Learn About Drug and Device Approvals

The development of drugs and medical devices follows well-established paths to make sure that they are safe and effective when they reach the public. From concept to approval and beyond, FDA:

- Reviews research data and information about drugs and devices before they become available to the public.
- Watches for drug problems once drugs and devices are available to the public.
- Monitors drug information and advertising.
- Protects drug quality.

Drug and Device Development Processes

The development processes for drugs and devices are similar–each involves five basic steps. However, the processes differ within those steps. Click on either Drug Development or Device Development in the graphic below to learn more.

Step 1

Discovery/Concept

Discovery/Concept

Research for a new drug or device begins in the laboratory.

Drug Development Device Development

Step 2

Preclinical Research

Preclinical Research

Drugs and devices undergo laboratory and animal testing to answer basic questions about safety.

Drug Development Device Development

Step 3

Clinical Research

Clinical Research

Drugs and devices are tested on people to make sure they are safe and effective.

Drug Development Device Development

Step 4

FDA Review

FDA Review

FDA review teams thoroughly examine all of the submitted data related to the drug or device and make a decision to approve or not to approve it.

Drug Development Device Development

Step 5

FDA Post-Market Safety Monitoring

FDA Post-Market Safety Monitoring

FDA monitors all drug and device safety once products are available for use by the public.

Drug Development Device Development

Resources For You

- Search for FDA-Approved Drugs
- Report Side Effects on MedWatch

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Step 1: Discovery and Development

Discovery

Typically, researchers discover new drugs through:

- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects.
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

At this stage in the process, thousands of compounds may be

potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.

Development

Once researchers identify a promising compound for development, they conduct experiments to gather information on:

- How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action.
- The best dosage.
- The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be referred to as toxicity.
- How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- How it interacts with other drugs and treatments.
- Its effectiveness as compared with similar drugs.

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Step 1: Device Discovery and Concept

It is important to understand how devices are classified since the development process differs depending on the device's classification.

Classifications

FDA classifies medical devices based on the risk posed by a device. Medical devices can change classification systems depending on the results of scientific data.

Class 1: General Controls

Class 1 devices pose the least amount of risk to consumers. These low-risk devices, such as oxygen masks or surgical tools, are subject to "general controls." General controls ensure the safety and effectiveness of devices once they're manufactured. General controls consider the following factors:

- Good manufacturing practices
- Standards and Reporting Adverse Events to FDA
- registration,
- general recordkeeping requirements

Class 2: General Controls With Special Controls

Class 2 devices pose more risk to consumers than do Class 1 devices. Therefore, Class 2 devices are subject to special controls in addition to general controls. Special controls include:

- Labeling requirements (information that must be included on a product label)
- Device specific mandatory performance standards
- Device specific testing requirements

Class 2 devices are also subject to general controls.

Class 3: General Controls and Premarket Approval

Usually, Class 3 devices support or sustain life, are implanted in the body, or have the potential for unreasonable risk of illness or injury. Examples include pacemakers, breast implants, and HIV diagnostic tests. As a result, Class 3 devices require premarket approval. To receive this, a manufacturer must prove that a device is safe and effective. Class 3 devices are also subject to general controls.

Development/Concept

Medical device development follows a well-established path. Many of these steps overlap with each other as scientists invent, refine, and test the devices.

Typically, the development process begins when researchers see an unmet medical need. Then, they create a concept or an idea for a new device. From there, researchers build a “proof of concept,” a document that outlines the steps needed to determine whether or not the concept is workable. Many times, concepts are not practical. The concepts that do show promise move to the later stages of development.

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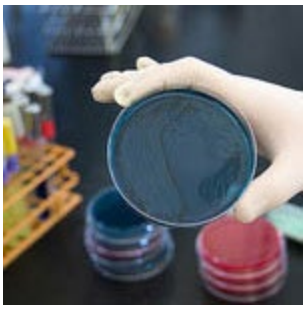
Step 2: Preclinical Research

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are:

- In Vitro



- In Vivo

FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. The GLP regulations are found in 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies. These regulations set the minimum basic requirements for:

- study conduct
- personnel
- facilities
- equipment
- written protocols
- operating procedures
- study reports

- and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people.

