It takes 12 years on average for an experimental drug to travel from lab to medicine chest. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

Clinical Trials

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

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In reviewing this report, it is important to keep in mind the realities of the drug discovery and development process. The U.S. system of new drug approvals is perhaps the most rigorous in the world. On average, it costs a company $359 million to get one new

medicine from the laboratory to the pharmacist's shelf, according to a February 1993 report by the Congressional Office of Technology Assessment.

The flow chart accompanying this article gives the success rate of drugs and the length of time each step takes. Overall, about one in five of the medicines that begins clinical testing makes it through the trials and the approval process.

New medicines are developed as follows:

Preclinical Testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety. These tests take approximately three and one-half years.

Investigational New Drug Application (IND). After completing preclinical testing, the company files an IND with FDA to begin to test the drug in people. The IND becomes effective if FDA does not disapprove it within 30 days. The IND shows results of previous experiments, 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. In addition, the IND must be reviewed and approved by the Institutional Review Board where the studies will be conducted, and progress reports on clinical trials must be submitted at least annually to FDA.

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

Clinical Trials, Phase II. In this phase, controlled studies of approximately 100 to 300 volunteer patients (people with the disease) assess the drug's effectiveness and take about two years.

Clinical Trials, Phase III. This phase lasts about three years and usually involves 1,000 to 3,000 patients in clinics and hospitals. Physicians monitor patients closely to determine efficacy and identify adverse reactions.

New Drug Application (NDA). Following the completion of all three phases of clinical trials, the company analyzes all of the data and files an NDA with FDA if the data successfully demonstrate safety and effectiveness. The NDA must contain all of the scientific information that the company has gathered. NDAs typically run 100,000 pages or more. By law, FDA is allowed six months to review an NDA. In almost all cases, the period between the first submission of an NDA and final FDA approval exceeds that limit; the average NDA review time for new molecular entities approved in 1992 was 29.9 months.

Approval. Once FDA approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional studies (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult and expensive process. The research-based pharmaceutical industry will invest $12.6 billion in research and development this year, and that investment has been doubling every five years.

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