



# Continuing Education



## Overview of pharmaceutical research

### Learning Objectives

**Differentiate** basic and applied research, and list various research settings.

**Describe** the role of the FDA and peer review in assuring the quality of research.

**Describe** the strategies and processes that guide the planning of research.

**Describe** the stages of the product development process.

**Explain** how patents protect drug developers.

This first article in a three-part series presents an overview of pharmaceutical research. Topics include: basic and applied research, various research settings, assuring the quality of research, planning research, the standard product development process, and patent protection.

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**B**asic and applied research is performed by a variety of public and private institutions, differentiated by their sources of funding and the focus of their research work.

In basic research, scientists attempt to define the fundamental mechanisms underlying normal and abnormal biological processes in human health and disease. Results often become the basis for developing new treatments for human disorders.

Applied research investigates the diagnosis, treatment or prevention of a disease or the mechanisms surrounding the symptoms of a disease. Applied research is intended to relate directly or indirectly to clinical medicine. Large clinical trials, dosage testing and research for product labeling are all examples of applied research.

Research personnel may include a variety of doctoral-level health professionals as well as engineers, biostatisticians, project managers, laboratory and medical technicians, nurses, pharmacists, data processing specialists, lawyers, and technical and medical writers. A research project may also include a clinical research associate (CRA). This individual

manages projects and acts as a liaison between the research sponsor and the personnel conducting the clinical trials.

The CRA profession has emerged with the advent of contract research organizations. These are private corporations hired by pharmaceutical or medical device companies to conduct certain aspects of clinical research during virtually any phase of clinical development. Their principal goal is to speed up the clinical research process.

Research is conducted in a variety of settings:

**Private pharmaceutical companies.** A large majority of the pharmaceutical industry's collective research investment is spent on companies' own internal research and development activities. An increasingly common approach is for two or more pharmaceutical companies to work cooperatively, forming agreements for the development and marketing of new products, especially in therapeutic areas where they are critically needed.

**Government agencies.** The federal government supports and performs both basic and applied research. It is more involved in the funding and regulation of research but also performs some intra-

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mural (in-house) studies. The National Institutes of Health is the dominant force in federal support and performance of research.

**Academic institutions.** While academic institutions primarily perform basic research, professional schools of health usually focus on applied research. Medical schools in the United States receive over 50% of the national research funds.

**Research institutes.** Government agencies and pharmaceutical companies tend to use private research institutes to complete research tasks that are beyond their own expertise or resources. Some of these private organizations are known as research-only pharmaceutical companies. They develop new drugs but license other pharmaceutical firms to manufacture or market the products.

### Assuring the quality of research

The U.S. Food and Drug Administration oversees the research behind the development of marketable medical products. Its mission is to protect the public from unsafe or clinically ineffective products. It also prevents the interstate shipping of medical products that do not satisfy its requirements for proof of safety and efficacy. The FDA reviews only the basic or applied research results of medical products that have been submitted for marketing approval.

Other aspects of research are controlled by peer review, a critical evaluation of research plans or progress by qualified scientists. Peer review is used in several ways:

**Funding decisions.** Agencies that grant funds to academic or other research institutes use peer review during the selection process. Typically, representatives of relevant scientific fields review the research proposals, evaluating the research design, the theoretical framework, the qualifications of the personnel and institution, and the likelihood of producing useful results.

**Journal publications.** Refereed journals rely on peer reviewers (known as editorial review boards) to decide which articles to publish. Qualified scientists review the merits of each research report, evaluating the research methodology and the quality of the discussion.

**Institutional review boards.** Institutions and individuals that conduct research sponsored by an outside source are required to have review boards to oversee the quality and ethical standards of the research. The mission of institutional review boards (IRBs) is to protect the interests of the human subjects involved in research and to see that their health and safety are not unnecessarily endangered. An IRB is composed of at least five people. The members of the board represent a variety of scientific disciplines and social interests. At least one member must be from outside the institution – often a clergy member, lawyer or other nonscientist. The impact of IRBs extends beyond the protection of subjects in that

## Drug development

Major stages in the drug development process

Stage 1: Screening for lead compounds

Stage 2: Conducting preclinical trials

Stage 3: Filing for IND exemption

Stage 4: Conducting clinical trials  
(animal toxicity studies continue)

Stage 5: Submitting an NDA  
(clinical trials continue)

Stage 6: Gaining NDA approval

Stage 7: Conducting phase IV investigations



the potential risk to subjects of the research is weighed against the potential gain from the research. The study must be well-designed, well-controlled and well-conducted to produce reliable results. Thus, IRBs not only protect the subjects but also may ensure other aspects of quality in the process.

### Planning research

Private industry and academic institutions must plan their research activities to respond to the priorities of the marketplace or the funding community. In private industry, effective marketing begins with research and development. Initially, a market evaluation is performed to describe the size of the market and its trends. To predict future demand and priorities, the marketing researcher may consult international scientific literature, new product patents, or analyses of social or market behavior.

The market evaluation yields a picture of unmet medical needs that drive the research effort. The size of the need is the number of patients with the untreatable disease or the number who are dissatisfied with available treatments. When the market is large enough to return a profit, the pharmaceutical company pursues the development of a product.

