NEW DRUG DEVELOPMENT PROCESS (IND, NDA & ANDA)

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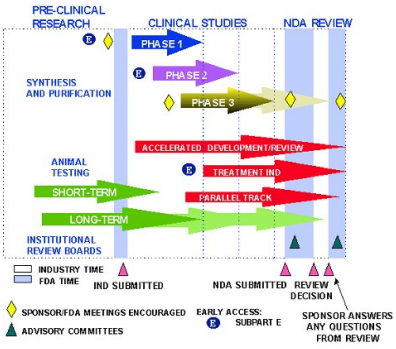
NEW DRUG APPROVAL PROCESS



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INVESTIGATIONAL NEW DRUG (IND) APPLICATION

Introduction

- Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development.
- When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.
- FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans.
- THIS IS WHEN THE IND IS FILLED.

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TYPES OF IND

There are three types of IND:

- An **Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- **Emergency Use IND** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

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CONTENT OF IND

- The IND application must contain information in three broad areas:
- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

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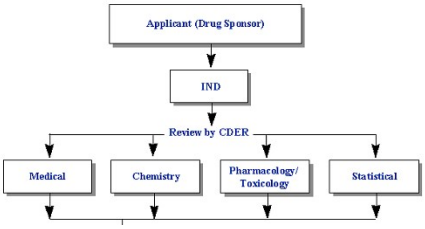
IND Review Process



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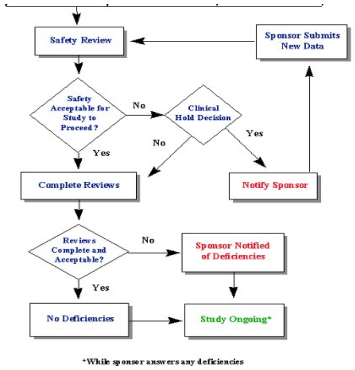

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Resources for IND Applications

The following resources include the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures.

- **Pre-IND Consultation Program**

  CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List.

- **Guidance Documents for INDs**

  Guidance documents represent the Agency's current thinking on a particular subject. These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures.

  Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both.

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Guidance documents to help prepare INDs include (See list below)

- **Laws, Regulations, Policies and Procedures**

  The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.
- ***Code of Federal Regulations* (CFR)**
- The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *Code Of Federal Regulations (CFR)*. The *CFR* is divided into 50 titles that represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *The Federal Food, Drug, and Cosmetic Act* and related statutes. *Section 21 of the CFR* contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

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- The following regulations apply to the IND application process:
- 21CFR Part 312Investigational New Drug Application
- 21CFR Part 314INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
- 21CFR Part 316Orphan Drugs
- 21CFR Part 58Good Lab Practice for Nonclinical Laboratory [Animal] Studies
- 21CFR Part 50Protection of Human Subjects
- 21CFR Part 56Institutional Review Boards
- 21CFR Part 201Drug Labeling
- 21CFR Part 54Financial Disclosure by Clinical Investigators.
- Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans
- Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs

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NEW DRUG APPLICATION (NDA)

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

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

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.
- The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

NDA.pdf

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Types of NDA

NDA Classifications

CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1 through 7 are used to describe the type of drug:

1- New Molecular Entity
2- New Salt of Previously Approved Drug (not a new molecular entity)
3- New Formulation of Previously Approved Drug (not a new salt OR a new molecular entity)
4- New Combination of Two or More Drugs
5- Already Marketed Drug Product - Duplication (i.e., new manufacturer)
6- New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription to OTC)
7- Already Marketed Drug Product - No Previously Approved NDA

The following letter codes describe the review priority of the drug:

S- Standard review for drugs similar to currently available drugs.
P- Priority review for drugs that represent significant advances over existing treatments.

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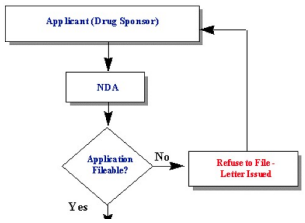
NDA Review Process



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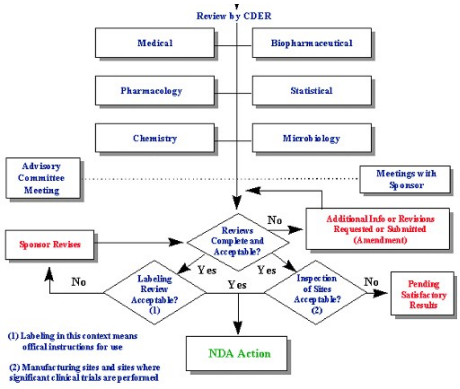

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ACTION TO BE TAKEN ON NDA

At the conclusion of CDER's review of an application, there are three possible action letters that can be sent to the sponsor:

- Not Approvable Letter — Lists the deficiencies in the application and explains why the application cannot be approved.
- Approvable Letter — Signals that, ultimately, the drug can be approved. Lists minor deficiencies that can be corrected, often involves labeling changes, and possibly requests commitment to do post-approval studies.
- Approval Letter — States that the drug is approved. May follow an approvable letter, but can also be issued directly.

