Challenges and Opportunities in Bringing New Medications to Market for Pediatric Patients

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The discovery and development of new chemical entities (NCEs) is a risky and costly proposition that proceeds in a highly regulated global environment. Only one or two of every 10,000 compounds generated will display safety and efficacy profiles to enable approval. Because of the large number of preclinical and clinical studies required for registration of an NCE, the average time from synthesis to market exceeds 10 years, and average cost per drug is approaching $1 billion (Fig. 1). In addition, the period that a drug is on the market before similar medication becomes available has been reduced from 10 years to approximately 1.2 years. Bringing a new drug to market often involves thousands of people with different areas of expertise who synthesize the NCE, investigate its putative mechanisms of action and toxicology, evaluate its pharmacokinetics and clinical pharmacology, develop formulations and manufacturing processes, and finally, demonstrate its efficacy and safety in humans (Fig. 1). Each of the steps in this process is complex and requires extensive documentation. Of equal importance to a demonstration of efficacy is the focus on the safety of the compound. In fact, the effort devoted to acquisition and analysis of safety data by the sponsors (the pharmaceutical companies) is usually greater than the effort devoted to demonstrate efficacy.[1]

TARGET IDENTIFICATION/SELECTION

Based on disease pathophysiology, teams of scientists work to identify potential therapeutic targets and to synthesize stable and bioavailable molecules that selectively modulate the target. Early in the process, NCEs are tested for potential efficacy in animal models, and the most promising candidates are selected for further development. The low predictive validity of animal models of psychiatric disorders is a challenge to the identification of NCEs. Compounds with possible pediatric indications are also tested in juvenile animals, but the predictive validity of these models is also poorly established.

PRECLINICAL PHASE

When an NCE has shown promising results in preclinical efficacy models, extensive pharmacokinetic and safety data are obtained in several animal species. A battery of assays is used to investigate the compound's effects on the central nervous, cardiovascular, respiratory, and gastrointestinal systems. Investigation of reproduction and mutagenicity is conducted. One of the main goals of these studies is early identification of signs of intolerance and/or safety signals that will either eliminate the compound from further development or define maximal safe doses for testing in humans. As a consequence of early identification of potential safety signals, the vast majority of tested compounds are not considered suitable for further development. If the data support further testing, a sponsor will submit an investigational new drug application (NDA) that includes extensive preclinical safety and efficacy information and outlines the clinical development plan to the Food and Drug Administration (FDA) to request approval for the initial human studies.

CLINICAL TRIALS: PHASE I

The goal of this phase of drug development is to characterize the pharmacokinetics, safety, and tolerability of different doses of the NCE in human subjects and to define a maximum tolerated dose of the NCE. Consistent with guidance from the FDA and with the International Committee on Harmonization principles,[2,3] these studies are preferably conducted first in adult subjects. Once the pharmacokinetic, safety, and tolerability information in adults is evaluated, similar studies are conducted in pediatric subjects. Unlike phase I studies in adults that are generally performed in

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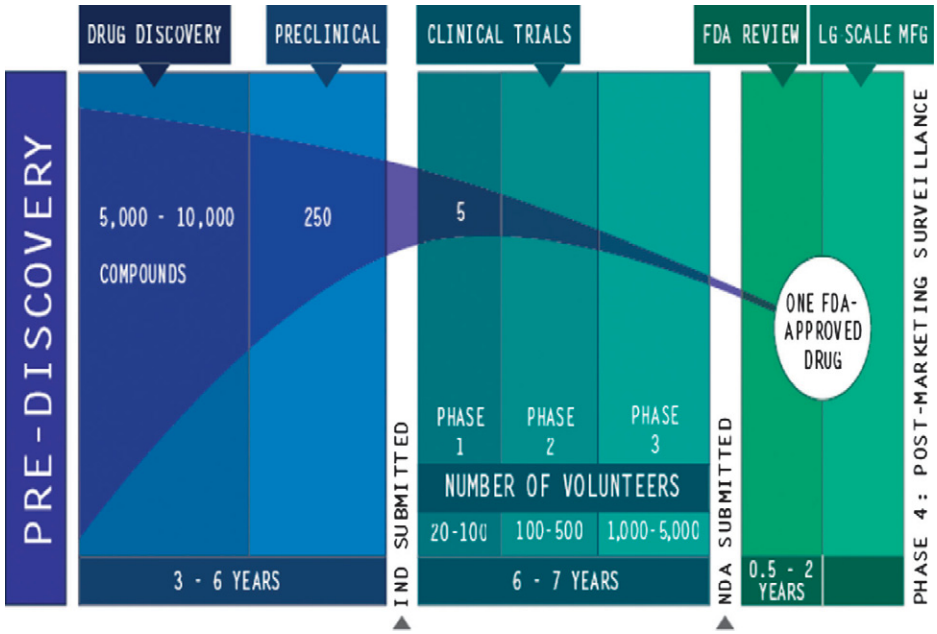

Fig. 1 Pharmaceutical research and development process. Reproduced with permission from Pharmaceutical Research and Manufacturers of America, Innovation.org.

control volunteers, studies in children enroll subjects with the target disorder because it is not considered ethical to expose subjects who cannot provide full informed consent to an NCE without any potential expected benefit.

CLINICAL TRIALS: PHASE II

After extensive preclinical investigations, the NCE is tested for efficacy in humans. Phase II studies are typically small, involving 100 to 500 patients with the target disorder.[4] When the target disorder is present in a similar form in adults, efficacy may be tested in adults prior to children. The goals of this phase of development are to determine if evidence of clinically significant efficacy exists and to begin to optimize the dosing regimen. Continued surveillance for safety signals occurs. The NCEs intended for the pediatric population may work to develop a child-friendly formulation or new dosage increments. Once a compound has exhibited convincing proof of efficacy, the risk for failing in further development is reduced substantially, with approximately 50% of compounds at this stage ultimately meeting regulatory endpoints for registration. Phase II studies are a critical part of the development program because the results of the phase II studies influence the decision to move forward to larger (significantly more expensive) phase III trials.

CLINICAL TRIALS: PHASE III

These are typically large (1,000–5,000 patients) placebo-controlled, double-blind, randomized trials in patients with the target disorder. The main aim of these trials is to gather efficacy and safety data for regulatory submission. These trials are resource intensive, taking several years to complete at a cost in excess of $300 million. Phase III trials typically involve many investigative sites in multiple countries. Demonstration of efficacy in at least two phase III studies is necessary for registration with the FDA.

The information from phase III trials, along with phases I and II information, preclinical studies, chemistry, and manufacturing information, is submitted to the regulatory agency (e.g., the U.S. FDA) as an NDA. Submittals are electronic and generally contain more than 100,000 pages of information. The time from application to the FDA Center for Drug Evaluation and Review usually takes approximately 60 days. Time from review to NDA action (letter of support) usually takes approximately 12 months under the Prescription Drug User Fee Act.[5] The FDA may request additional information from the company before approval or, in some cases, decline to approve a new drug.

CLINICAL TRIALS: PHASE IV (INCLUDING POSTMARKETING SURVEILLANCE)

These are postapproval studies undertaken for various purposes (e.g., provide further safety data, meet regulatory commitments). Increasingly, phase III and/or phase IV studies include quality of life/health outcomes that evaluate improvement in the health outcomes (beyond improvement in the symptoms of a disorder) that payers (e.g., Medicaid, insurers) want to see before including a new drug on their "covered" list. Depending on the objective, phase IV studies can be placebo-controlled and randomized, open label, or observational in nature. Compared with phases I to III trials, far more