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Step 2: Preclinical Research-Prototype

Researchers build a device prototype, or an early version of a medical device. At this stage, the device prototype is not for human use. Researchers test the prototypes in controlled laboratory settings. Refining the prototype provides researchers with important information about the product's potential use for people. The prototype process attempts to reduce risk of harm in people. However, it is not possible to eliminate risk entirely.

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Step 3: Clinical Research

While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body. "Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins.

On this page you will find information on:

- Designing Clinical Trials
- Clinical Research Phase Studies
- The Investigational New Drug Process
- Asking for FDA Assistance
- FDA IND Review Team
- Approval

Designing Clinical Trials

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol, that is developed by the researcher or manufacturer. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- Who qualifies to participate (selection criteria)
- How many people will be part of the study
- How long the study will last
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage

- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies.

What are the Clinical Trial Phases?

Watch this video to learn about the three phases of clinical trials.

Clinical Research Phase Studies

Phase 1

Study Participants: 20 to 100 healthy volunteers or people with the disease/condition.

Length of Study: Several months

Purpose: Safety and dosage

Approximately 70% of drugs move to the next phase

Phase 2

Study Participants: Up to several hundred people with the disease/condition.

Length of Study: Several months to 2 years

Purpose: Efficacy and side effects

Approximately 33% of drugs move to the next phase

Phase 3

Study Participants: 300 to 3,000 volunteers who have the disease or condition

Length of Study: 1 to 4 years

Purpose: Efficacy and monitoring of adverse reactions

Approximately 25-30% of drugs move to the next phase

Phase 4

Study Participants: Several thousand volunteers who have the disease/condition

Purpose: Safety and efficacy

Learn more about Clinical Trials.

The Investigational New Drug Process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

In the IND application, developers must include:

- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

Asking for FDA Assistance

Drug developers are free to ask for help from FDA at any point in the drug development process, including:

- Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research
- After Phase 2, to obtain guidance on the design of large Phase 3 studies
- Any time during the process, to obtain an assessment of the IND application

Even though FDA offers extensive technical assistance, drug developers are not required to take FDA's suggestions. As long as clinical trials are thoughtfully designed, reflect what developers know about a product, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.

FDA IND Review Team

The review team consists of a group of specialists in different scientific fields. Each member has different responsibilities.

- ***Project Manager:*** Coordinates the team's activities throughout the review process, and is the primary contact for the sponsor.
- ***Medical Officer:*** Reviews all clinical study information and data before, during, and after the trial is complete.
- ***Statistician:*** Interprets clinical trial designs and data, and works closely with the medical officer to evaluate protocols and safety and efficacy data.
- ***Pharmacologist:*** Reviews preclinical studies.
- ***Pharmakineticist:*** Focuses on the drug's absorption, distribution, metabolism, and excretion processes.Interprets blood-level data at different time intervals from clinical trials, as a way to assess drug dosages and administration schedules.
- ***Chemist:*** Evaluates a drug's chemical compounds. Analyzes how a drug was made and its stability, quality control, continuity, the presence of impurities, etc.
- ***Microbiologist:*** Reviews the data submitted, if the product is an antimicrobial product, to assess response across different classes of microbes.

Approval

The FDA review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials. FDA responds to IND applications in one of two ways:

- Approval to begin clinical trials.
- Clinical hold to delay or stop the investigation. FDA can place a clinical hold for specific reasons, including:
    - Participants are exposed to unreasonable or significant risk.
    - Investigators are not qualified.
    - Materials for the volunteer participants are misleading.

- The IND application does not include enough information about the trial's risks.

A clinical hold is rare; instead, FDA often provides comments intended to improve the quality of a clinical trial. In most cases, if FDA is satisfied that the trial meets Federal standards, the applicant is allowed to proceed with the proposed study.

