

Drug Development and Review Definitions

Accelerated Development/Review

Accelerated development/review (*Federal Register*, April 15, 1992) is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists. This process incorporates several novel elements aimed at making sure that rapid development and review is balanced by safeguards to protect both the patients and the integrity of the regulatory process.

Accelerated development/review can be used under two special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate endpoint is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives, but is still considered likely to predict therapeutic benefit for the patient.

The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient. If not, the FDA can withdraw the product from the market more easily than usual.

Advisory Committee Meeting

The Center for Drug Evaluation and Research (CDER) uses advisory committees to obtain outside advice and opinions from expert advisors so that final agency decisions will have the benefit of wider national expert input. Committee recommendations are not binding on CDER, but the agency considers them carefully when deciding drug issues.

CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information, or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug are adequate for marketing approval.

For additional information about FDA advisory committee meetings, call 800-741-8138. In the metropolitan Washington, D.C. area, call 301-443-0572.

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Animal Testing

In animal testing, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Generally, two or more species (one rodent, one non-rodent) are tested because a drug may affect one species differently from another. Animal testing is used to measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body.

Applicant (Drug Sponsor)

An applicant, or drug sponsor, is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the ***Federal Food, Drug, and Cosmetic Act*** and related regulations. The "sponsor" is usually an individual, partnership, corporation, government agency, manufacturer or scientific institution.

For a list of addresses to send applications to, go to the [Address \(/drugs/investigational-new-drug-ind-application/addresses-send-applications\)](#) page.

Biopharmaceutical Review

Pharmacokineticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed in, metabolized by, and eliminated from the human body.

Chemistry Review

Each review division employs a team of chemists responsible for reviewing the chemistry and manufacturing control sections of drug applications. In general terms, chemistry reviewers address issues related to drug identity, manufacturing control, and analysis. The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable. If the drug is either unstable or not reproducible, then the validity of any clinical testing would be undermined because one would not know what was really being used in the patients, and, more importantly, the studies may pose significant risks to participants.

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At the beginning of the Chemistry and Manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product, or the manufacturing of either the drug substance or the drug product, present any signals of potential human risk. If so, these signals should be discussed, with steps proposed to monitor for such risks.

In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

Clinical Hold Decision

A clinical hold is the mechanism that CDER uses when it does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subjects/patients. If this occurs, the Center will contact the sponsor within the 30-day initial review period to stop the clinical trial. CDER may either delay the start of an early-phase trial on the basis of information submitted in the IND, or stop an ongoing study based on a review of newly submitted clinical protocols, safety reports, protocol amendments, or other information. When a clinical hold is issued, a sponsor must address the issue that is the basis of the hold before the order is removed.

CDER's authority concerning clinical holds is outlined in Federal regulations. The regulations specify the clinical hold criteria that CDER applies to various phases of clinical testing. In addition, all clinical holds are reviewed by upper management of CDER to assure consistency and scientific quality in the Center's clinical hold decisions.

Clinical Studies

The new drug application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale in the United States. To obtain this authorization, a drug manufacturer submits in an NDA nonclinical (animal) and clinical (human) test data and analyses, drug information, and descriptions of manufacturing procedures.

An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including:

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- Whether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks
- Whether the drug's proposed labeling is appropriate, and, if not, what the drug's labeling 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 purpose of preclinical work--animal pharmacology/toxicology testing--is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

Although the goal of clinical trials is to obtain safety and effectiveness data, the overriding consideration in these studies is the safety of those in the trials. CDER monitors the study design and conduct of clinical trials to ensure that people in the trials are not exposed to unnecessary risks.

Subject-Related CDER Guidances of Interest:

- [Content and Format of Investigational New Drug Applications \(INDs\) for Phase 1 Studies of Drugs \(PDF - 42KB\) \(/media/71203/download\)](#)
- [Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro \(PDF - 109KB\) \(/media/71265/download\)](#)

Institutional Review Board

Institutional Review Boards (IRB) are used to ensure the rights and welfare of people participating in clinical trials both before and during their trial participation. IRBs at hospitals and research institutions throughout the country make sure that participants are fully informed and have given their written consent before studies ever begin. IRBs are monitored by the FDA to protect and ensure the safety of participants in medical research.

