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MINIREVIEW

How the Pharmaceutical Industry Brings an Antibiotic Drug to Market in the United States

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INTRODUCTION

The modern pharmaceutical industry is only about 65 years old, but in that time it has revolutionized the practice of medicine by providing the infectious disease specialist with life-saving drugs, such as sulfonamides, penicillins, cephalosporins, aminoglycosides and quinolones, and others. During the last 50 years, medications produced by the pharmaceutical industry have saved more than 1.5 million lives and $140 billion in the treatment of tuberculosis, poliomyelitis, coronary artery disease, and cerebrovascular disease alone (2). Diseases once considered killers, such as smallpox, have been eradicated; a patient's average hospital stay has been shortened, and institutional space requirements have been reduced.

The process by which pharmaceutical companies bring such innovative medicines to market requires a period of preclinical testing with animals, three phases of clinical trials, two stages of approval from the Food and Drug Administration (FDA), about 12 years of research, and some $359 million in resources. Even after the FDA approves a drug, a pharmaceutical company may continue research with a fourth phase of clinical trials that will allow the practitioner to derive maximum benefits from the drug.

The drug development process is rigorous, for only 1 of every 6,000 compounds tested has a chance of reaching the market. Development of a compound typically requires more than 7 years from the time the drug is first tested with humans. Before 1967, 823 new, single-entity drugs had been introduced into the U.S. pharmaceutical market. Of these, 502 were discovered in the United States, and American pharmaceutical manufacturers were responsible for developing 437. Between 1967 and 1992, nearly 500 new, single-entity drugs were introduced into the U.S. market (2).

The investment in time is not the only factor involved. The cost of developing new drug entities has escalated over the past 17 years. In 1976, for example, developing a new drug entity cost $54 million, according to an estimate by the University of Rochester (2). By 1993, that cost had increased by more than 500% (Fig. 1) (1). This estimate takes into account the 12 years now projected for the development of a new pharmaceutical product.

To keep up with the demand for new medicines, U.S. pharmaceutical companies have dramatically increased their investments in research and development (R&D). In 1970, American pharmaceutical firms spent $618.5 million on R&D alone. By 1993, that number rose to $12.6 billion (2). More than half of these R&D allocations were spent on development (Fig. 2) (2). In 1993, the Pharmaceutical Manufacturers Association compared the percentages of sales invested in R&D by various U.S. industries. It found that the pharmaceutical industry reinvested a higher percentage of its sales revenues in R&D than did the manufacturing, aerospace, and electronics industries combined (Fig. 3) (2). Despite their sizable investments, pharmaceutical manufacturers are able to realize a profit on only 3 of every 10 products that survive development and reach the marketplace.

Industry's investment in R&D covers a broad range of chemical entities. These include pharmaceuticals, medications manufactured in finished dosage forms; ethical pharmaceuticals, products promoted only to members of the medical profession; and proprietary products, which are offered without prescription. Biological products manufactured by pharmaceutical firms include vaccines and genetically engineered entities. The industry also manufactures bulk medicinal chemicals and botanicals (such as antisera made from certain poisonous plants). Pharmaceutical research includes any activity that could result in a new drug or diagnostic product. The goals of research are to understand the disease process and to find ways to prevent, detect, and treat disease. Specifically, new antibiotics will provide the medical profession with agents that have specific therapeutic activity but few untoward effects. A more detailed definition of pharmaceutical research would also include an itemization of all work required for discovery or synthesis of the new compound, characterization of its medical impact, submission of the compound to extensive in vitro and in vivo animal testing, and ultimately, testing of the investigational entity in humans.

PRECLINICAL PHASE

Development of a chemotherapeutic product. All new molecular entities (synthetic, naturally occurring, or recombinant) are tested in animals for preliminary evidence of pharmacologic activity and safety. Drug compounds are eliminated at this point if they fail to show sufficient or specific pharmacologic activity or if they appear to be too toxic for use in humans.

Compounds that survive preliminary testing are subjected to a comprehensive screening program designed to characterize their unique chemotherapeutic activities as antibacterial, antiviral, antiparasitic, antifungal, or antitumor agents. If a potential chemotherapeutic compound shows activity in one of these pharmacologic classes, it is subjected to a more thorough investigation in a secondary screening series to evaluate the effects the compound may have on major body systems and to help scientists estimate what doses may be safely tested in human subjects.