The developer is responsible for informing the review team about new protocols, as well as serious side effects seen during the trial. This information ensures that the team can monitor the trials carefully for signs of any problems. After the trial ends, researchers must submit study reports.

This process continues until the developer decides to end clinical trials or files a marketing application. Before filing a marketing application, a developer must have adequate data from two large, controlled clinical trials.

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Step 3: Pathway to Approval

The pathway to approval for a medical device depends on its risk classification.

Device Application Process

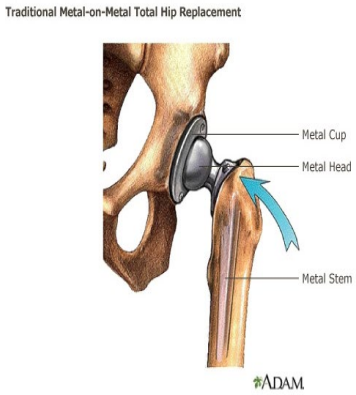
Because there is so much variation in the classification of devices, developers have a variety of options.

Federal Food, Drug, and Cosmetic Act, section 513, established the risk-based device classification system for medical devices. Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness.

As device class increases from Class I, to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most regulatory control.

	Device Pathways to Market
	**Most exempt from premarket submission (Class I)**
	**Premarket Notification [510(k) (Class II)**

Special Controls - E.g., meeting FDA-recognized performance standards, postmarket surveillance, patient registr



Premarket Application [PMA] (Class III)

Life-supporting, life-sustaining or important in preventing impairment of human health

"De Novo"

Device “types” that have never been marketed in the U.S., but whose safety profile and technology are now reas

Humanitarian Device Exemption (HDE)

Devices for orphan diseases
Intended to benefit patients in diagnosis and/or treatment of disease or condition affecting or manifested in fewer

The regulatory controls for each device class include:

510(k)

Requires proof that the devices is **substantially equivalent (SE)** to a legally marketed device that is not subject to Premarket Approval (PMA).

Substantial Equivalence

A device is considered substantially equivalent if it has the same intended use and the same

technological characteristics as a legally marketed device. A legally marketed device was:

- legally marketed prior to May 28, 1976 ("preamendments device"), for which a PMA is not required, or
- reclassified from Class III to Class II or Class I, or
- found substantially equivalent through the 510(k) process.

Applicants must compare their device to one or more similar legally marketed devices and make and support their substantially equivalent claims. If the device is substantially equivalent to an approved medical device, it is placed in the same class. If it is not substantially equivalent, it becomes non-SE and is placed into Class III.

Examples of 510(k)s include x-ray machines, dialysis machines, fetal monitors, lithotripsy machines, and muscle stimulators.

Premarket Approval (PMA)

PMA refers to the scientific and regulatory review necessary to evaluate:

- the safety and effectiveness of Class III devices or
- devices that were found not substantially equivalent to a Class I or II predicate through the 510(k) process.

PMA is the most involved process. To reasonably determine that a device is safe and effective. PMA requires:

- scientific evidence that the possible benefits to health from the intended use of a device outweigh the possible risks
- that the device will significantly help a large portion of the target population.

Independence is an important concept for PMAs, meaning that each PMA should establish the safety and effectiveness of the device under review, and that data about one device cannot be used to support another.

Examples of PMAs include digital mammography, minimally invasive and non-invasive glucose testing devices, implanted defibrillators, and implantable middle ear devices.

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Step 4: FDA Drug Review

If a drug developer has evidence from its early tests and preclinical and clinical research that a drug is safe and effective for its intended use, the company can file an application to market the drug. The FDA review team thoroughly examines all submitted data on the drug and makes a decision to approve or not to approve it.

Find out how the FDA is Speeding Up the Approval Process.

New Drug Application

A New Drug Application (NDA) tells the full story of a drug. Its purpose is to demonstrate that a drug is safe and effective for its intended use in the population studied.

