercial)

The IND application must contain information in three broad areas:

1. Animal Pharmacology and Toxicology Studies: Before testing in humans, preclinical data is necessary to determine the safety of the product. This includes any prior human use experiences, often from international sources.
2. Manufacturing Information: This section covers details about the composition, stability, and manufacturing processes of both the drug substance and product. It ensures that the company can consistently produce and supply the drug.
3. Clinical Protocols and Investigator Information: Detailed protocols for initial clinical studies are reviewed to minimize risks to participants. This section also outlines the qualifications of clinical investigators, typically physicians, to ensure they are capable of fulfilling their trial responsibilities. Additionally, it includes commitments to obtain

informed consent, undergo institutional review board (IRB) review, and comply with investigational new drug regulations.

Once the Investigational New Drug (IND) application is submitted, the sponsor must await FDA review for 30 days before commencing any clinical trials. This review period ensures that potential research subjects are not exposed to undue risks.

Labeling of an Investigational New Drug: The labeling of an investigational new drug must include the statement: "Caution: New Drug-Limited by Federal (or United States) law to investigational use." This statement must not be false or misleading, and it should not imply that the drug is safe or effective for its investigational purpose.

Control of an Investigational New Drug: An investigational new drug can only be administered to participants under the supervision of the principal investigator or a sub-investigator, typically a physician. The investigator is prohibited from supplying the drug to unauthorized individuals.

Use of Controlled Substances: Research involving investigational new drugs classified as controlled substances must adhere to U.S. Drug Enforcement Administration regulations (21 CFR 1300-end). Measures must be taken to prevent theft or diversion of these drugs into illegal channels, including secure storage in locked cabinets or similar secure enclosures.

Promotion and Distribution: Neither the investigator nor the sponsor may promote or advertise an investigational new drug as safe or effective for its investigational purpose. The drug cannot be commercially distributed or used in a test market. If sufficient data from the investigation indicates the drug is safe and effective, the study should be concluded, and further enrollment halted.

Charging for Investigational New Drugs: Charging for an investigational new drug in a clinical trial is not allowed without FDA approval, except in cases where the drug is provided for treatments.

Phases of Clinical Trials for Investigational New Drugs

Clinical trials for investigational new drugs typically progress through four main phases, designated as Phase 1 to Phase 4. Additionally, there are Phase 0 trials, also known as

"exploratory" trials, which involve minimal dosing typically below therapeutic levels and include only a small number of participants. While less common than Phases 1 to 4, Phase 0 trials serve a specific purpose in early drug development. Each phase aims to gather distinct types of information, although these phases may occasionally overlap.

Eligibility for participation in these trials varies based on factors such as age, overall health, the specific disease and its stage, and any prior treatments received.

1. **Phase 1 Trials**

   Phase 1 trials mark the initial introduction of an investigational new drug into human testing. They typically involve healthy volunteers, though individuals with the targeted disease may also participate. These trials generally include a small group, often between 20 and 80 participants. Phase 1 trials are primarily designed to:

- Assess the safety of the drug in humans.
- Identify early side effects associated with its use.
- Establish a preliminary safe dosage range for therapeutic purposes.

2. **Phase 2**

   Trials Phase 2 trials are conducted with individuals who have the disease targeted by the drug or those at high risk of developing it. These trials are larger in scale than Phase 1, typically involving several hundred participants. Phase 2 trials focus on:

- Evaluating the drug's effectiveness in treating or preventing the targeted disease.
- Determining the optimal dosage for further studies.
- Identifying common short-term side effects and risks associated with the drug.

3. **Phase 3**

   Trials Phase 3 trials proceed when earlier phases suggest the drug's safety and potential effectiveness. These trials enroll several hundred to several thousand participants and are crucial for:

   - Gathering extensive data on the drug's safety and effectiveness.
   - Comparing its benefits versus risks, often against standard treatments or placebos in blinded studies.
   - Investigating interactions with other concurrent therapies.
   - Providing sufficient evidence to support the drug's labeling, specifying approved uses and any restrictions (e.g., age limitations).

These phases collectively form a systematic approach to assessing new drugs, ensuring that only those demonstrating safety and efficacy proceed toward approval and wider clinical use.

Phase 4 Trials

Phase 4 trials occur after a drug or treatment has received marketing approval. These trials are undertaken to achieve several objectives:

- **Continued Safety Evaluation:** Phase 4 trials continue to monitor the drug's safety profile, focusing on gathering additional short-term safety data in larger populations.
- **Effectiveness in Diverse Populations:** These trials aim to assess how the drug performs in various populations, beyond those studied in earlier phases.
- **Long-term Side Effects:** Phase 4 trials also investigate any potential side effects that may arise with prolonged or widespread use of the drug, providing crucial insights into its long-term safety profile.

Phase 4 trials play a pivotal role in further refining our understanding of a drug's benefits and risks once it reaches the broader market, ensuring ongoing safety and effectiveness monitoring.

Protocol Amendments for Investigational New Drugs (IND)

When sponsoring an Investigational New Drug (IND), it is mandatory to submit protocol amendments to the FDA under specific circumstances. These include changes to Phase 1 protocols that significantly impact participant safety, or alterations to Phase 2 or Phase 3 protocols that affect participant safety, the scope of the study, or its scientific quality.

Safety Reporting for INDs

Sponsors are required to promptly review and investigate all relevant safety information concerning the investigational drug, received from any source worldwide. This encompasses clinical and epidemiological studies, animal research, commercial experience, scientific literature, unpublished papers, and reports from foreign regulatory bodies. In the event of an unexpected fatal or life-threatening experience linked to the drug, sponsors must notify the FDA within 7 calendar days of first receiving the information. Additionally, sponsors must inform both the FDA and participating investigators in writing within 15 calendar days of any serious adverse event that is unexpected and likely related to the investigational drug. They must also provide follow-up information as it becomes available. Furthermore, sponsors must promptly notify the FDA, within 15 calendar days of receipt, of any findings from animal studies suggesting significant risks to human participants.

Information Amendments and Annual Reports for INDs

Aside from protocol amendments, safety reports, and annual reports, sponsors must file information amendments to report critical IND-related details that do not fall within these categories. Examples include new technical information about the drug's toxicology or chemistry, and discontinuation of a clinical investigation.

Furthermore, within 60 days of the IND's first anniversary and annually thereafter, sponsors must submit a concise report on the investigation's progress. This report should include a summary of each ongoing or completed study's status, the most frequent and severe adverse experiences observed, all IND safety reports submitted, a list of participant deaths with causes specified, details on participants who discontinued due to adverse experiences regardless of relatedness, an outline of the upcoming year's investigational plan, an updated Investigator's Brochure if available, a summary of foreign market developments, and any unresolved matters with the FDA regarding the IND (such as responses to FDA requests for information).

Investigational New Drugs Responsibilities

1. **Responsibilities of Sponsors** Sponsors, whether individuals or organizations overseeing clinical trials conducted under an FDA-issued Investigational New Drug (IND) application, are obligated to fulfill specific duties:
    - Selecting qualified investigators.
    - Providing investigators with necessary trial information.
    - Ensuring proper trial monitoring.
    - Overseeing adherence to the IND's plan and protocols.
    - Promptly notifying the FDA and investigators of significant new adverse effects or risks attributable to the investigational new drug.
    - Maintaining accurate records and disposing of unused investigational new drug supplies.
    - Except when serving as both sponsor and investigator, sponsors do not conduct the investigation themselves.

In accordance with Good Clinical Practice (GCP) guidelines (ICH GCP E6, 5.12; 5.13; 5.14), additional sponsor responsibilities include:

- Ensuring investigational product manufacturing aligns with Good Manufacturing Practices.
- Packaging investigational products to prevent contamination and deterioration during transport and storage.

- Supplying investigators or institutions with the investigational product.
- Establishing written procedures for investigational product handling and storage.
- Maintaining adequate investigational product quantities for specification verification if necessary.

These responsibilities may be delegated to a Contract Research Organization (CRO), but the sponsor retains ultimate accountability for the investigational product.

2. **Responsibilities of Investigators** Investigators involved in clinical trials have distinct responsibilities:
    - Providing the sponsor with a completed and signed Statement of Investigator (Form FDA 1572).
    - Conducting the trial in accordance with the signed investigator statement, protocol, and relevant regulations.
    - Safeguarding the rights, safety, and welfare of trial participants.
    - Securing informed consent from all participants.
    - Maintaining accurate records throughout the trial.
    - Submitting required progress reports, safety reports, financial disclosures, and a final report.
    - Adhering to Institutional Review Board (IRB) oversight and ensuring proper handling of controlled substances.

Additional investigator responsibilities under GCP guidelines (ICH GCP E6, 4.6) include:

- Ensuring accountability of investigational products.
- Designating a pharmacist or licensed individual for investigational product dispensing.
- Recording the journey of investigational product from delivery, through use by participants, to return or destruction.
- Ensuring investigational product use aligns with approved protocols.
- Educating participants on correct investigational product usage and verifying compliance regularly.

New Drug Application (NDA)

For many decades, the regulation and oversight of new drugs in the United States have centered around the New Drug Application (NDA). Since 1938, every new pharmaceutical intended for U.S. commercialization has required an approved NDA. The NDA serves as the formal proposal from drug sponsors seeking FDA approval for sale and marketing in the United States. Data collected from animal studies and human clinical trials conducted under an Investigational New Drug (IND) application are integral parts of the NDA submission.

The primary objectives of the NDA are to provide sufficient information for FDA reviewers to make critical decisions:

- Determining the safety and effectiveness of the drug for its intended use(s), and assessing whether its benefits outweigh its risks.
- Evaluating the appropriateness of the drug's proposed labeling (package insert) and its contents.
- Ensuring that the drug manufacturing methods and quality controls are adequate to maintain the drug's identity, strength, quality, and purity.

An NDA is a comprehensive application submitted to the FDA that includes preclinical and clinical test data, drug information, and descriptions of manufacturing procedures. Upon receipt, the NDA undergoes technical screening to ensure that all necessary data and information have been included, preparing it for formal FDA review ("filing"). Following FDA review, there are three possible outcomes for the application:

- "Not approvable": The FDA lists deficiencies and explains the reasons why the drug cannot be approved.
- "Approvable": The drug can be approved pending minor corrections, such as labeling changes or commitments to post-approval studies.
- "Approval": The FDA grants approval for the drug.

If an NDA receives an "approvable" or "not approvable" status, the FDA provides the sponsor an opportunity to discuss and address the identified deficiencies.

New Drug Application (NDA): An NDA is a crucial document submitted to the FDA to request approval for marketing a new drug in the United States.