An IRB must be composed of no less than five experts and lay people with varying backgrounds to ensure a complete and adequate review of activities commonly conducted by research institutions. In addition to possessing the professional competence needed to review specific activities, an IRB must be able to ascertain the acceptability of applications and proposals in [^]Top ()

terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. Therefore, IRBs must be composed of people whose concerns are in relevant areas.

For more information, see the IRB Operations and Clinical Requirements list provided by FDA's Office of Health Affairs. This document is intended to help IRB's carry out their responsibilities for protection of research subjects. Also see the March 13, 1975, Federal Register, and the Technical Amendments concerning "Protection of Human Subjects" (45 CFR Part 46).

Investigational New Drug Application

In many ways, the investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials).

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.

Generally, this includes data and 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.

- **Manufacturing Information**

Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure 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

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experimental compound--to assess whether they are qualified to fulfill their clinical trial duties.

The IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce. Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA; however, its main purpose is to detail the data that provide documentation that it is indeed reasonable to proceed with certain human trials with the drug.

Types of INDs

"Commercial INDs" are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as "noncommercial" INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs."

For a list of addresses to send applications to, go to the [Address \(/drugs/investigational-new-drug-ind-application/addresses-send-applications\)](/drugs/investigational-new-drug-ind-application/addresses-send-applications) page.

Subject-Related CDER Guidances of Interest:

- [Content and Format of Investigational New Drug Applications \(INDs\) for Phase 1 Studies of Drugs \(PDF - 42KB\) \(/media/71203/download\)](/media/71203/download)
- [Guideline for Drug Master Files \(/drugs/guidances-drugs/drug-master-files-guidelines\)](/drugs/guidances-drugs/drug-master-files-guidelines)

Labeling

Professional labeling for human prescription drugs includes the prescribing information (PI), patient labeling (e.g., Medication Guide, Patient Information, Instructions for Use), and carton and container labeling. The PI, which is directed to the healthcare provider, must:

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug
- Be informative and accurate and neither promotional in tone nor false or misleading

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On January 24, 2006, the U.S. Food and Drug Administration (FDA) issued final regulations governing the content and format of PI for human prescription drugs. The rule is commonly referred to as the “Physician Labeling Rule” (PLR) because it addresses prescription drug labeling that is used by prescribers and other health care providers. For additional information regarding the PLR, regulations, related guidance documents, and additional labeling resources for PLR, PLLR, and non-PLR labeling, see [PLR Requirements for Prescribing Information \(/drugs/laws-acts-and-rules/plr-requirements-prescribing-information\)](https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information).

PLR format has 3 components (Highlights; Contents; Full Prescribing Information):

HIGHLIGHTS (HL): Contains a high-level half-page summary of critical prescribing information.

CONTENTS: Also known as “Table of Contents.” It allows easy reference to FPI.

FULL PRESCRIBING INFORMATION (FPI):: Has consistent order and numbering of sections (i.e., BOXED WARNING plus 17 numbered sections):

BOXED WARNING

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
- 6 ADVERSE REACTIONS**
- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy**
 - 8.2 Lactation**

[if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use Labor and Delivery]
 - 8.3 Females and Males of Reproductive Potential** (if not required to be in PLLR format, use Nursing Mothers)
 - 8.4 Pediatrics**
 - 8.5 Geriatrics**
- 9 DRUG ABUSE AND DEPENDENCE**
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
- 13 NONCLINICAL TOXICOLOGY**
- 14 CLINICAL STUDIES**

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15 REFERENCES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

Medical Review

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review, and are responsible for synthesizing the results of the animal toxicology, human pharmacology and clinical reviews to formulate the overall basis for a recommended Agency action on the application.

Meetings with Sponsors

During the course of reviewing an application, CDER usually communicates often with sponsors about scientific, medical, and procedural issues that arise during the review process. Communications may take the form of telephone conversations, letters, faxes or meetings (either face-to-face or via videoconferencing).

Notification of Easily Correctable Deficiencies

CDER makes every effort to communicate promptly to applicants easily correctable deficiencies found during the review of an application. CDER also informs applicants of the need for more data or information, or for technical changes in the application needed to facilitate the agency's review. This type of early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency final decision makers as well as by reviewing staff. Instead, major scientific issues are usually addressed in an action letter at the end of the initial review process.