A drug developer must include everything about a drug—from preclinical data to Phase 3 trial data—in an NDA. Developers must include reports on all studies, data, and analyses. Along with clinical results, developers must include:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Any data from studies that may have been conducted outside the United States
- Institutional review board compliance information
- Directions for use

FDA Review

Once FDA receives an NDA, the review team decides if it is complete. If it is not complete, the review team can refuse to file the NDA. If it is complete, the review team has 6 to 10 months to make a decision on whether to approve the drug. The process includes the following:

- Each member of the review team conducts a full review of his or her section of the application. For example, the medical officer and the statistician review clinical data, while a pharmacologist reviews the data from animal studies. Within each technical discipline represented on the team, there is also a supervisory review.
- FDA inspectors travel to clinical study sites to conduct a routine inspection. The Agency looks for evidence of fabrication, manipulation, or withholding of data.
- The project manager assembles all individual reviews and other documents, such as the inspection report, into an "action package." This document becomes the record for FDA review. The review team issues a recommendation, and a senior FDA official makes a decision.

FDA Approval

In cases where FDA determines that a drug has been shown to be safe and effective for its intended use, it is then necessary to work with the applicant to develop and refine prescribing information. This is referred to as "labeling." Labeling accurately and objectively describes the basis for approval and how best to use the drug.

Often, though, remaining issues need to be resolved before the drug can be approved for marketing. Sometimes FDA requires the developer to address questions based on existing data. In other cases, FDA requires additional studies. At this point, the developer can decide whether or not to continue further development. If a developer disagrees with an FDA decision, there are mechanisms for formal appeal.

FDA Advisory Committees

Often, the NDA contains sufficient data for FDA to determine the safety and effectiveness of a drug. Sometimes, though, questions arise that require additional consideration. In these cases, FDA may organize a meeting of one of its Advisory Committees to get independent, expert advice and to permit the public to make comments. These Advisory Committees include a Patient Representative that provides input from the patient perspective. Learn more about FDA Advisory Committees.

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Step 4: FDA Device Review

If medical device developers have enough information on a device's safety and effectiveness, they can file an application to market the device to the public. The type of application they file depends on the device's class.

- **Humanitarian Device Exemption**
  Humanitarian Use Devices benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 people. Before they can market a Humanitarian Use Device, developers must submit a human device exemption and must demonstrate that there are no similar, legally approved devices on the market and that there is no other way to bring a Humanitarian Use Device to market.
- **Premarket Notification or 510(k)–Class 1, 2 and 3 Devices**
  Premarket Notification, also known as a 510(k), indicates that the Class 2 medical device is similar to others on the market. To support the claim, the developer compares the new device to one or more similar, legally marketed devices.
- **Premarket Approval Application–Class 3 Devices**
  Premarket Approval applications must be submitted for Class 3 devices and must include data from all nonclinical studies and clinical studies. During the approval process, FDA will inspect the manufacturing laboratories and facilities where the device will be made to check for good manufacturing practices.

If appropriate, FDA will consult an Advisory Committee at a public meeting. FDA Advisory Committees consist of groups of experts who provide FDA with independent advice on an issue. The panels recommend whether a product should be approved or not.

After the Advisory Committee meets, FDA decides whether the device is approvable or not approvable, or request additional information. By law, FDA must publish its decision with all supporting evidence in the Federal Register.

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Step 5: FDA Post-Market Drug Safety Monitoring

Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace. FDA reviews reports of problems with prescription and over-the-counter drugs, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues.

On this page you will find information on:

Supplemental Applications

Developers must file a supplemental application if they wish to make any significant changes from the original NDA. Generally, any changes in formulation, labeling, or dosage strength must be approved by FDA before they can be made.

INDs for Marketed Drugs

If sponsors want to further develop an approved drug for a new use, dosage strength, new form, or different form (such as an injectable or oral liquid, as opposed to tablet form), or if they want to conduct other clinical research or a post-market safety study, they would do so under an IND.