NDA Classifications: The FDA's Center for Drug Evaluation and Research (CDER) categorizes NDAs based on the type of drug and its intended uses, including:

- New Molecular Entity
- New Salt of Previously Approved Drug
- New Formulation of Previously Approved Drug

- New Combination of Two or More Drugs
- Already Marketed Drug Product (Duplication by a new manufacturer)
- New Indication for Already Marketed Drug, including switching from prescription to over-the-counter (OTC) status
- Already Marketed Drug Product without a previously approved NDA

NDA Requirements:

- Content and format of the application
- Formatting, assembly, and submission guidelines for new drug and antibiotic applications
- NDA summary format and content
- Technical sections of the NDA
- Abbreviated New Drug Application

1. **Application Content and Format** The content and format requirements for a New Drug Application (NDA) vary based on the specific drug being submitted. However, each NDA must include comprehensive data and information collected during the drug's research and development phase.
2. **Formatting, Assembly, and Submission of NDA and Antibiotic Applications**

A. Application Format

NDA regulations necessitate the submission of two types of copies: the Archival Copy and the Review Copy. i. Archival Copy: This complete submission serves as a reference for FDA reviewers and includes additional information not found in the Review Copy. ii. Review Copy: Divided into five or six sections, this copy contains technical and scientific details required by FDA reviewers. Each section is separately bound and includes a cover letter, FDA Form 356h, an overall summary, an index to the entire application, and a section-specific index. Both copies are submitted in hard copy.

B. Assembly of the Application Folders: Colored folders are required to bind the Archival Copy and each technical section for ease of filing and retrieval at the FDA document rooms. Each folder cover should include the NDA number (if known), applicant's name, and drug product name.

Paper Size and Binding: All pages must adhere to the US standard size (8.5" x 11") and be left-side bound using loose leaf pages.

Pagination: Page numbers must be consistent across both the Review Copy and corresponding pages in the Archival Copy.

Volume Size and Identification: Hard copy volumes should not exceed 2 inches in thickness. **Packing Carton:** For shipment to the FDA, a box size of 14" x 12" x 9.5" is recommended. Smaller boxes may be suitable for ANDAs (Abbreviated New Drug Applications).

Supplements, Amendments, and Post-Marketing Reports: Amendments and supplements follow the same submission format as the original application, requiring an Archival Copy and segmented Review Copy. Correspondence should be directed to the appropriate FDA reviewing division.

C. Application Content Full Application: Archival Copy: This copy confirms agreement between the FDA and the applicant, referencing relevant meetings and identifying contacts for FDA inquiries. It includes:

- FDA Form 356h as a cover sheet,
- an index,
- a summary,
- patent information, and
- a patent certification.

3. NDA Summary Format and Content The summary must provide detailed information, potentially using tables or graphs, and typically spans.

Annotated Package Insert: This section presents proposed labeling text with references to the summary and technical sections of the application by volume and page number.

Pharmacological Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits: A brief statement identifies the drug's pharmacological class, scientific rationale, intended use, and potential clinical benefits.

Chemistry, Manufacturing, and Controls: This section offers an overview of both the drug substance and drug product:

1. Drug Substance: Details include the substance's description, physical and chemical characteristics, and stability.
2. Drug Product: Information covers composition, dosage form, manufacturer details, container and closure system, stability, and specifications with corresponding test methods.

For products marketed outside the United States, regardless of formulation, strength, salt, ester, or complex, comprehensive foreign marketing history is required. This entails listing countries where the drug product has been marketed, along with corresponding dates. Additionally, any countries from which the drug has been withdrawn due to safety or efficacy concerns must be identified, accompanied by specific reasons for withdrawal.

The non-clinical pharmacology and toxicology summary includes:

- Pharmacology studies
- Acute toxicity studies
- Multi-dose toxicity studies
- Carcinogenicity studies
- Special toxicity studies
- Reproduction studies
- Mutagenicity studies
- ADME (Absorption, Distribution, Metabolism, Excretion) studies

The human pharmacokinetics and bioavailability summary provides a concise overview of bioavailability studies, pharmacokinetic characteristics of the active ingredient, and dissolution profiles of the drug.

The microbiology summary presents findings from microbiological studies conducted with anti-infective and antiviral drugs, detailing the mechanism of action, antimicrobial spectrum, and mechanisms of resistance.

The clinical data summary and results of statistical analysis form the basis for evaluating efficacy and safety in seeking NDA approval. This section includes:

- Clinical pharmacology overview
- Controlled clinical studies
- Uncontrolled clinical studies
- Other relevant studies and information
- Safety summary with general safety conclusions

4. The NDA technical sections include a brief description of the following:

- **Chemistry, Manufacturing, and Controls:** Critical for NDA or ANDA submissions, this section comprehensively describes the drug substance's composition (active ingredient), its synthesis or isolation process, purification methods, process controls, specifications, and analytical test methods.

- **Nonclinical Pharmacology and Toxicology:** Provides a summary or description of all animal and in vitro studies conducted with the drug, covering pharmacology studies, acute toxicity studies, and subchronic/chronic/carcinogenicity studies, Special Toxicity Studies, Reproduction Studies, Mutagenicity Studies, ADME Studies.

Human Pharmacokinetics and Bioavailability Section

For a new chemical entity (NCE), it is important to assess its bioavailability and pharmacokinetics from the dosage form. For certain dosage forms like intravenous solutions, 100% bioavailability can be assumed. However, for solid oral dosage forms such as capsules or tablets, a bioequivalence study is typically required to demonstrate that the formulation intended for marketing is equivalent to earlier formulations used in clinical trials. The section should include a table detailing key pharmacokinetic parameters: Cmax, AUC, Tmax, kel, Vd, plasma and renal clearance, and urine excretion.

Microbiology

This section is crucial for anti-infective drugs and includes information on the biochemical mechanisms of the drug's action, its spectrum of antimicrobial activity, any known mechanisms of drug resistance, and clinical laboratory methods.

Clinical Data Section

This is the most critical and complex section of a New Drug Application (NDA). It provides essential safety and efficacy data on the drug for its intended therapeutic use.

Outline of Clinical Section

1. **List of Investigators and Regulatory History**
    - List of investigators involved in the clinical trials.
    - Overview of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).
2. **Background and Overview of Clinical Investigations**
    - Introduction providing context for the clinical studies conducted.
3. **Clinical Pharmacology**
    - Detailed description of the drug's pharmacokinetic and pharmacodynamic properties.
4. **Controlled Clinical Studies**

- Summary and results of controlled clinical trials evaluating efficacy and safety.

5. **Uncontrolled Clinical Studies**
    - Findings from uncontrolled or observational studies, if applicable.
6. **Other Studies and Information**
    - Additional relevant studies or data, such as pharmacokinetic studies in special populations.
7. **Integrated Summary of Efficacy**
    - Comprehensive analysis and interpretation of the efficacy data from all clinical trials.
8. **Integrated Summary of Safety**
    - Comprehensive analysis and interpretation of the safety data, including adverse events.
9. **Drug Abuse and Overdosage Information**
    - Information regarding potential abuse of the drug and management of overdosage.
10. **Integrated Summary of Benefits and Risks**
    - Evaluation of the overall benefit-risk profile based on efficacy and safety data.

Samples, Methods Validation, and Labeling

- **Samples:** Samples should not be submitted with the FDA application. The reviewing chemist will provide instructions for sending samples to designated laboratories.
- **Labeling:** The application must include copies of proposed labels and labeling for the drug product.
- **Methods Validation:** Validation data for analytical methods must be provided in triplicate for review by FDA laboratories.

Case Report Forms and Tabulations

The sponsor is required to provide data tabulations from each Phase II and Phase III study, as well as case report forms for any clinical trial patient who experienced death or withdrawal due to adverse events. Additionally, information must be submitted concerning any patents held by the sponsor that cover the drug substance, formulation, composition of the drug product, or method of use. This information, upon approval of the New Drug Application (NDA), is published in the FDA's Orange Book, which acts as a reference for companies interested in developing generic versions of the original product.

An Abbreviated New Drug Application (ANDA) contains data submitted to the FDA for review and potential approval of a generic drug product. Once approved, the applicant can manufacture and market the generic drug as a safe, effective, and lower-cost alternative to the brand-name drug it references.

The content and format requirements for NDAs and their supplements include specific information tailored to each submission type. For a new chemical entity, the NDA typically includes an application form, index, summary, technical sections, patient data tabulations, case report forms, drug samples, and labeling, including any required Medication Guide. Other types of NDAs, such as those under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, amendments, or supplements, contain relevant information necessary to support their specific submission.

All NDAs must include reports of all investigations sponsored by the applicant related to the drug product, as well as any other pertinent information obtained from external sources. FDA guidance documents provide detailed instructions on the format and content requirements to aid applicants in preparing their submissions. The NDA application form itself requires completion with applicant details, NDA specifics, proposed indications for use, and identification numbers for related submissions under FDA regulations.

The NDA must be signed by the applicant or their authorized representative, such as an attorney or agent. If the signer does not reside or have a business address within the United States, the NDA must also include the name and address of a U.S.-based attorney, agent, or authorized official who countersigns the document. This requirement ensures that there is a responsible party within the United States who can be contacted regarding the NDA submission.

(b) Index.

The archival copy of the NDA must include a comprehensive index organized by volume number and page number. This index should reference the summary detailed in paragraph (c), the technical sections outlined in paragraph (d), and the supporting information specified in paragraph (f).

(c) Summary.

(1) An NDA must feature a detailed summary that allows readers to grasp a comprehensive understanding of the data and information contained within. This includes quantitative aspects of the data. Note that supplements under § 314.70 are exempt from this requirement. Resubmissions of an NDA should provide an updated summary when necessary. The

summary should cover all facets of the NDA, synthesizing the information into a cohesive document. It should be written at a level of detail comparable to that expected in refereed scientific and medical journals. Additionally, FDA may provide this summary to advisory committee members and agency officials who require an understanding of the NDA. Where possible, data should be presented in tabular or graphical formats. FDA guidelines under § 10.90(b) offer further details on preparing such summaries. The summary required under this paragraph may also be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) upon NDA approval.

(2) The summary should include the following details:

(i) The proposed text of the drug labeling, incorporating any Medication Guide required under part 208 of this chapter. Annotations should link this information to the relevant sections of the summary and technical portions of the NDA that support each statement in the labeling. For prescription drugs, explanations should be provided for any omissions of sections or subsections as per the format in § 201.57 of this chapter.

(ii) Identification of the pharmacologic class of the drug, along with a discussion of the scientific rationale behind its intended use and potential clinical benefits.

(iii) A brief overview of the drug's international marketing history, if applicable. This should include a list of countries where the drug has been marketed, withdrawn for safety or effectiveness reasons, or where marketing applications are pending. Both the applicant's marketing history and, if known, that of other parties should be described.