The IND. When preclinical testing is completed, usually after 2 to 3 years, the data are summarized and presented to the FDA with an application for an Investigational New Drug exemption, or IND (see Appendix). This exemption from the food and drug law allows the compound of interest to be administered to humans, but only under rigorously controlled

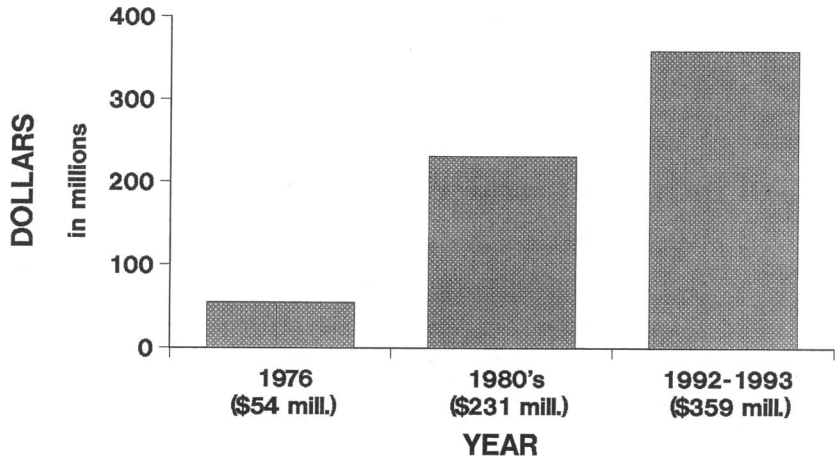

FIG. 1. Costs of developing new drug entities in the United States, 1976 to 1993 (1, 2).

conditions. After the IND application is approved by the FDA, human testing typically proceeds in three stages, or phases, and usually takes 3 to 7 years before marketing can be considered.

CLINICAL STUDIES

The phase I clinical trial program. The phase I program is conducted with small numbers of healthy volunteer subjects. These individuals generally are males or postmenopausal females. Phase I studies are conducted principally to study the safety of the experimental drug in humans and to derive important information about the route of administration, dose-range estimation, tolerance, and toxicity and the drug's effect on selected organ systems. The program may also study the pharmacokinetics (absorption, distribution, metabolism, and elimination) and bioequivalence of different dosage forms. Phase I studies may be placebo-controlled, single-dose trials or multiple-dose trials (see Appendix). The phase I program usually takes about a year or two and enrolls 100 to 300 subjects.

Close medical surveillance is maintained throughout all phase I studies, and all effects of the test drug are carefully recorded. Extensive clinical observation and laboratory testing, in addition to evaluation of the drug's metabolic pathways, are performed to derive maximum information about the drug in humans. Data from phase I studies are evaluated to determine whether further investigation of the drug is warranted. If a decision to proceed to phase II trials can be reached before the end of the phase I studies, phase II studies may begin at that time. Informed written consent is necessary from all subjects participating in the phase I clinical trial program.

The phase II clinical trial program. This phase of clinical study targets 300 to 1,000 subjects with the infection for which the antibiotic will be indicated. The safety of the drug continues to be evaluated, but attention is also focused on the therapeutic efficacy of the investigational drug. Phase II trials typically begin with open-label pilot studies, a limited number of patients, and concentration on the infections of interest. They also evaluate safety, including laboratory studies, and the potential for prophylaxis. They can progress to a double-blind study design that may include a known comparator. Written informed consent is required from each patient enrolled. Phase II trials generally require 1 to 2 years to complete.

In addition to the evaluation of efficacy, phase II trials may include dose-response studies, establishment of an effective dose regimen, studies of potential drug interactions, ophthalmologic examinations for drugs that are administered for more than a few weeks, specialized safety evaluations, such as evaluation of the potential for ototoxicity with aminoglycosides, and correlation of concentrations in plasma and tissue with the clinical outcome.

Women with childbearing potential may be included in the phase II program only after results from reproduction studies with animals suggest that the drug would be safe in this group of women and that the benefits of taking such an antibiotic to treat the infection outweigh its risk for adverse effects. Children and neonates may also be included in the phase II patient population, usually toward the end of the phase II program. It should be clear that these populations can be studied only after teratology studies, including evaluation of the compound with animal neonates, have been completed and experience has been gained from studies with adult humans. The latter caveat has been changed in regard to drugs developed to treat AIDS. Treatment programs are currently being initiated simultaneously with adults and children.