End of Review Conference

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.

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Approval Letter States that the drug is approved. May follow an approvable letter, but can also be issued directly.

If the action taken is either an approvable or a not approvable action (as opposed to an approval action), CDER provides applicants with an opportunity to meet with Agency officials and discuss the deficiencies. The purpose of this "end of review conference" is to discuss what further steps are necessary before the application can be approved. This meeting is available on all applications, with priority given to applications for priority review drugs and major new indications for marketed drugs. Requests for such meetings are directed to the director of the division responsible for reviewing the application.

Other Meetings

Other meetings between CDER and applicants may be held to discuss scientific, medical, and other issues that arise during the review process. CDER makes every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

Microbiology Review

The Clinical Microbiology information is required only in NDAs for anti-infective drugs. Since these drugs affect microbial, rather than human physiology, reports on the drug's in vivo and in vitro effects on the target microorganisms are critical for establishing product effectiveness.

An NDA's Microbiology section usually includes data describing:

- the biochemical basis of the drug's action on microbial physiology;
- the drug's antimicrobial spectra, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use;
- any known mechanisms of resistance to the drug, including results of any known epidemiologic studies demonstrating prevalence of resistance factors; and
- clinical microbiology laboratory methods needed to evaluate the effective use of the drug.

More specific guidance on developing the microbiology component of the NDA is available from the CDER's *Guideline for the Format and Content of the Microbiology Section of an Application* (February 1987).

New Drug Application

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The data gathered during the animal studies and human



clinical trials of an Investigational New Drug (IND) become part of the NDA.

The NDA has evolved considerably during its history. When the Food, Drug, and Cosmetic Act (FD&C Act) was passed in 1938, NDAs were only required to contain information pertaining to the investigational drug's safety. In 1962, the Kefauver-Harris Amendments to the FD&C Act required NDAs to contain evidence that a new drug was effective for its intended use as well, and that the established benefits of the drug outweighed its known risks.

The NDA was again the subject of change in 1985, when the FDA completed a comprehensive revision of the regulations pertaining to NDAs. While this revision, commonly called the NDA Rewrite, modified content requirements, it was mainly intended to restructure the ways in which information and data are organized and presented in the NDA to expedite FDA reviews.

Fundamentals of NDA Submissions

Although the quantity of information and data submitted in NDAs can vary significantly, the components of NDAs are more uniform. The components of any NDA are, in part, a function of the nature of the subject drug and the information available to the applicant at the time of submission. As outlined in Form FDA-356h, *Application to Market a New Drug for Human Use Or As An Antibiotic Drug For Human Use*, NDAs can consist of as many as 15 different sections:

- Index;
- Summary;
- Chemistry, Manufacturing, and Control;
- Samples, Methods Validation Package, and Labeling;
- Nonclinical Pharmacology and Toxicology;
- Human Pharmacokinetics and Bioavailability;
- Microbiology (for anti-microbial drugs only);
- Clinical Data;
- Safety Update Report (typically submitted 120 days after the NDA's submission);
- Statistical;
- Case Report Tabulations;
- Case Report Forms;
- Patent Information;
- Patent Certification; and
- Other Information.

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NDA Content and Format Requirements

Although the exact requirements are a function of the nature of a specific drug, the NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.

The FDA has numerous guidelines that relate to NDA content and format issues. These guidelines can be obtained from CDER's Drug Information Branch (DIB). Below is a partial list of some Guidances of interest. See DIB's [Guidance Documents \(/drugs/guidances-drugs/newly-added-guidance-documents\)](/drugs/guidances-drugs/newly-added-guidance-documents) for a complete list of available guidelines online and instructions on how to obtain them.

Subject-Related CDER Guidances of Interest (examples): [Drug Master Files \(/drugs/guidances-drugs/drug-master-files-guidelines\)](/drugs/guidances-drugs/drug-master-files-guidelines)

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 10 are used to describe the type of drug:

Code Meaning

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| 1 | New molecular entity (NME) |
| 2 | New active ingredient (new salt, new noncovalent derivative, new ester) |
| 3 | New dosage form |
| 4 | New combination |
| 5 | New formulation or new manufacturer |
| 6 | New indication [no longer used] |
| 7 | Drug already marketed without an approved NDA |
| 8 | OTC (over-the-counter) switch |
| 9 | New indication submitted as distinct NDA, consolidated with original NDA after approval |
| 10 | New indication submitted as distinct NDA - not consolidated |

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

Code Meaning

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

For a list of addresses to send applications to, go to the [Address \(/drugs/investigational-new-drug-ind-application/addresses-send-applications\)](/drugs/investigational-new-drug-ind-application/addresses-send-applications) page.