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Resources for NDA Submissions

The following resources have been gathered to provide the legal requirements of a new drug application.

- **Guidance Documents for NDAs**

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

- **Laws, Regulations, Policies and Procedures**

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

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- ***Code Of Federal Regulations*** **(CFR)**

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

  21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.
- **CDER's Manual of Policies and Procedures (MaPPs)**

  These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPPS of particular interest to NDA applicants can be found in the list below:
- **Prescription Drug User Fee Act (PDUFA)**

  This act includes authorization for FDA to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications. FDA was first authorized to collect user fees under the Prescription Drug User Fee Act (PDUFA) of 1992.

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ABBREVIATED NEW DRUG APPLICATION (ANDA)

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations) in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's) are submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for review and approval. Once approved an applicant may manufacture and market the generic drug product provided all patent protection and exclusivity associated with the RLD have expired.

Generic drug applications are termed "abbreviated" in that they are not required to provide clinical data to establish safety and efficacy, since these parameters have already been established by the approval of the innovator drug product (first approved version of the drug product marketed under a brand name).

ANDA.pdf

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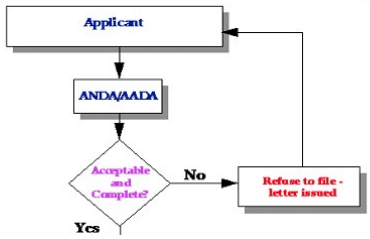
Generic Drug (ANDA/AADA) Review Process



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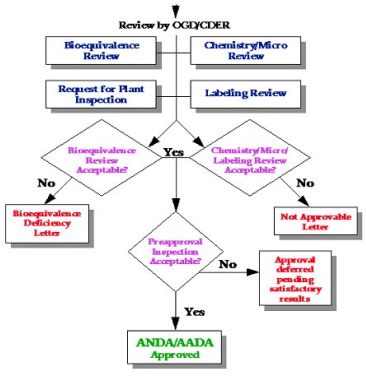

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ANDA/AADA Approved

After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant detailing the conditions of the approval and providing them with the ability to market the generic drug product.

If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the tentative approval of the generic drug product until the patent/exclusivity condition has expired. A tentative approval does not allow the applicant to market the generic drug product.

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Resources for ANDA Submissions

- The following resources provide ANDA applicants with the statutory and regulatory requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies, and procedures. Summary tables, application forms, and other ANDA submission resources are available in ANDA Forms & Submission Requirements.
- **Guidance Documents for ANDAs**
- Guidance documents represent the Agency's current thinking on a particular topic. These documents provide guidelines for the content, evaluation, and ultimate approval of applications and also to the design, production, manufacturing, and testing of regulated products for FDA review staff, applicants, and ANDA holders.
- Generic Drugs Guidances
- Biopharmaceutics Guidances
- Product-Specific Guidances for Generic Drug Development
- **Laws, Regulations, Policies, and Procedures**
- *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the United States. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

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- **Code of Federal Regulations**

  The final regulations published in the Federal Register (a daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code of Federal Regulations (CFR). Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug applicants that are required under Federal law. The following regulations directly apply to the ANDA process:
- Reference Listed Drug (RLD) Access Inquiries: A list identifying all products about which FDA has received an inquiry from a prospective generic applicant indicating that they are unable to purchase the samples of the RLD necessary to support their application because of limitations on the distribution of the drug.
- 21CFR Part 314: Applications for FDA Approval to Market a New Drug
- 21CFR Part 320: Bioavailability and Bioequivalence Requirements
- **Manual of Policies and Procedures**

  CDER's Manual of Policies and Procedures (MAPPs) document internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external. Chapter 5200 covers generic drugs processes and activities.

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Additional Resources

- Reference Listed Drug (RLD) Access Inquiries: A list identifying all products about which FDA has received an inquiry from a prospective generic applicant indicating that they are unable to purchase the samples of the RLD necessary to support their application because of limitations on the distribution of the drug.
- Investigational New Drug Application (IND): Resources to assist drug sponsors with submitting applications for approval to begin new drug experiments on human subjects.
- New Drug Application (NDA): Resources to assist drug applicants with submitting applications for approval to market a new drug.
- General Information on Manufacturing and Product Quality: Resources to help meet compliance with the approval process for new drug applications; includes a review of the manufacturer's compliance with Current Good Manufacturing Practice.
- Information for Clinical Investigators: Regulations and guidelines for scientists who design and run experiments (clinical trials) to test the safety and effectiveness of new drugs on human subjects.
- Post Drug-Approval Activities: FDA's post drug-approval activities to monitor the ongoing safety of marketed drugs by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk.
- Small Business & Industry Assistance Program (SBIA): CDER's SBIA program offers a variety of multimedia learning resources. The SBIA Learn web page has many helpful courses and recordings in the "Generic Drugs" section.

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ANY QUERIES

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