(iv) A summary of the chemistry, manufacturing, and controls section of the NDA.

(v) A summary of the nonclinical pharmacology and toxicology section of the NDA.

(vi) A summary of the human pharmacokinetics and bioavailability section of the NDA.

(vii) A summary of the microbiology section of the NDA (applicable to anti-infective drugs only).

(viii) A summary of the clinical data section of the NDA, including detailed results from statistical analyses conducted during clinical trials.

(ix) A concluding discussion that evaluates the benefit and risk considerations associated with the drug. This section should also address any proposed additional studies or surveillance plans that the applicant intends to undertake postmarketing.

(d) Technical sections.

The NDA must include the technical sections outlined below. Each technical section should provide detailed data and information to enable the agency to make an informed decision

regarding approval of the NDA or potential grounds for refusal under section 505(d) of the Federal Food, Drug, and Cosmetic Act. The necessary technical sections are as follows: (1) Chemistry, manufacturing, and controls section. This section should detail the composition, manufacturing process, and specifications of both the drug substance and the drug product, encompassing:"

The Chemistry, Manufacturing, and Controls (CMC) section of a regulatory submission details comprehensive information about the drug substance and drug product. This includes:

1. **Drug Substance**:
    - Description of physical and chemical properties, stability, and manufacturing address.
    - Synthesis or isolation method, purification process, and manufacturing controls.
    - Specifications ensuring identity, strength, quality, and purity, including tests and criteria for stability and bioavailability.
    - Reference to US Pharmacopeia and National Formulary for compliance.
2. **Drug Product**:
    - List of all components used, regardless of inclusion in the final product, and their specifications.
    - Manufacturing and packaging procedures, in-process controls, and manufacturing addresses.
    - Specifications for identity, strength, quality, purity, potency, and bioavailability, with tests and acceptance criteria (e.g., sterility, dissolution rate).
    - Stability data with proposed expiration dating.
    - Reference to US Pharmacopeia and National Formulary for compliance.
3. **Environmental Impact**:
    - Includes claim for categorical exclusion or environmental assessment as required.
4. **Submission Details**:
    - Option for early submission of the CMC section before the full NDA submission.
    - Certification of providing a field copy of the NDA to the FDA district office.

(2) Nonclinical Pharmacology and Toxicology Section:

This section outlines animal and in vitro studies related to the drug, including:

1. Studies on the drug's pharmacological actions in relation to its intended use and other properties relevant to potential side effects.
2. Toxicological studies assessing acute, subacute, chronic toxicity, carcinogenicity, and specific toxicity related to the drug's method of administration.
3. Studies on the drug's effects on reproduction and fetal development as appropriate.
4. Absorption, distribution, metabolism, and excretion studies in animals.
5. Compliance statements with Good Laboratory Practice regulations for applicable studies.

(3) Human Pharmacokinetics and Bioavailability Section:

This section covers human pharmacokinetic and bioavailability data, or justification for waiver of in vivo bioavailability data submission, including:

1. Description of each human bioavailability and pharmacokinetic study, detailing analytical procedures and statistical methods used, and compliance with institutional review board and informed consent regulations.
2. Rationale for tests, analytical procedures, and acceptance criteria related to bioavailability in the Chemistry, Manufacturing, and Controls section, supported by data and information.
3. Summarized discussion and analysis of pharmacokinetics, metabolism of active ingredients, and bioavailability or bioequivalence of the drug product.

(4) Microbiology Section:

This section pertains to anti-infective drugs and includes:

1. Explanation of the biochemical mechanism by which the drug affects microbial physiology.
2. Overview of the drug's antimicrobial spectrum, supported by in vitro preclinical studies demonstrating effective drug concentrations.
3. Description of known mechanisms of microbial resistance, including epidemiological data on resistance prevalence.
4. Details on clinical microbiology laboratory procedures necessary for effective drug use, such as in vitro sensitivity testing methods.

(5) Clinical Data Section:

This section covers clinical investigations of the drug, including:

1. Analysis of each clinical pharmacology study, comparing human study results with animal pharmacology and toxicology data.

2. Analysis of each controlled clinical study relevant to proposed drug uses, including study protocols and descriptions of statistical analyses. If interim analyses exist, their status and projected completion dates are noted. Discontinued or incomplete studies are also included.
3. Summary of each uncontrolled clinical study with results and rationale for its classification.
4. Analysis of any additional relevant data obtained from domestic or foreign sources, including clinical investigations not related to proposed uses, commercial experience, scientific literature reports, and unpublished papers.
5. Integrated summary of data demonstrating substantial evidence of effectiveness for claimed indications. This includes support for dosage and administration details, with specific considerations for gender, age, racial subgroups, and any necessary dose modifications.

(vi) Effectiveness data should be provided for appropriate subgroups of the patient population, such as those with renal failure or varying disease severity levels.

(a) Safety information must include a comprehensive summary of all available data concerning the drug product's safety. This should encompass relevant animal data, identified or potential adverse effects, significant drug interactions, and other safety considerations. Data should be categorized by gender, age, and racial groups, and where applicable, by other patient subgroups like those with renal failure or differing disease severity. Statistical analyses conducted on safety data should also be described, unless covered elsewhere.

(b) Periodic updates on safety information under section 505(i) of the Federal Food, Drug, and Cosmetic Act are required to be submitted. These updates should reflect new safety findings that could impact the drug's contraindications, warnings, precautions, and adverse reactions in the proposed labeling and, if applicable, any required Medication Guide. Reports should follow the same format as the integrated safety summary mentioned in section (a). Additionally, they must include case report forms for patients who died during a clinical study or discontinued due to adverse events, unless waived. Reports are to be submitted 4 months after the initial submission, following receipt of a complete response letter, and as requested by the FDA.

(vii) If the drug carries potential for abuse, the submission must include a description and analysis of relevant studies or information on drug abuse, including a proposal for scheduling under the Controlled Substances Act. Details on studies related to overdose, including dialysis, antidotes, or other treatments if known, must also be provided.

(viii) An integrated summary assessing the benefits and risks of the drug is required, including justification as to why the benefits outweigh the risks under the specified conditions in the labeling.

(ix) A statement confirming compliance with institutional review board regulations (part 56) and informed consent regulations (part 50) must be included for each clinical study involving human subjects.

(x) If a sponsor has transferred any obligations for conducting a clinical study to a contract research organization, the submission must include the name and address of the organization, study identification, and a list of transferred obligations. Alternatively, if all obligations have been transferred, a general statement confirming this transfer may be submitted instead of a detailed list.

(xi) If the sponsor audited or reviewed original subject records during the monitoring of any clinical study to validate the accuracy of submitted case reports, the submission must include a list identifying each clinical study subject to such audits or reviews.

(e) Samples and labeling:

(1) Upon FDA's request, the applicant must provide the following samples to designated Agency laboratories for testing:

(i) Four representative samples of the drug product intended for marketing, the drug substance used in the product, and reference standards and blanks (excluding those recognized in an official compendium). Each sample should be sufficient for FDA to conduct three tests per the NDA specifications.

(ii) Samples of the finalized market packaging, if specified by FDA.

(2) The archival copy of the NDA must include:

(i) Three copies of the analytical procedures and related descriptive information from the chemistry, manufacturing, and controls section (under paragraph (d)(1)). These are necessary for FDA laboratories to perform required tests and validate the applicant's analytical methods. Descriptive information includes sample descriptions, proposed regulatory specifications, detailed analysis methods, supporting accuracy, specificity, precision, and ruggedness data, and comprehensive test results from the applicant.

(ii) Copies of the drug product label and all associated labeling (including any required Medication Guide under part 208), comprising either four draft labeling copies or twelve copies of the finalized printed labeling.

Case Report Forms and Tabulations

Archival Copy Requirements for the NDA

1. **Case Report Tabulations**:
    - The NDA must include tabulations of data from each adequate and well-controlled study as defined in § 314.126, covering Phase 2 and Phase 3 studies as outlined in §§ 312.21(b) and (c).
    - It must also include tabulations from the earliest clinical pharmacology studies (Phase 1 as per § 312.21(a)) and safety data from other clinical studies.
    - Routine submission of patient data from uncontrolled studies is not required unless specified. These tabulations should detail data on each patient unless the FDA agrees in advance that certain data is not necessary for the drug's safety or effectiveness review.
    - If agreed upon during a "pre-NDA" conference, certain data can be excluded, and such exclusions will not be requested later unless unforeseen circumstances arise. Any additional requests for these excluded tabulations must be authorized by the director of the relevant FDA division.
2. **Case Report Forms**:
    - The NDA must include individual case report forms for each patient who died or discontinued the study due to an adverse event, regardless of whether the event is believed to be drug-related, including those on reference drugs or placebos.
    - This requirement can be waived for specific studies if deemed unnecessary for proper review.
3. **Additional Data**:
    - The FDA may request further case report forms and tabulations to ensure a thorough review of the NDA.
    - Failure to provide the requested information within 30 days can result in the submission being treated as a major amendment, potentially extending the review period.
    - If requested orally, the applicant can ask for written verification from the FDA division director.
4. **Presentation and Format**:
    - Applicants are encouraged to consult with the FDA before submitting an NDA to discuss the format and presentation of the supporting data.

- If agreed upon, the applicant may submit the tabulations and case report forms in an alternative format.

General Requirements

1. **Previously Submitted Information**:
    - Applicants generally do not need to resubmit previously submitted information and can incorporate it by reference.
    - References must clearly identify the previous submission by name, reference number, volume, and page number.
    - If referring to information submitted by someone else, a written authorization signed by the original submitter is required.
2. **Translations**:
    - The NDA must include accurate and complete English translations for any non-English parts.
    - A copy of the original publication must be submitted alongside its English translation.

Requirements for NDA Submission under Section 505(b)

Right of Reference or Use

1. **Right of Reference or Use**:
    - If an applicant submitting an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act obtains a "right of reference or use" (as defined in § 314.3(b)), to an investigation described in section 505(b)(1)(A) of the Act, they must include a written statement from the owner of the data.
    - This statement must confirm that the applicant may rely on the data for the NDA approval and allow the FDA access to the raw data underpinning the investigation report included in the NDA.

Patent Information

2. **Patent Information**:
    - The NDA must contain the patent information as required by § 314.53.

Patent Certification

3. **Patent Certification**:
    - **Contents**: A 505(b)(2) application must include the following regarding patents claiming the drug substance, product, or method of use:

- A patent certification or statement for each relevant patent issued by the U.S. Patent and Trademark Office. This certification must state, to the best of the applicant's knowledge, that the patent either:
    1. Has not been submitted to the FDA (Paragraph I Certification).
    2. Has expired (Paragraph II Certification).
    3. Will expire on a specific date (Paragraph III Certification).
    4. Is invalid, unenforceable, or not infringed by the proposed drug product (Paragraph IV Certification). This certification should be in the form:

kotlin

I, (name of applicant), certify that Patent No. ____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this 505(b)(2) application is submitted.