The key to developing a marketable product is product differentiation. A new product must not only be effective therapeutically; it must also be unique in a way that consumers value. Dosage forms are often a point of product differentiation.

Competitive pressure from other pharmaceutical companies and constant change in the marketplace require product development research to be focused and to move as quickly as possible. The earliest products in the marketplace benefit from increased market share, patent protection, brand recognition and profits.

In planning research, academic institutions reflect the research interests of their faculty and the funding sponsor. The primary sources of funding are grants and contracts. Government and private agencies will provide support to investigators who produce new knowledge, new interpretations of poorly understood events, and technologically transferable findings. There is no expectation that investigators will produce a particular result, but only that they will continue to contribute to the field.

Universities are less concerned about developing products that return

a profit, but they are interested in the development of intellectual property, the transfer of new technologies and the royalties they can gain from these achievements.

## The product development process

The process a pharmaceutical company uses to develop a new drug typically follows several stages, summarized below.

### Stage 1 – Screening for lead compounds.

Researchers screen thousands of chemicals for a particular chemical activity. The compounds that appear promising are known as “leads,” and researchers follow them – as a detective follows a lead – through subsequent evaluations. When a lead compound is identified, the drug company files documents to initiate the drug patent process.

**Stage 2 – Conducting preclinical trials.** These trials are meant to uncover any harmful effects of the lead compound on living organisms. Although preclinical trials focus largely on drug toxicity and pharmacology, they also provide an opportunity to get an initial reading on whether a drug will be active in a specific disease model.

**Stage 3 – Filing for IND exemption.** When pre-clinical test results indicate that a new molecular entity (NME) can be developed into a marketable drug, researchers file a Notice of Claimed Investigational Exemption for a New Drug, or investigational new drug (IND) application, with the FDA. The exemption allows the investigational use of unapproved drugs.

**Stage 4 – Conducting clinical trials.** Clinical trials are conducted in three phases (known as phases I, II and III). At the same time clinical trials are being performed in humans, chronic toxicity testing is conducted on animals. The average total time required to conduct human trials is nearly six years.

**Stage 5 – Submitting the new drug application (NDA).** When the company is satisfied with the results of all the animal toxicity and human clinical trials, it may apply to the FDA for approval to market the new drug. The NDA documents the research methods and findings.

**Stage 6 – Gaining NDA approval.** NDA approval is granted when, in the final analysis, the FDA believes the preclinical and clinical evidence indicates that the drug is effective in treating the identified indications and is safe when used as directed on the label. Upon receipt of the approval letter, the manufacturer can launch the product.

**Stage 7 – Conducting phase IV investigations.** Phase IV (post-marketing) studies evaluate the use of the drug in uncontrolled clinical settings and in certain clinical situations. The intent is to evaluate the drug as it is used in the “real world.” Only when the drug is used by many thousands of patients can its long-term efficacy and actual rate of adverse effects be known.

## Article Summary

- **Basic and applied research is performed by a variety of public and private institutions, differentiated by their sources of funding and the focus of their research work.**
  - Scientists perform basic research to define the fundamental mechanisms underlying normal and abnormal biological processes in human health and disease.
  - Applied research investigates the diagnosis, treatment or prevention of a disease or the mechanisms surrounding the symptoms of a disease.
- **The U.S. Food and Drug Administration oversees the research behind the development of marketable medical products.**
  - Other aspects of the research are controlled by peer review, a critical evaluation of research plans or progress by qualified scientists.
- **Private industry and academic institutions must plan their research activities to respond to the priorities of the marketplace or the funding community.**
- **Pharmaceutical companies generally follow standard stages in the development of a new drug.**
- **Drug patents protect the developer from competitors who could essentially steal the profits from a new drug if they were allowed to copy and sell it.**

## Patent protection

Drugs are very expensive to develop but relatively inexpensive to duplicate. Therefore, drug patents protect the developer from competitors who could essentially steal the profits from a new drug if they were allowed to copy and sell it. The patent grants the developer exclusive rights to the drug for 20 years.

The 20-year patent starts at the date of patent application. Drug patents are filed at least by the time the IND application is filed. The effective patent life is the number of years remaining on the patent when the product goes to market. The period from IND to NDA approval can be 10 to 12 years, which leaves only eight to 10 years of patent protection.

The cost of developing a drug must be amortized to include all other investigated chemical/biological entities that do not eventually become drug products. These costs are now estimated to reach more than \$800 million per NME. Patent protection is one way to help drug manufacturers reduce their financial risk.

Drug patents are general, all-purpose industry patents. The category is subdivided into process patents and product patents. Both subtypes last 20 years. Companies sometimes extend their total time of patent protection by patenting first the product and later a unique aspect of the production process. They may also extend the length of their patent protection by developing a new dosage form that is sufficiently different from the first drug to be considered unique for patent purposes.

The patent holder has the option of cross-licensing, which involves licensing someone else to manufacture or distribute the product or to use the process. This allows the developer company to recover the investment in drug development without getting involved in marketing the drug. Cross-licensing may also be advantageous when a company develops a product that is different from the therapeutic classes its sales force normally sells. By cross-licensing with a firm already in that field, the company allows its drug to reach the market more efficiently and, ultimately, more profitably.

The next article will focus on the design, methodology and analysis of research.