Manufacturer Inspections

FDA officials conduct routine inspections of drug manufacturing facilities across the United States, and abroad if approved products are manufactured overseas. Manufacturers may be informed of inspections in advance, or the inspections may be unannounced. Inspections may be routine or caused by a particular problem or concern. The purpose of these inspections is to make sure that developers are following good manufacturer practice. FDA can shut down a facility if minimum standards are not met.

Drug Advertising

FDA regulates prescription drug advertisements and promotional labeling. By law, a developer is prohibited from advertising unapproved uses of their product.

All advertisements, such as product claims or reminder ads, cannot be false or misleading. They must contain truthful information about a drug's effectiveness, side effects, and prescribing information. These advertisements can be found in medical journals, newspapers, and magazines, and on the Internet, television, or radio.

Promotional labeling differs from drug advertisements in the way it is distributed. Pharmaceutical companies give out brochures or other promotional materials to physicians or consumers. The drug's prescribing information must accompany promotional labeling. Learn more at Prescription Drug Advertising.

Generic Drugs

New drugs are patent protected when they are approved for marketing. This means that only the sponsor has the right to market the drug exclusively. Once the patent expires, other drug manufacturers can develop the drug, which will be known as a generic version of the drug. Generic drugs are comparable to brand name drugs and must have the same:

- Dosage form
- Strength
- Safety
- Quality
- Performance characteristics
- Intended use

Because generic drugs are comparable to drugs already on the market, generic drug manufacturers do not have to conduct clinical trials to demonstrate that their product is safe and effective. Instead, they conduct bio-equivalence studies and file an Abbreviated New Drug Application. Learn more at Generic Drugs: Questions and Answers.

Reporting Problems

FDA has several programs that allow manufacturers, health professionals, and consumers to report problems associated with approved drugs.

- MedWatch is a gateway for reporting problems with medical products (drugs and devices) and learning about new safety information. You can subscribe to regular MedWatch safety alerts.
- Medical Product Safety Network (MedSun) monitors the safety and effectiveness of medical devices. FDA recruits 350 healthcare providers throughout the United States to report any medical device problems that result in serious injury or death. Each month, FDA publishes the MedSun newsletter. The newsletter gives consumers important information about medical device safety.

Active Surveillance

Under the Sentinel Initiative, FDA is developing a new national system to more quickly spot possible safety issues. The system will use very large existing electronic health databases—like electronic health records systems, administrative and insurance claims databases, and registries—to keep an eye on the safety of approved medical products in real time. This tool will add to, but not replace, FDA's existing postmarket safety assessment tools. Learn more about the Sentinel Initiative and its major activities.

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Step 5: FDA Post-Market Device Safety Monitoring

Although premarket clinical trials provide important information on a device's safety and effectiveness, it is possible that new safety concerns will emerge once the device is on the market. As a result, FDA continues to monitor device performance after a device has been approved.

Manufacturer Inspections

FDA officials conduct routine inspections of medical device manufacturing facilities across the United States. Manufacturers may be informed of inspections in advance, or the inspections may be unannounced. Inspections may be routine or caused by a particular problem. The purpose of these inspections is to make sure developers are following good manufacturing practices. FDA can shut down a manufacturing facility if standards are not met.

Reporting Problems

FDA has several programs that allow manufacturers, health professionals, and consumers to report problems associated with approved medical devices.

- MedWatch, FDA's adverse event reporting program, is a gateway for reporting problems with medical products (drugs and devices) and learning about new safety information. You can subscribe to regular MedWatch safety alerts.
- Medical Product Safety Network (MedSun), an adverse events reporting program, monitors the safety and effectiveness of medical devices. FDA recruits 350 health care providers throughout the United States to report any medical device problems that result in serious injury or death. Each month, FDA publishes the MedSun newsletter. The newsletter gives consumers important information about medical device safety.

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Learn more about Medical Devices.

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