- The certification must include a statement that the applicant will comply with the notice requirements under § 314.52(a), providing notice to each patent owner or their representative, the NDA holder, or their authorized representative if they are not based in the U.S. Additionally, the applicant must follow the requirements for sending the notice (§ 314.52(b)) and its content (§ 314.52(c)).
- If the drug used in the investigations relied upon by the applicant is a licensed generic of a patented drug first approved under section 505(b) of the Act, appropriate patent certifications must be included.

Certification and Statements for Patent Claims in NDAs

Patent Certification Requirements

1. **First-Approved Patented Drug**:
    - If the 505(b)(2) application pertains to a first-approved patented drug, the applicant must include a certification or statement for each patent claiming the drug or an approved use of the drug.
2. **Pharmaceutically Equivalent Drug Products**:
    - If there is already an approved NDA for a drug product that is pharmaceutically equivalent to the drug product in the 505(b)(2) application, the applicant must provide a certification or statement for each patent claiming the drug substance, drug product, or an approved use of such drug.
3. **No Relevant Patents**:

- If, to the best of the applicant's knowledge, no relevant patents exist, the applicant must provide a certification in the following form:

css

Copy code

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

4. **Method-of-Use Patents**:
    - If a method-of-use patent is submitted and the proposed drug labeling does not include the patented use, the applicant must provide a statement explaining that the patent does not claim any proposed indication or condition of use.
    - If the labeling includes an indication or condition of use claimed by a method-of-use patent, the applicant must submit a relevant certification.

Additional Provisions

1. **Licensing Agreements**:
    - If the 505(b)(2) application involves a patented drug or method of use and the applicant has a licensing agreement with the patent owner, a paragraph IV certification and a statement regarding the licensing agreement must be submitted.
    - If the patent owner consents to the approval of the application as of a specific date, a written statement from the patent owner indicating this consent must be included in the application.
2. **Untimely Filing of Patent Information**:
    - If the NDA holder fails to submit required patent information within 30 days of the patent issuance, and the applicant had already included a proper certification or statement before the submission of the patent information, the applicant is not required to submit a new certification or statement for the late-listed patent for the pending 505(b)(2) application.

These requirements ensure that the applicant provides all necessary patent information and certifications, enabling the FDA to review the NDA thoroughly and efficiently.

The filing of patent information will be considered late unless:

(A) An amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of the patent issuance;

(B) An amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or
(C) An amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office, a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that specifically alters the construction of a method-of-use claim(s) of the patent, including a copy of the decision.
(ii) An applicant with a 505(b)(2) application submitted after the NDA holder's late filing of patent information, or whose 505(b)(2) application was previously filed but lacked an appropriate patent certification or statement at the time of patent submission, must provide a certification under paragraph (i)(1)(i) of this section and/or a statement under paragraph (i)(1)(iii) of this section concerning that patent.

Disputed Patent Information

(5) Contesting Patent Information Accuracy: If an applicant disputes the accuracy or relevance of patent information submitted to the FDA, they may request verification of the patent details as per the procedures outlined in § 314.53(f). If the patent information is not withdrawn, the applicant must provide the appropriate certification or statement for each listed patent.

(6) Revised Certifications: Applicants may amend a patent certification or statement submitted under paragraphs (i)(1)(i) through (iii) at any point before the approval of the 505(b)(2) application. This amendment must be submitted as an update to a pending 505(b)(2) application. If an applicant voluntarily includes a patent certification for a late-filed patent in their pending application, they may subsequently withdraw this certification. Once an amendment to change the certification is submitted, the 505(b)(2) application will no longer contain the previous certification.

(i) Post-Infringement Decision: An applicant who has submitted a paragraph IV certification and is then sued for patent infringement must amend their certification if a court issues a final, non-appealable decision, or if a settlement order or consent decree, which includes a finding of infringement, is signed and entered. This is required unless the final decision, settlement order, or consent decree also finds the patent invalid. The amended certification must specify the patent's expiration date or, for a method-of-use patent, may include a statement under paragraph (i)(1)(iii) if the applicant is no longer seeking approval

for the claimed method. After this amendment, the 505(b)(2) application will not contain the previous paragraph IV certification. No amendment is needed if the final decision finds the patent both invalid and infringed.

(ii) Following a Patent Removal Request: If an NDA holder requests the removal of a patent or patent information from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or information will be removed. Any applicant with a pending 505(b)(2) application (including those tentatively approved) who has made a certification regarding that patent must submit an amendment to withdraw the certification. The amendment must state the reason for withdrawal (i.e., the patent's removal from the list). If one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until the exclusivity expires or is extinguished. A 505(b)(2) applicant does not need to provide or maintain certification to a patent listed solely for the purpose of another applicant's 180-day exclusivity. Once the amendment to withdraw the certification is submitted, the 505(b)(2) application will no longer include the paragraph IV certification to the patent. If the patent's removal leaves no patents listed for the drugs identified in the 505(b)(2) application, the applicant must submit an amended certification indicating that no listed patents remain.

(iii) Other amendments. (A) Except as specified in paragraphs (i)(4) and (i)(6)(iii)(B) of this section: (1) An applicant must revise a submitted certification or statement if, prior to the approval of the 505(b)(2) application, the applicant discovers that the submitted certification or statement is no longer accurate; and (2) An applicant must submit an appropriate patent certification or statement under paragraph (i)(1) of this section if, following the submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the applicant's opinion and based on its best knowledge, claims a listed drug that was relied upon or claims an approved use for such listed drug for which information is required under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53.
B) An applicant is not obligated to submit a supplement to modify a submitted certification when information regarding an otherwise applicable patent is provided subsequent to the approval of the 505(b)(2) application.
(j) Claimed exclusivity. Upon approval, a new drug product may qualify for a period of marketing exclusivity under § 314.108. If an applicant believes its drug product is eligible for exclusivity, it must include the following information with the NDA before approval:

(1) A statement asserting the applicant's claim of exclusivity.
(2) Reference to the relevant paragraph in § 314.108 supporting the claim.
(3) If claiming exclusivity under § 314.108(b)(2), evidence demonstrating that, to the best of the applicant’s knowledge or belief, no drug previously approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act contains any active moiety present in the drug for which approval is sought.
(4) If claiming exclusivity under § 314.108(b)(4) or (b)(5), the following information demonstrating that the NDA includes "new clinical investigations" that are "essential to approval of the NDA or supplement" and were "conducted or sponsored by the applicant":

(i) "New clinical investigations." A certification that each clinical investigation included in the NDA meets the definition of "new clinical investigation" as defined in § 314.108(a), to the best of the applicant’s knowledge.
(ii) "Essential to approval." A list of all published studies or publicly available reports of clinical investigations identified by the applicant through a comprehensive literature search, accompanied by a certification that the search was thorough and complete, and that in the applicant’s opinion, these studies or reports do not sufficiently support approval of the conditions for which the applicant seeks approval without referencing the new clinical investigations in the NDA, along with an explanation of why the studies or reports are inadequate.
(iii) "Conducted or sponsored by." If the applicant was the named sponsor in FDA Form 1571 for an IND under which the new clinical investigation(s) essential to its NDA approval was conducted, identification of the IND by number is required. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) essential to its NDA approval, along with supporting information. To demonstrate "substantial support," the applicant must provide either a certified statement from a certified public accountant affirming that the applicant funded 50 percent or more of the study’s costs, or an explanation justifying why the FDA should consider the applicant to have conducted or sponsored the study if the applicant’s financial contribution was less than 50 percent or if the applicant did not sponsor the investigational new drug. A predecessor in interest refers to an entity, such as a corporation, that the applicant has acquired, merged with, or purchased, or from which the applicant has acquired all rights to the drug. Purchasing

non-exclusive rights to a completed clinical investigation is insufficient to satisfy this definition.

(k) Financial Certification or Disclosure Statement: The NDA must include either a financial certification, a disclosure statement, or both, as mandated by part 54 of this chapter.

(l) Original NDA Format:

1. Archival Copy: Applicants must provide a complete archival copy of the NDA containing information specified in paragraphs (a) through (f) of this section. The FDA will maintain this archival copy throughout the NDA review process. This allows individual reviewers to access information not included in their specific technical sections, permits other agency personnel to review the NDA for official purposes, and ensures that a comprehensive copy of the NDA is centrally stored. Applicants may submit the archival copy on paper or electronically, adhering to electronic submission guidelines outlined in part 11 of this chapter, with exceptions as detailed in paragraph (l)(1)(i).

(i) Labeling: The labeling content required under § 201.100(d)(3) of this chapter (commonly known as the package insert or professional labeling), including text, tables, and figures, must be submitted to the agency in electronic format as specified in paragraph (l)(5) of this section. This requirement supplements paragraph (e)(2)(ii), which mandates submission of formatted labels and all labeling copies. Submissions under this paragraph must comply with part 11 of this chapter, with exceptions for § 11.10(a), (c) through (h), and (k), and corresponding § 11.30 requirements.

(ii) [Reserved]

2. **Review Copy:** Applicants must submit a review copy of the NDA. Each technical section outlined in paragraphs (d)(1) through (6) of this section must be separately bound with a copy of the application form from paragraph (a) and a summary from paragraph (c).
3. **Field Copy:** Applicants must submit a field copy of the NDA containing the technical section specified in paragraph (d)(1), along with copies of the application form from paragraph (a) and the summary from paragraph (c). A certification affirming the field copy's fidelity to the technical section in the archival and review copies must also be included.
4. **Binding Folders:** FDA can provide sufficient folders for binding the archival, review, and field copies of the NDA upon request from the applicant.

5. **Electronic Format Submissions:** Electronic submissions must be in a format that FDA can process, review, and archive. Periodic guidance from FDA will outline methods of transmission, acceptable media, file formats, and preparation and organization of electronic files.

Data Presentation For FDA Submission

Data presentation for FDA submission Followings are the ways to present data that facilitate NDA review of submission.

Text exposition

Tabular presentation

Content in NDA submissions often contains extensive data that cannot feasibly fit entirely within the main document body. While data specific to individual patients is crucial, it's essential to exercise discretion in selecting key data for presentation and discussion within the document. Data essential for developing the thesis should be integrated into the main body rather than relegated to appendices, which can hinder review processes. Less critical data can be summarized briefly and placed in appendices. Data that do not contribute to assessing the safety or effectiveness of the therapeutic agent may be omitted entirely.

Tone: The tone should be formal yet accessible, avoiding both overly technical legal language and informal expressions.

