

THE DRUG DEVELOPMENT AND APPROVAL PROCESS IN THE US

Early Research/Preclinical Testing		Human Clinical Trials			FDA Review Process	Phase IV
Years	6	Phase I	Phase II	Phase III	2	
Test Population	Laboratory & animal studies	1	2.0	3.5	Review Process & Approval	<div style="display: flex; align-items: center; justify-content: center;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg); font-weight: bold; margin-right: 10px;">15 years total</div> <div style="border: 1px solid black; padding: 5px; text-align: center;">Additional post-marketing monitoring and testing required by FDA</div> </div>
Purpose	Assess Safety and biological activity	20 to 80 healthy volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	FILE NDA WITH FDA	
Success Rate	5,000 compounds evaluated	Determine safety and dosage	Evaluate dosage, effectiveness, side effects	Confirm effectiveness, monitor long-term adverse reactions	1 approved	
		5 enter human trials				

The Food and Drug Administration (FDA) regulates the development of novel drugs. Both prescription and over-the-counter drugs are regulated by the Center for Drug Evaluation and Research (CDER). CDER has been established to ensure that drug products are safe and effective. All new drug products must undergo a rigorous process of pre-clinical and clinical evaluation. According to a 1999 report from PhRMA, it takes 15 years and \$500 million for an experimental drug to travel from the lab bench to the patient. For every 5000 compounds that enter pre-clinical testing, only five will continue on to clinical trials in humans and only one will be approved for marketing in the United States. After each stage of development, the sponsor of the new product meets with the FDA to determine next steps and establish end points for future trials. Similar processes are required in other countries.

Preclinical Testing. A pharmaceutical or biotechnology company conducts laboratory and animal studies to demonstrate biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, the company files an IND with the FDA to begin to test the drug in humans. The IND becomes effective if the FDA does not disapprove it within 30 days. The IND shows results of previous experiments and studies; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must be reviewed and approved by the Institutional Review Board (IRB) where the studies will be conducted, and progress reports on clinical trials must be submitted to the FDA at least once annually.

Phase I Human Clinical Trials. These tests involve approximately 20 to 80 normal, healthy volunteers. These tests study a drug's safety profile, including the safe dosage range. The studies also analyse how a drug is absorbed, distributed, metabolised and excreted, and the duration of its action.

Phase II Human Clinical Trials. Controlled studies of approximately 100 to 300 volunteer patients (people with disease being treated) to assess the drug's effectiveness and further analyse safety. Dose ranges may also be analysed during Phase II studies. More than one Phase II study may be conducted.

Phase III Clinical Trials. Approximately 1,000 to 3,000 patients in clinics and hospitals. This phase is used to determine whether the drug's effectiveness is statistically significant. Patients are continuously monitored for safety or adverse reactions. Typically, more than one Phase III study is conducted.

New Drug Application (NDA). Following successful completion of all three phases of human clinical trials, the company analyses all of the data and files an NDA with the FDA if the data successfully demonstrate safety and effectiveness. The NDA must contain all of the scientific information that the company has gathered on the compound. NDAs can exceed 100,000 pages or more. By legislation, the FDA is allowed six months to review an NDA filing. In 2000, the average review time for approved products was 16 months.

FDA Panel Review. Once CDER has reviewed the NDA, the product's sponsor presents the data to a panel of experts. The members of the panel may ask for clarification of specific data points, request explanations for certain outcomes or events observed in the trial or pose questions on potential issues that may occur if the product is approved for marketing. The members of the panel then vote in favour of or against recommending marketing approval. While the FDA does not have to take the recommendation of the panel, it usually does.

FDA Approval. Once the Review Panel has issued its recommendation, the FDA makes the final decision on product approval. Marketing of the drug is then permitted.