[List of general drug categories for drug products \(/drugs/investigational-new-drug-ind-application/general-drug-categories\)](/drugs/investigational-new-drug-ind-application/general-drug-categories)

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New Drug Application Actions

Once an approval, approvable, or non-approvable recommendation is reached by the reviewers and their supervisors, the decision must be evaluated and agreed to by the director of the applicable drug review division or office. For the director's review, the consumer safety officer assembles an "action package" that contains the action letter and any data, CDER reviews and memos, and other information supporting the reviewers' recommendation.

Following his/her review of the action package, the division director may begin a dialogue with the reviewers and their supervisors. The division director generally serves as the final FDA ruling. In this sense, the division director is said to have "sign-off" authority for such drugs. The level of "sign-off" authority needed is determined by the classification of the drug under consideration. Class 1 drugs, for example, cannot be "signed off" by division directors; they require office level "sign-off" on action letters.

Once the division director (or office director, as appropriate) signs an approval action letter, the product can be legally marketed starting that day in the United States.

Parallel Track

Another mechanism to permit wider availability of experimental agents is the "parallel track" policy (***Federal Register of May 21, 1990***) developed by the U.S. Public Health Service in response to AIDS. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be promising.

Pharmacology/Toxicology Review

The pharmacology/toxicology review team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans.

Pharmacology and Drug Distribution (21 CFR 312.23(a)(8)(I)):

This section of the application should contain, if known: 1) a description of the pharmacologic effects and mechanism(s) of action of the drug in animals, and 2) information on the absorption, distribution, metabolism, and excretion of the drug. The regulations do not further describe the presentation of these data, in contrast to the more detailed description of how to submit toxicologic data. A summary report, without individual animal records or individual study results, usually suffices.

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To the extent that such studies may be important to address safety issues, or to assist in the evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness should not generally be a reason for a Phase 1 IND to be placed on clinical hold.

Toxicology Data

Present regulations (**21 CFR 312.23(a)(8)(ii)(a)**) require an integrated summary of the toxicologic effects of the drug in animals and in vitro. The particular studies needed depend on the nature of the drug and the phase of human investigation. When species specificity, immunogenicity, or other considerations appear to make many or all toxicological models irrelevant, sponsors are encouraged to contact the agency to discuss toxicological testing.

Subject-Related CDER Guidances of Interest:

- [Single Dose Acute Toxicity Testing for Pharmaceuticals \(PDF - 63KB\)](#)
(</media/72288/download>).
- [Content and Format of Investigational New Drug Applications \(INDs\) for Phase 1 Studies of Drugs \(PDF - 42KB\)](#) (</media/71203/download>).

Phase I Clinical Studies

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

In Phase 1 studies, CDER can impose a clinical hold (i.e., prohibit the study from proceeding or stop a trial that has started) for reasons of safety, or because of a sponsor's failure to accurately disclose the risk of study to investigators. Although CDER routinely provides advice in such cases, investigators may choose to ignore any advice regarding the design of Phase 1 studies in areas other than patient safety.

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Phase 2 Clinical Studies

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3 Clinical Studies

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

In both Phase 2 and 3, CDER can impose a clinical hold if a study is unsafe (as in Phase 1), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

Pre-Clinical Research

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past *in vitro* laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the

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drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

Review by CDER

Much of the primary review process involves reviewer attempts to confirm and validate the sponsor's conclusion that a drug is safe and effective for its proposed use. The review is likely to involve a reanalysis or an extension of the analyses performed by the sponsor and presented in the NDA. For example, the medical reviewer may seek to reanalyze a drug's effectiveness in a particular patient subpopulation not analyzed in the original submission. Similarly, the reviewer may disagree with the sponsor's assessment of evaluable patients and seek to retest effectiveness claims based on the reviewer-defined patient populations.