Conciseness: Ways to enhance NDA submissions include using straightforward language to promote clarity and efficiency. Avoiding unnecessary complexity, such as replacing verbose phrases like "prior to the initiation of the study" with simpler alternatives like "before the study began," helps streamline content. Acronyms and initialisms, if widely recognized and defined upon first use, can expedite readability. Redundancies should be eliminated to improve the document's flow and coherence.

Correctness: Ensure consistency between textual descriptions and tabular data within the document, and verify that both align accurately with the data source. Inconsistencies may lead to prolonged review times as reviewers must validate conclusions against raw data.

Consistency: Maintain uniformity in punctuation, capitalization, abbreviations, and other stylistic elements throughout the document.

Clarity: The FDA reviewer should be able to comprehend the application without difficulty. Clear writing is facilitated by attention to punctuation, sentence structure, the placement of modifiers, and parallelism.

Outline of Sections and Subsections: A clear and structured outline is crucial for document review. The decimal outlining system, such as 3.1.2.1.2.1.1.1, aids in organizing sections and subsections logically. Avoid excessive indentation; instead, use headers to delineate sections and bullets to break up large blocks of text.

Tabular Presentation Guidelines

In-text tables should be utilized to streamline information presentation and significantly reduce textual content. Data from tables should not be reiterated in the text unless integrated into a concluding statement about the tabulated information.

Title

Each table requires a concise yet descriptive title. Sequences of similar tables should differentiate themselves in the title, such as through age, sex, or race specifications (e.g., "Treatment-Related Adverse Events: by Age," "by Sex," "by Race").

Data Source

Every table should specify its data source in a footnote (e.g., data source: Statistical Table 23, Volume XX, p. xx). Volume and page numbers will be finalized at the project's completion.

Footnotes

Footnotes should use letters for clarity, avoiding symbols or numbers that could be confused with the data.

Orientation

Tables in portrait orientation are generally preferred over landscape orientation.

Order of Data Presentation

When presenting multiple tables with similar data, maintain consistent ordering as much as possible. For instance, if the first column consistently features the active drug and the second column the placebo or comparator, maintain this order across all tables.

Coherent Data Presentation

Efforts should be made to present data intended for evaluation and comparison in proximity within the table, rather than scattered throughout. For example, group evaluable patients together rather than categorizing them by previous treatment status.

FDA Application Review Process

Upon receiving a New Drug Application (NDA), the FDA conducts a thorough review to assess its completeness. Within 60 days, the FDA will either accept the application or issue a "refusal-to-file" letter. If the latter occurs, the applicant may request a conference with the FDA.

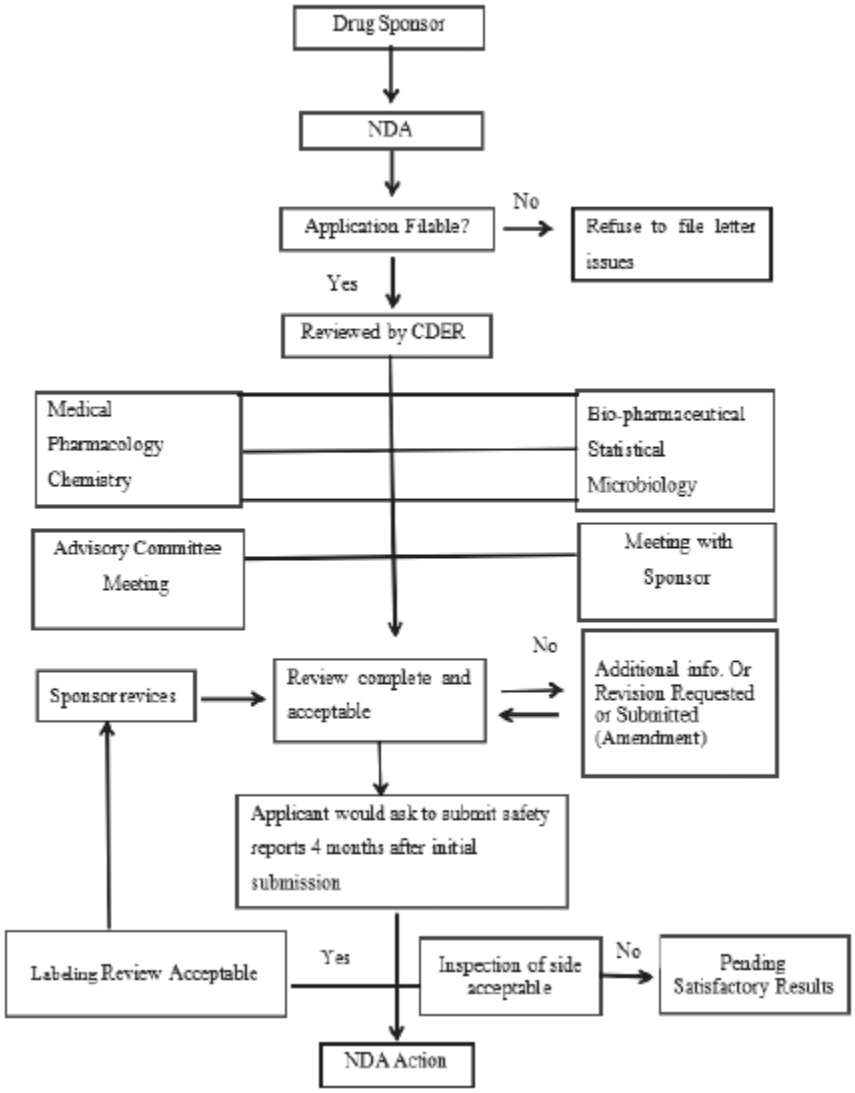
Grounds for refusal to file may include:

- Incomplete Form FDA 356h.
- Incorrect application format or missing content items as per regulations.
- Unready manufacturing facilities for inspection.
- Incomplete and accurate translations of non-English application parts.
- Lack of statements on Good Laboratory Practice (GLP) compliance for non-clinical studies.
- Absence of statements on Institutional Review Board (IRB) and informed consent compliance for clinical studies.
- Overlapping coverage with an existing approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA).

Following review, the FDA may issue one of three possible action letters:

- A "Not Approvable Letter," detailing deficiencies and reasons for non-approval.
- An "Approvable Letter," indicating potential approval pending minor deficiencies and necessary labeling changes, possibly with requests for post-approval study commitments.
- An "Approval Letter," signifying full approval for marketing the drug product. An applicant might receive both an Approvable and Approval Letter. The Division Director of the Center for Drug Evaluation and Research (CDER) signs and approves the letter, allowing legal market authorization from that date onward.

Regulatory Agencies that are involved in drug regulation in India



1. The regulation of clinical research in India falls under the jurisdiction of the Drug Controller General of India (DCGI), operating within the Central Drugs Standard Control Organization (CDSCO). The DCGI is primarily responsible for overseeing clinical trials in the country, as well as matters concerning product approval, standards, the introduction of new drugs, and the issuance of import licenses for new drugs.
2. The Drugs Technical Advisory Board (DTAB) consists of technical experts who advise both the central and state governments on technical issues related to drug regulation. Any rules proposed by the central government pertaining to drug control must first be reviewed and advised upon by the DTAB.

3. The Drugs Consultative Committee includes members from central and state drug control authorities. Its primary function is to ensure uniform enforcement of drug control measures across all states.
4. The Genetic Engineering Approval Committee (GEAC) is responsible for approving recombinant DNA (r-DNA) pharmaceutical products. The GEAC assesses the bio-safety and environmental safety aspects of biotechnological products.

In addition to these regulatory bodies, several rules and guidelines govern the regulation of drugs in India, including:

- Drugs and Cosmetics Act, 1940, and Rules, 1945
- Narcotic Drugs and Psychotropic Substances Act, 1985
- Drugs Price Control Order, 1995
- Consumer Protection Act, 1986
- Factories Act, 1948
- Law of Contracts (Indian Contract Act, 1872)
- Monopolistic and Restrictive Trade Practices Act, 1969
- ICH GCP Guidelines
- Schedule Y Guidelines
- ICMR Guidelines
- Registry of Trial

To obtain permission for the approval of new drugs, manufacturers or sponsors must submit an application on Form 44 under the provisions of the Drugs and Cosmetics Act, 1940, and Rules, 1945. The document design conforms to international submission requirements outlined in the Common Technical Document (CTD), which consists of five modules.

Module I contains specific regional administrative and legal documents, such as application forms and proposed labels tailored for each jurisdiction, with their content and format determined by respective regulatory authorities.

Module II provides a concise introduction to the pharmaceutical product, including its pharmacological class, mode of action, and intended clinical uses within a single page. It details essential information like proprietary and non-proprietary names, company details, dosage forms, strengths, routes of administration, and proposed indications. This module is crucial as it summarizes key aspects of the Common Technical Document (CTD), covering quality, safety, and efficacy data in depth.

Module III focuses on quality information, following the structured format outlined in guidance M4Q. It includes comprehensive documentation concerning the chemistry, manufacturing, and controls of both the drug substance and its product.
Module IV addresses non-clinical data, structured according to guidance M4S, providing a critical analysis of safety-related information crucial for evaluating the medicinal product's safety profile in the target population.

Module V presents clinical information as per guidance M4E, encompassing biopharmaceutics, pharmacokinetics, pharmacodynamics, clinical pharmacology studies, efficacy data, safety data, study synopses, and detailed clinical study reports.
Additionally, the preparation for drug submission includes detailed sections on drug substance characterization, physicochemical and biological characteristics, drug product control, facilities, equipment, safety evaluations, and applications for new drug import permissions under specific regulatory conditions.

Application for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) (122-B)

(a) New drugs cannot be manufactured for sale without approval from the Licensing Authority as defined in clause (b) of rule 21.
(b) To obtain approval for manufacturing a new drug and its formulations, an application must be submitted in Form 44 to the Licensing Authority defined in clause (b) of rule 21. This application must be accompanied by a fee of fifty thousand rupees. If the application pertains to both importing a new drug (bulk drug substance) and obtaining approval to manufacture its formulations, the fee remains fifty thousand rupees.
Furthermore, if the same applicant submits a subsequent application for the same drug, whether in a modified dosage form or with new claims, the fee for such subsequent application is fifteen thousand rupees.
Additionally, any application received more than one year after the initial approval for manufacturing the new drug for sale must be accompanied by a fee of fifteen thousand rupees. It should also include the necessary information and data as specified in Appendix I or Appendix I A of Schedule Y, depending on the case.

When applying for approval to manufacture a new drug under sub-rule (1) to the licensing authority mentioned therein, the manufacturer must submit data outlined in Appendix I to Schedule Y. This includes the results of clinical trials conducted within the country, adhering to the guidelines specified in Schedule Y. Additionally, the manufacturer must submit the report of these clinical trials in the format specified in Appendix II to Schedule Y.
The Licensing Authority, defined in clause (b) of rule 21, will review the data provided. If satisfied that the drug, whether as raw material (bulk drug substance) or finished formulation, is effective and safe for use in the country, the Authority will issue approval in Form 46 and/or Form 46 A, subject to specified conditions.