The phase III clinical trial program. This is the largest and most extensive segment of the clinical testing program. It focuses almost exclusively on comparing the investigational antibiotic's therapeutic efficacy with those of marketed antibiotic agents. Safety is always studied extensively, as is verification of the optimum dosage for the new drug. Phase III trials

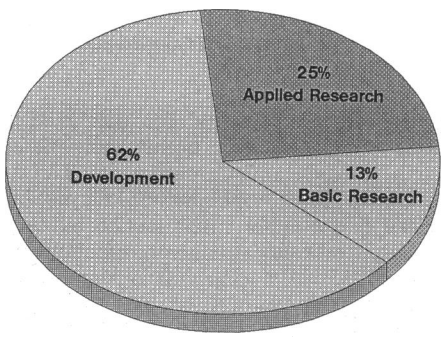

FIG. 2. Portion of funds U.S. pharmaceutical companies allocated for R&D (2).

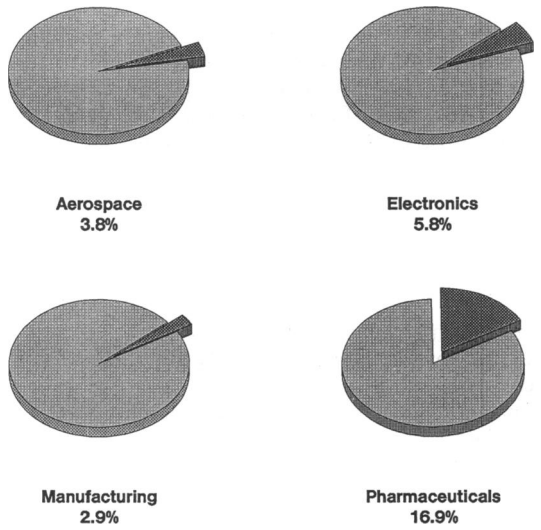

FIG. 3. Comparative proportions of sales invested by U.S. industries in R&D, 1993 (2).

may also evaluate the effect of an antibiotic's use for prophylaxis against postoperative infection. Clinical studies in the phase III program are typically double-blind trials and always require written informed consent. The use of placebo-controlled designs for the testing of antibiotics is not usually ethical. Exceptions may be surgical prophylaxis studies or the treatment of a disease for which no current therapy has been shown to be effective.

Broad-scale clinical trials, which include studies that enroll patient populations large enough to provide statistical power, are the hallmark of the phase III program. Ideally, the pharmaceutical manufacturer would like as varied a population as possible, including subjects from several geographic locales, to represent a broad demographic distribution. The population also can include outpatients (if appropriate) and inpatients (from both acute-care and extended-care facilities). Comparisons are made between the investigational drug and standard or alternative treatments for that infection. This program provides results that are considered pivotal for FDA approval of the intended product. Comprehensive statistical analyses of data, in addition to careful and complete reports of safety, are done in the phase III clinical trial program. These analyses are combined with those accumulated from the phase II trials. Depending on the targeted diseases, between 1,000 and 3,000 patients may be enrolled, and the program may take 2 to 3 years to complete.

Phase III studies may be designed to address special situations, such as infections in cancer patients and life-threatening infections. By definition, studies with these special populations are not likely to accrue large numbers of patients. Studies with special populations might, for example, target nursing home residents, in whom infections may be of particular concern. Another type of study might focus on drug interactions in immunocompromised or immunocompetent patients taking a number of other medications.

It is not unusual for the three clinical trial phases to overlap, or even for phase I, II, and III trials to be conducted simultaneously. One occasionally hears the term "phase zero" in connection with investigational drugs. This refers to the preclinical testing program conducted for approval of the IND application.

The NDA. When phase III trials have been completed, the pharmaceutical company will assemble the New Drug Application (NDA). "Assemble" is a key term, because this massive document is put together from the clinical, statistical, and bacteriologic findings of many studies, all integrated to provide the required information in a systematic and logical sequence (see Appendix).

An NDA contains both clinical and preclinical information, the latter having been submitted as part of the IND process, as well as additional information gathered since the IND submission. A summary of the contents of a typical NDA for an antibiotic is provided in the Appendix.