There is also extensive communication between review team members. If a medical reviewer's reanalysis of clinical data produces results different from those of the sponsor, for example, the reviewer is likely to forward this information to the statistical reviewer with a request for a statistical reanalysis of the data. Likewise, the pharmacology reviewer may work closely with the statistical reviewer in evaluating the statistical significance of potential cancer-causing effects of the drug in long-term animal studies.

When the technical reviews are completed, each reviewer develops a written evaluation of the NDA that presents their conclusions and their recommendations on the application. The division director or office director then evaluates the reviews and recommendations and decides the action that the division will take on the application. The result is an action letter that provides an approval, approvable or non-approvable decision and a justification for that recommendation.

Refuse to File Letter

New Drug Applications that are incomplete become the subject of a formal "refuse-to-file" action. In such cases, the applicant receives a letter detailing the decision and the deficiencies that form its basis. This decision must be forwarded within 60 calendar days after the NDA is initially received by CDER.


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Site Inspection

A division's decision to file an NDA begins the review process and, when needed, initiates a request for a preapproval inspection of the sponsor's manufacturing facilities and clinical trial sites. During such inspections, FDA investigators audit manufacturing-related statements and commitments made in the NDA against the sponsor's manufacturing practices. More specifically, the FDA conducts inspections to:

- verify the accuracy and completeness of the manufacturing-related information submitted in the NDA;
- evaluate the manufacturing controls for the preapproval batches upon which information provided in the NDA is based;
- evaluate the manufacturer's compliance with Current Good Manufacturing Practices (CGMPs) and manufacturing-related commitments made in the NDA; and
- collect a variety of drug samples for analysis by FDA field and CDER laboratories. These samples may be subjected to several analyses, including methods validation, methods verification, and forensic screening for substitution.

According to CDER policy, product-specific preapproval inspections generally are conducted for products: (1) that are new chemical or molecular entities; (2) that have narrow therapeutic ranges; (3) that represent the first approval for the applicant; or (4) that are sponsored by a company with a history of CGMP problems or that has not been the subject of a CGMP inspection over a considerable period. More specific guidance on CDER's preapproval inspection program is available from CDER's ***Compliance Program Guide 7346.832***.

The results of the preapproval inspection may also affect the final approval decision. When such inspections discover significant CGMP problems or other issues, the reviewing division may withhold approval until these issues are addressed and corrected. The division's response to such deficiencies is likely to depend on several factors, including the nature of the problem, the prognosis for the problem's correction, and the potential effect of the problem on the safety and efficacy of the drug.

Statistical Review

Statisticians evaluate the statistical relevance of the data in the NDA with the main tasks of evaluating the methods used to conduct studies and the various methods used to analyze the data. The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country.

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Synthesis and Purification

The research process is complicated, time-consuming, and costly and the end result is never guaranteed. Literally hundreds and sometimes thousands of chemical compounds must be made and tested in an effort to find one that can achieve a desirable result.

FDA estimates that it takes approximately eight-and-a-half years to study and test a new drug before it can be approved for the general public. This estimate includes early laboratory and animal testing, as well as later clinical trials using human subjects.

There is no standard route through which drugs are developed. A pharmaceutical company may decide to develop a new drug aimed at a specific disease or medical condition. Sometimes, scientists choose to pursue an interesting or promising line of research. In other cases, new findings from university, government, or other laboratories may point the way for drug companies to follow with their own research.

New drug research starts with an understanding of how the body functions, both normally and abnormally, at its most basic levels. The questions raised by this research help determine a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. This provides the researcher with a target. Sometimes, scientists find the right compound quickly, but usually hundreds or thousands must be screened. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some effect. This process may require testing hundreds of compounds since some may not work, but will indicate ways of changing the compound's chemical structure to improve its performance.

Computers can be used to simulate a chemical compound and design chemical structures that might work against it. Enzymes attach to the correct site on a cell's membrane, which causes the disease. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there. But even though computers give chemists clues as to which compounds to make, a substance must still be tested within a living being.

Another approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what is known as a "fermentation broth," with one type of organism per broth. Sometimes, 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

Treatment Investigational New Drug

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Treatment Investigational New Drugs (*Federal Register*, May 22, 1987) are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the drug's safety and effectiveness.