However, if the data provided on the drug is found inadequate, the Licensing Authority will notify the applicant in writing. The applicant must then fulfill the specified conditions before further consideration of the approval.
When applying for approval to manufacture a new drug under sub-rule (1) or its preparations to the state licensing authority, the applicant must include evidence that the drug in question has already received approval from the licensing authority mentioned in Rule 21. It's noteworthy that the requirement to submit results of local clinical trials may be waived if the drug's nature allows the licensing authority to grant permission based on data from other countries, in the public interest.
Furthermore, the submission requirements regarding animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity, and carcinogenicity may be adjusted for new drugs that have been approved and marketed for several years in other countries, provided there is sufficient published evidence regarding the drug's safety, while adhering to other provisions of these rules.

Authorization for Fixed Dose Combination (122-D)

An application seeking permission to import or manufacture a fixed dose combination of two or more drugs, as defined in clause (c) of rule 122 E, must be submitted to the Licensing Authority specified in clause (b) of rule 21 using Form 44. This application should be accompanied by a fee of fifteen thousand rupees and must include the information and data specified in Appendix VI of Schedule Y. Upon review, if the Licensing Authority is satisfied that the proposed fixed dose combination is safe and effective for use in the country, permission will be granted in Form 45 or Form 46, subject to specified conditions. In cases where the data provided on the fixed dose combination is deemed inadequate, the applicant

will be notified in writing of the conditions that must be met before approval can be considered.

Application for Clinical Trials of New Drugs (122-D)

No clinical trial involving a new drug, whether for clinical investigation or any clinical experiment by any institution, may commence without prior written permission from the Licensing Authority defined in clause (b) of rule 21. Applications for permission to conduct:

- Phase-I human clinical trials of a new drug must be submitted in Form 44 along with a fee of fifty thousand rupees and necessary information as per Schedule Y.
- Phase-II exploratory clinical trials of a new drug should be based on data from Phase-I trials, accompanied by a fee of twenty-five thousand rupees.
- Phase-III confirmatory clinical trials of a new drug should be based on data from Phase-II trials and, where necessary, Phase-I data as well. These applications must be accompanied by a fee of twenty-five thousand rupees.

No additional fee is required for applications to import or manufacture a new drug following successful completion of clinical trial phases by the applicant. Similarly, Central Government or State Government institutes involved in clinical research for academic or research purposes are exempt from paying fees with their applications.

Upon satisfactory review of the clinical trial data, the Licensing Authority will grant permission in Form 45, Form 45A, Form 46, or Form 46-A, subject to specified conditions. If the data provided on the clinical trials is found inadequate, the Licensing Authority will inform the applicant in writing within six months, or within an extended period not exceeding another six months, detailing the conditions that must be fulfilled before permission can be considered.

Suspension or Cancellation of Permission/Approval (122-DB) If an importer or manufacturer under this Part fails to comply with any conditions of the granted permission or approval, the Licensing Authority may suspend or cancel it after providing an opportunity for the concerned party to present their case. This action will be documented in writing, stating the reasons for the decision.

Appeals (122-DC) Any person aggrieved by an order issued by the Licensing Authority under this Part may appeal to the Central Government within sixty days of the order date. The Central Government will conduct an enquiry as necessary and issue an appropriate order in response.

Resources for NDA Submissions The following resources have been compiled to assist in understanding the legal requirements for a new drug application, receiving guidance from CDER to meet these requirements, and understanding internal NDA review principles, policies, and procedures.

Suspension or Cancellation of Permission/Approval (122-DB)

If an importer or manufacturer fails to comply with any conditions of the granted permission or approval under this Part, the Licensing Authority may suspend or cancel it. Prior to issuing such an order, the Licensing Authority will provide an opportunity for the importer or manufacturer to explain why such action should not be taken. The decision to suspend or cancel will be communicated through a written order stating the reasons for the decision.

Appeal (122-DC) Any individual who is dissatisfied with an order issued by the Licensing Authority under this Part may appeal to the Central Government within sixty days from the date of the order. The Central Government will conduct an inquiry as deemed necessary and may issue an appropriate order in response.

Resources for NDA Submissions The resources compiled here aim to assist in understanding the legal requirements for new drug applications (NDAs), provide guidance from CDER to help meet these requirements, and outline internal NDA review principles, policies, and procedures.

Guidance Documents for NDAs

Guidance documents reflect the FDA's current stance on specific topics. They are intended for FDA review staff, applicants, and sponsors, offering guidelines on application processing, content, evaluation/approval, and the design, production, manufacturing, and testing of regulated products. These documents establish policies to ensure consistency in regulatory approaches and set forth inspection and enforcement procedures. While guidance documents themselves are not enforceable like regulations or laws, alternatives may be acceptable if they meet statutory and regulatory requirements. For details on specific guidance documents, please contact the originating office or refer to the Guidance Index on CDER's website.

These guidance documents provide essential information for preparing Non-Disclosure Agreements (NDAs):

- Bioavailability and Bioequivalence Studies in NDAs or INDs, including General Considerations
- Modifications to an Approved NDA or ANDA
- FAQ on Changes to an Approved NDA or ANDA
- Container Closure Systems for Packaging Human Drugs and Biologics
- Microbiology Section Format and Content in Applications
- Clinical and Statistical Sections Format and Content in Applications
- Summary Format and Content for New Drug and Antibiotic Applications
- Procedures for Formatting, Assembling, and Submitting New Drug and Antibiotic Applications
- Guidelines for Submitting Supporting Documentation in Drug Applications for Drug Product Manufacturing
- Impurities in Drug Substances for NDAs
- Format and Content of Human Pharmacokinetics and Bioavailability Section in Applications
- Format and Content of Nonclinical Pharmacology/Toxicology Section in Applications
- Clinical Evidence Requirements for Human Drug and Biological Products
- Guidelines for Drug Master Files
- FDA IND, NDA, ANDA, or Drug Master File Binders
- PET Drug Applications Content and Format for NDAs and ANDAs

In addition to these guidance documents, the FDA's mission is to enforce laws and regulations to safeguard consumer health, safety, and financial interests. The Federal Food, Drug, and Cosmetic Act, along with its amendments, ensures the purity and safety of food, the effectiveness of drugs and devices, the safety of cosmetics, and truthful and informative labeling and packaging. The Code of Federal Regulations (CFR) interprets these laws and outlines requirements for drug sponsors, including those specified in 21CFR Part 314 for FDA approval of new drugs and antibiotics.

CDER's Manual of Policies and Procedures (MaPPs) outlines approved internal practices and procedures for CDER staff. These documents aim to standardize processes such as new drug reviews and other activities within the FDA. MaPPs also define external activities and

are accessible to the public, offering insights into office policies, staff responsibilities, and operational procedures.

Of particular relevance to NDA applicants are several key MaPPs:

- Review of the Same Supplemental Change to More than One NDA or ANDA Across Review Divisions
- NDAs and BLAs: Filing Review Issues
- Action Packages for NDAs and Efficacy Supplements
- Refusal to Accept Application for Filing from Applicants in Arrears
- Requesting and Accepting Non-Archivable Electronic Material for CDER Applications

The Prescription Drug User Fee Act (PDUFA), enacted on November 21, 1997, authorizes the FDA to collect user fees from applicants submitting certain new drug and biological product applications. This legislation builds upon the initial authorization provided by the Prescription Drug User Fee Act (PDUFA) of 1992.

Key documents related to PDUFA include:

- NDA Forms and Electronic Submissions
- Form FDA-356h: Application to Market a New Drug, Biologic, or Antibiotic Drug for Human Use
- Form FDA-356h instructions
- Form FDA-3397: User Fee Cover Sheet
- Form FDA-3331: New Drug Application Field Report
- Guidance Documents for Electronic Submissions

Advisory Committees play a crucial role by providing independent scientific and technical advice to the FDA on product development and evaluation. These committees, consisting of scientific experts and public representatives, advise on various aspects such as clinical investigations and marketing approval applications. While advisory committees offer recommendations, final decisions rest with the FDA.

Key resources related to Advisory Committees include:

- FDA Advisory Committees
- CDER Advisory Committees
- CFR 21 Part 14 Public Hearing before a Public Advisory Committee
- Guidance for Industry: Advisory Committees
- Advisory Committee Meeting Calendar. Several dates have been set aside by CDER advisory committees for possible future meetings. The subject matter and location of

the meetings (if they are held) will be published in the Federal Register in the month prior to the meeting date.

Approval of new drug in India

In India, when a company intends to manufacture or import a new drug, it must apply for permission from the Drug Controller General of India (DCGI). This involves submitting Form 44 along with data specified in Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945. To establish the drug's efficacy and safety for the Indian population, the company must conduct clinical trials in accordance with Schedule Y guidelines and submit the trial reports in a specified format.