FDA review. After the FDA thoroughly reviews the NDA, the pharmaceutical company may receive a letter of approvability if the data are acceptable. This communication from the FDA initiates a meeting between the FDA and representatives of the manufacturer in order to provide the FDA with samples of promotional materials and advertising that will be used to promote the product and to reach an agreement on the contents of the product's package insert. When agreement is reached, the FDA will issue its approval for the pharmaceutical company to begin marketing the new product.

The package insert. The package insert, which is also called the P.I., is the product's complete prescribing information contained in a compact pamphlet that is packaged with the product for distribution to prescribers and pharmacists. The package insert information also appears adjacent to or as part of advertisements and promotional materials that mention the product's name and its intended use. For some products, the mere mention of the product's name requires the printing of full prescribing information with the advertisement. The labelling of some products contains a "black box" warning that alerts the prescriber to a significant toxic or adverse effect(s) that may occur when the drug is used.

Marketing and phase IV studies. The pharmaceutical company continues to conduct clinical studies, even after marketing has begun. These phase IV trials are designed to enhance the efficacy and safety database for the product, to generate reports that can become part of the medical literature, and to compare the product with competitors. The drug's use in phase IV trials is restricted to indications and dosages detailed in the package insert. In enhancing the product's database, postmarketing studies may be used to refine existing dosage forms, to develop new dosage forms, and to evaluate potential interactions with other drugs, foods, and the results of certain laboratory tests.

CONCLUSION

An ethical pharmaceutical company invests a great deal of human effort and financial resources into bringing an antibiotic drug to the marketplace. The clinical investigators and industry personnel expend tremendous effort in this type of endeavor because they believe new antibiotics can eradicate infectious diseases that incapacitate, maim, and kill. Once a drug is marketed, a company's efforts to achieve maximum benefit from that product do not stop. Ongoing studies explore the possibility of new indications and in today's climate, also look at evaluating quality of life and financial outcomes. They may specifically define new therapeutic timed regimens to fit within a cost containment environment, by shortening length of stay and length of treatment for a particular disease or allowing total outpatient treatment for a patient who previously required extensive hospitalization.

APPENDIX

Contents of a Typical IND

Includes data on:

- Identification of raw materials and solvents
- Chemical synthesis
- Manufacturing facilities
- Preparation of dosage form
- Packaging
- Reference standards and analytical methods
- Results of stability tests
- Evaluations of in vitro-in vivo animal models and animal toxicology
- In vitro results for testing against bacteria
- Foreign clinical reports
- Foreign clinical experience
- Lists and curricula vitae for proposed monitors and investigators
- Proposed clinical protocols

Clinical Trial Glossary

Investigator: clinician who conducts the study

Medical monitor: sponsor's representative who oversees all work

Sponsor: party who assumes all responsibility for the study and compliance with regulations; can be an individual, partnership, corporation, government agency, or nonprofit institution

Protocol: detailed plan for conducting the study

Investigational drug brochure: document that reports to the investigator all pertinent information about the experimental drug now on file with the FDA

Approved protocol: protocol that has been reviewed and found acceptable by the sponsor and by the investigator's Institutional Review Board

New drug: pharmacologic entity not yet recognized by regulatory authorities as being safe and effective under the conditions recommended for its use

Efficacy: effectiveness of a drug; ability of the drug to produce a specific, desired action under a given condition

Safety: absence of human toxicity; the potential of a drug substance to cause harm or undesirable pharmacologic effects

Forms FD1572 and FD1573: signed statements by the investigator to the FDA; these must be on file before investigational drug can be shipped for use in phase I, II, or III studies. The completed form contains information on the investigator, clinical laboratory, and Institutional Review Board and names of the subinvestigators.

Contents of a Typical NDA

- Summary and evaluation of data
- Chemistry-manufacturing methods for dosage form and quality controls
- Chemistry of the drug, including stability studies and expiration date
- Scientific rationale for use of this drug to treat specific infection(s) in humans
- Summary of preclinical studies and individual reports, including pharmacology, toxicology, and microbiology
- Summary of clinical studies and individual reports, including pharmacokinetic analyses and bioavailability
- Review of published medical literature
- Case report forms
- Summary of safety information from other sources, foreign or domestic, marketed or investigated
- Lists of investigators and their curricula vitae
- Clinical study protocols
- Samples and proposed package labelling of the drug product
- Normal ranges for clinical laboratories used
- Adverse event reports

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