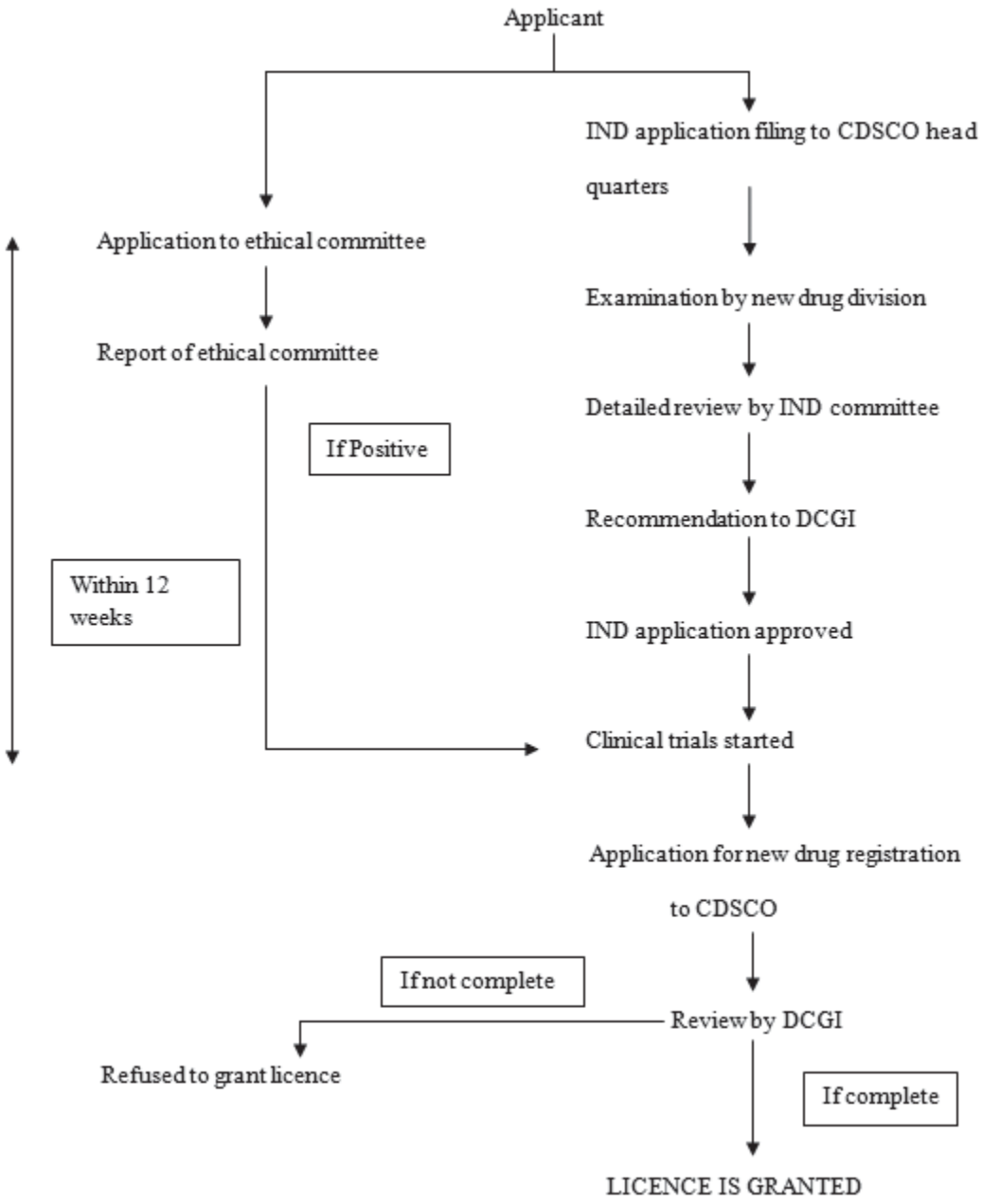
Under Rule 122A of the Drugs and Cosmetics Act 1940 and Rules 1945, the licensing authority has the discretion to waive certain trials in the interest of public health. This may be based on data from trials conducted in other countries or for drugs already approved and used for several years elsewhere.

Section 2.4(a) of Schedule Y mandates full clinical trials for drugs discovered in India, while Section 2.4(b) requires applicants for drugs discovered outside India to submit relevant data, with the licensing authority potentially requiring additional studies or allowing progression from Phase III trials.

Section 2.8 of Schedule Y allows the licensing authority to request pharmacokinetic studies (Bioequivalence studies) to compare data generated in Indian populations with that from abroad before proceeding to Phase III trials.

In essence, the specific clinical trial requirements vary case by case, contingent upon the licensing authority's satisfaction regarding the drug's safety and efficacy.

The approval process for new drugs in India is complex and must comply with stringent requirements, including submission of a New Drug Application (NDA) to the FDA. This study aims to document these approval requirements, focusing on clinical trials as mandated by the Drugs Control Department, Government of India.


Applicant
IND application filing to CDSCO head quarters
Application to ethical committee
Examination by new drug division
Report of ethical committee
Detailed review by IND committee
If Positive
Recommendation to DCGI
Within 12 weeks
IND application approved
Clinical trials started
Application for new drug registration to CDSCO
If not complete
Review by DCGI
Refused to grant licence
If complete
LICENCE IS GRANTED

Abbreviated New Drug Application (ANDA)

An abbreviated new drug application (ANDA) is submitted to the FDA for review and potential approval of a generic drug, allowing the applicant to manufacture and market a cost-effective alternative to the brand-name drug. Generic drugs must be comparable to innovator drugs in dosage form, strength, administration route, quality, performance, and intended use. Approved products, whether brand-name or generic, are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

ANDAs are termed "abbreviated" because they typically do not require preclinical (animal) and clinical (human) data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product performs similarly to the innovator drug. One method of demonstrating this similarity is through bioequivalence studies, which measure the rate and extent to which a generic drug reaches the bloodstream compared to the innovator drug. The FDA requires that generic versions deliver the same amount of active ingredients into the bloodstream in the same timeframe as the innovator drug to be approved.

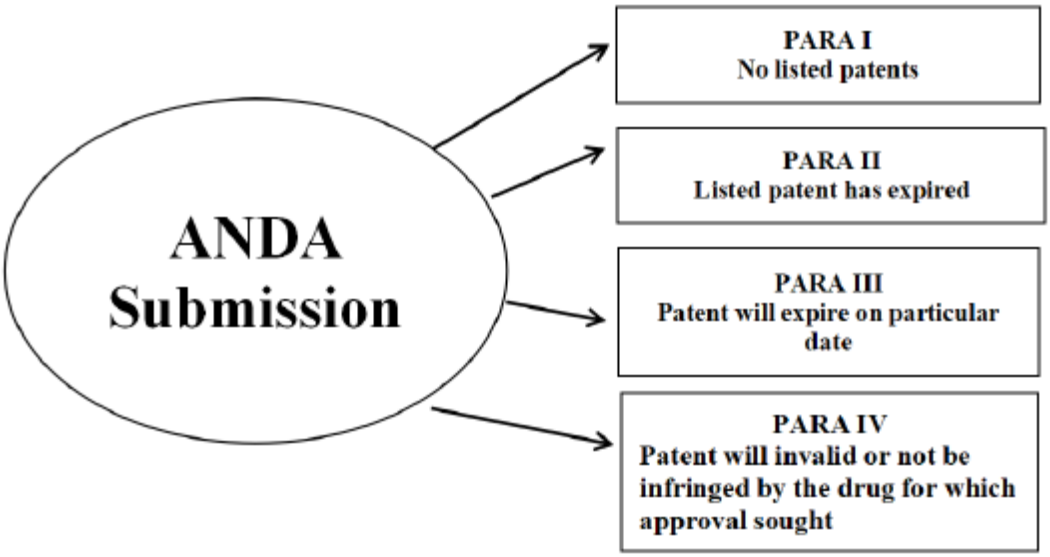
The Hatch-Waxman Amendments of 1984 established bioequivalence as the basis for approving generic drugs, allowing FDA approval without repeating costly clinical trials. These amendments also granted patent term extensions for innovator drugs undergoing FDA review and periods of marketing exclusivity. Additionally, generic companies gained the ability to challenge patents in court and a 180-day exclusivity period before other generics can enter the market.

Through the ANDA process, generic drug applicants can gain FDA approval without conducting clinical trials if their drug is proven bioequivalent to the branded (innovator) drug. All FDA-approved generic drugs ensure the same high quality, strength, purity, and stability as their brand-name counterparts.

Types of ANDA filings include:

1. **Paragraph I (Para I):** This filing occurs when the innovator drug's information is not listed in the FDA's Orange Book.
2. **Paragraph II (Para II):** A Para II filing is made when the drug's patent has expired, allowing for the generic version to enter the market.

3. **Paragraph III (Para III):** This filing is made when the applicant intends to market the generic drug only after the original drug's patent has expired.
4. **Paragraph IV (Para IV):** A Para IV filing is made when the applicant believes their product does not infringe on the innovator's patents, or that these patents are invalid or unenforceable. This type of filing typically triggers patent litigation between the generic and brand-name companies.



- **Paragraph I and II (Para I and II):** If an ANDA is certified under Para I or Para II, it can be approved immediately upon meeting all regulatory and scientific requirements (efficacy, safety, and bioequivalence). This means the generic drug manufacturer can start producing generic versions of the branded drug if either the branded drug's patent information is not filed or if the patent has expired.
- **Paragraph III (Para III):** A Para III filing is made when the applicant plans to sell the generic drug only after the original drug's patent expires. Approval of an ANDA under Para III certification depends on the patent's expiration date, and the approval becomes effective from that date.
- **Paragraph IV (Para IV):** When filing under Para IV, the ANDA applicant must notify the patent holder. The patent holder has 45 days to bring a patent infringement suit. If such a suit is filed, the FDA suspends the ANDA approval until:
    - The court decides the patent is invalid or not infringed,
    - The patent expires, if found infringed, or

- 30 months from the date the patent holder received notice of the Para IV filing (subject to court modifications).

During these 30 months, no ANDA can be approved unless the court finds the patent invalid or not infringed before that time. If the court rules the patent is invalid or not infringed before 30 months, the FDA can approve the ANDA. If the court upholds the patent's validity and infringement, the FDA delays approval until the patent expires.

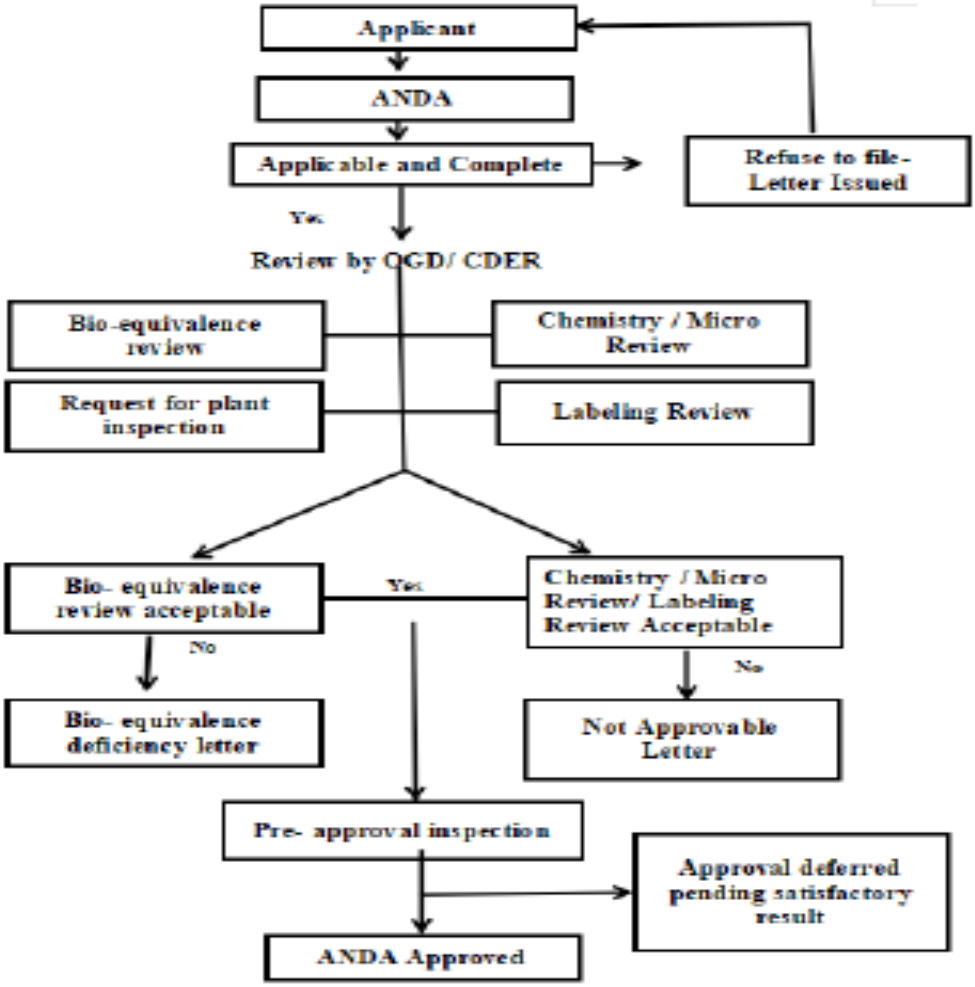
The FDA's review process for drugs intended for human use involves evaluation by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research for biological products. Here's a summary:

1. The FDA sends the applicant's application to the appropriate review team within CDER or another relevant center for evaluation and approval.
2. If the application is incomplete or deficiencies are identified, the FDA issues a "refuse to file letter" to the applicant.
3. Complete applications without deficiencies undergo internal review for bio-equivalence, chemistry/microbiology, plant inspection, and labeling issues.
4. If there are pending results or bio-equivalence deficiencies, the FDA issues corresponding deficiency letters and awaits satisfactory results from the applicant.
5. Upon completion of the ANDA submission and resolution of all queries, the applicant receives an FDA approval letter.

ANDA applicants can access a variety of resources to aid in their submissions. These resources include:

1. **Statutory and Regulatory Requirements:** Detailed guidelines outlining the legal and regulatory criteria for ANDA applications.
2. **CDER Assistance:** Support from the Center for Drug Evaluation and Research (CDER) to help applicants understand and fulfill these requirements.
3. **Internal Review Principles, Policies, and Procedures:** Guidelines and procedures followed by CDER during the internal review of ANDA submissions.
4. **Summary Tables, Application Forms, and Other Resources:** Accessible through the ANDA Forms & Submission Requirements, providing structured information and necessary forms for preparing and submitting an ANDA.

These resources are essential for ensuring that ANDA submissions meet all necessary standards for FDA approval.



For ANDA submissions, several key guidance documents and regulatory resources are critical:

1. **Guidance Documents:**
    - **Generic Drugs Guidance:** Provides comprehensive guidelines on various aspects of generic drug development and submission.
    - **Biopharmaceutics Guidance:** Focuses on the biopharmaceutical aspects relevant to generic drug approval.
    - **Product-Specific Guidance:** Offers specific requirements and considerations for the development of individual generic drug products.
2. **Laws, Regulations, Policies, and Procedures:**
    - **Federal Food, Drug, and Cosmetic Act (FD&C Act):** Establishes the foundational laws ensuring the safety and effectiveness of drugs, devices, and cosmetics in the United States.
    - **Code of Federal Regulations (CFR):**

        - **21 CFR Part 314:** Outlines the requirements for submitting applications for FDA approval to market new drugs, including ANDAs.
        - **21 CFR Part 320:** Sets forth the standards and requirements for demonstrating bioavailability and bioequivalence, crucial for ANDA approval.
3. **Manual of Policies and Procedures (MAPPs):**
    - **CDER's MAPPs:** Internal documents that detail the policies and procedures followed by CDER staff during the drug review process.
    - **Chapter 5200:** Specifically covers processes and activities related to generic drugs within CDER, ensuring consistency and standardization in review procedures.

These resources are essential for ANDA applicants, FDA review staff, and holders to understand the requirements, procedures, and standards for generic drug approval in the United States.

Changes to an approved NDA / ANDA

This guidance offers recommendations for holders of NDAs and ANDAs planning post-approval changes under section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70. It replaces the previous guidance issued in November 1999. The recommendations cover changes in:

1. Components and composition
2. Manufacturing sites
3. Manufacturing process
4. Specifications
5. Container closure system
6. Labeling
7. Miscellaneous changes
8. Multiple related changes

The guidance was developed under the oversight of the Chemistry, Manufacturing and Controls Coordinating Committee within the FDA's Center for Drug Evaluation and Research (CDER).

The FDA Modernization Act of 1997, signed on November 21, 1997, amended the Act by introducing section 506A, outlining requirements for initiating and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

The FDA has updated its regulations concerning supplements and other modifications to approved applications under 21 CFR 314.70 to align with section 506A of the Act. These changes aim to evaluate their impact on the drug product's identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities, degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) concerning the drug product's safety or effectiveness.

CDER has issued guidance, including the SUPAC (Scale-Up and Post Approval Changes) guidance, which provides recommendations on reporting categories:

- **Reporting Categories:** This guidance excludes components and composition changes. Section 506A of the Act and 21 CFR 314.70(c) outline two types of changes:
    - **A. Major Change:** A substantial change with potential adverse effects on the drug product's identity, strength, quality, purity, or potency concerning its

safety or effectiveness. Applicants may request expedited review for public health reasons, such as drug shortages, through a Prior Approval Supplement.

- **B. Moderate Change:** Changes with moderate potential adverse effects on the drug product's identity, strength, quality, purity, or potency. Two types exist:
  - **30-Day Supplement:** Requires submission to the FDA at least 30 days before distributing the modified drug product.
  - **Changes Being Effected (CBE):** Allows distribution upon FDA receipt.
- **C. Minor Change:** Changes with minimal potential adverse effects. Applicants must list these changes in their next Annual Report, including:
  - Editorial changes (e.g., spelling corrections).
  - Submission requirements for supplements or annual reports.

Applicants making changes under section 506A of the Act must also comply with other relevant laws and regulations, including current Good Manufacturing Practice (cGMP) requirements (21 U.S.C. 351(a)(2)(B)) and the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). Labeling changes under 21 CFR 314.70(c)(6)(iii) necessitate submission of 12 copies of the final printed labeling, as specified under 21 CFR 314.70(c)(1). Any labeling changes made under 21 CFR 314.70(b) or (c) must adhere to 21 CFR 314.70(a)(4).

Assessment of the Impact of Manufacturing Changes

1. Adherence to Specifications: Specifications refer to quality standards outlined in an approved application, including tests, analytical procedures, and criteria for acceptance. Compliance with specifications means that the material, when tested according to the specified analytical methods, meets the defined acceptance criteria.
2. Additional Testing: In cases where manufacturing changes may affect the identity, strength, quality, purity, or potency of a drug product, the applicant should conduct additional testing as necessary. This evaluation includes assessing changes in chemical, physical, microbiological, biological, bioavailability, or stability profiles. For instance: a. Assessment of impurities: Toxicology testing may be necessary to qualify new impurities. b. Assessment of physical characteristics such as hardness or friability of tablets. Equivalence testing should determine the extent of impact on the drug product's identity, strength, quality, purity, and potency. Equivalence does not imply identical performance but may include maintaining key quality attributes like stability. c. Identification of adverse effects: Certain manufacturing changes can

negatively impact the drug product. In such cases, the FDA recommends submission of a prior approval supplement, regardless of the reporting category. d. Changes in formulation, including inactive ingredients, typically require a prior approval supplement unless exempted by regulation (314.70(b)(2)(i)). e. Removal or reduction of ingredients intended solely for color alteration may be reported in an annual report (314.70(d)(2)(ii)).

3. Guidance on Changes: Detailed guidance on changes affecting components and composition, suitable for submission via a changes-being-effected supplement or annual report, is not included here due to its complexity but can be found in post-approval change guidance documents (e.g., SUPAC documents).

A. General Considerations: CDER must be informed if a manufacturer changes to a different manufacturing site than those specified in the approved application (314.70(a)). Sites encompass facilities used by an applicant:

1. Manufacturing or processing of drug products, including in-process materials, drug substances, or drug substance intermediates.
2. Packaging of drug products.
3. Labeling of drug products.
4. Testing of components, drug product containers, closures, packaging materials, in-process materials, or drug products. a. Testing sites encompass facilities conducting physical, chemical, biological, and microbiological tests to monitor, accept, or reject materials, including those conducting stability testing. b. FDA recommends that a change to a different manufacturing site, especially if the site type is routinely inspected by FDA and lacks a satisfactory Current Good Manufacturing Practice (CGMP) inspection for the operation type being relocated, be submitted as a prior approval supplement.

Major Changes: Here are examples of significant changes:

1. Changes that could impact controlled (or modified) release formulations.
2. Changes affecting drug product sterility assurance, including: a. Alterations in sterilization methods, such as transitioning from sterile filtration or aseptic processing to terminal sterilization. b. Addition of new equipment made from different materials to an aseptic processing line. c. Replacement of a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. d. Shift from bioburden-based terminal

sterilization to an overkill process. e. Changes in materials or pore size ratings of filters used in aseptic processing.

3. Changes in Manufacturing Process or Technology:
    - Drug Product:
        - Transition from dry to wet granulation.
    - Drug Substance:
        - Shift from filtration to centrifugation.
        - Change in the synthesis route of a drug substance.
    - Addition of an ink code imprint or change in ink used for an existing imprint, where the new ink is not currently used in CDER-approved drug products.

Specifications refer to quality standards such as tests, analytical procedures, and acceptance criteria outlined in an approved application. These standards confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, and container closure systems used in drug substance or drug product production. These specifications also apply to standards related to sterility assurance.

When making changes to or within the container closure system, the potential adverse effects on the drug product's identity, strength, quality, purity, or potency, and thus its safety or effectiveness, depend on factors like the drug product's route of administration, the performance of the container closure system, and the likelihood of interaction between packaging components and the dosage form. In some cases, there may be a significant risk of adverse effects, regardless of direct testing of the drug product against approved specifications.

A change to or within a packaging component often necessitates a new or revised specification for that component. This change does not typically trigger consideration as a multiple related change; only the reporting category for the packaging change needs to be addressed.

Changes in drug labeling encompass modifications to package inserts, package labeling, and container labels. All promotional labeling and advertising must promptly align with any implemented labeling changes. For ANDA drug products, all labeling changes must comply with section 505(j) of the Act.

Multiple related changes involve various combinations of individual changes. If an applicant has multiple related changes falling under different recommended reporting categories, CDER advises submission in accordance with the reporting category for each individual change.

This summary touches on general considerations provided in the guidance document. The FDA offers numerous examples of major, moderate, and minor changes.

For an overview of regulatory authorities such as those in India, United States, European Union, Australia, Japan, and Canada, including their organizational structure and types, additional specific details are available.