Drug Development Process for a Product With a Primary Pediatric Indication

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This article reviews the drug development process in the United States, focusing on practical issues and new U.S. Food and Drug Administration (FDA) regulations and guidance for developing a drug with a primary pediatric indication. Atomoxetine, a novel treatment for attention-deficit/hyperactivity disorder (ADHD), is used to illustrate how the modern drug development process works and to highlight changes in the development of ADHD treatments since the introduction of the stimulants over 50 years ago. In addition to dealing with unique regulatory requirements and guidance, developing a drug for use in a pediatric population poses novel challenges in diverse areas including biomedical ethics, developmental pharmacology, and clinical trial design and implementation.

(J Clin Psychiatry 2002;63[suppl 12]:44–49)

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The development of a new chemical entity (NCE) for use as a medication in the United States is an expensive and time-consuming process that is closely regulated by the U.S. Food and Drug Administration (FDA). Historically, industry-sponsored studies of medications were conducted primarily in adults. The relative lack of industry-sponsored studies in the pediatric population resulted in a labeling disclaimer for most drugs that indicated usage in children was not studied or approved. As a result, children were described as "therapeutic orphans"[1] and ultimately the FDA and U.S. Congress identified the lack of pediatric drug data as a major public health concern. In response, the FDA implemented a number of new regulations and guidances during the mid-1990s with the goal of expanding and improving the information available to clinicians who use medications to treat pediatric patients.

The development of atomoxetine, a novel investigational treatment for attention-deficit/hyperactivity disorder (ADHD), was heavily influenced by the new pediatric regulations and guidance from the FDA. Atomoxetine is one of the few NCEs developed for a chronic, nonfatal, primary pediatric indication, and one of the first developed under the modern FDA rules. In contrast, stimulants, the only medications currently indicated for the treatment of ADHD, were first developed and approved over 50 years ago under very different regulatory requirements. The development of atomoxetine for use in a pediatric population posed unique challenges in diverse areas including biomedical ethics, developmental pharmacology, and clinical trial design and implementation.

This article reviews drug development in the United States, including recent changes in the area of pediatrics as a result of FDA initiatives. The case of atomoxetine is contrasted with those of the stimulants to illustrate recent changes in pediatric drug development.

FUNDAMENTALS OF DRUG DEVELOPMENT IN THE UNITED STATES

The development of an NCE in the United States is an expensive and time-consuming process (Figure 1).[2] The total time from synthesis of an NCE through preclinical research and clinical studies to FDA approval has increased steadily from 8.1 years in the 1960s to 14.2 years in the 1990s.[3] The median length of the approval process itself, from the submission of the new drug application (NDA) to final FDA approval, was 14 months in 2001 for all new drugs and 6 months for potential breakthrough, or priority drugs.[4] During the 1990s, the cost of developing a new drug, including the costs of failures and opportunity costs, was estimated to be $802 million.[5] Overall, the pharmaceutical industry's investment into developing new drugs has more than tripled over the last decade, from $8.4 billion in 1990 to an estimated $30.5 billion in 2001.[3] The largest single research and development cost, almost a third of the total, is the clinical evaluation of new compounds in phase 1, 2, and 3 trials (see Figure 2).[3]

Investigational drug trials in humans occur in 3 phases. Phase 1 trials are designed to determine the pharmaco-

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Presented at the roundtable "Novel Treatments for Attention-Deficit/Hyperactivity Disorder in Children and Adults," which was held November 15–17, 2001, in Boston, Mass., and supported by an unrestricted educational grant from Eli Lilly and Company.

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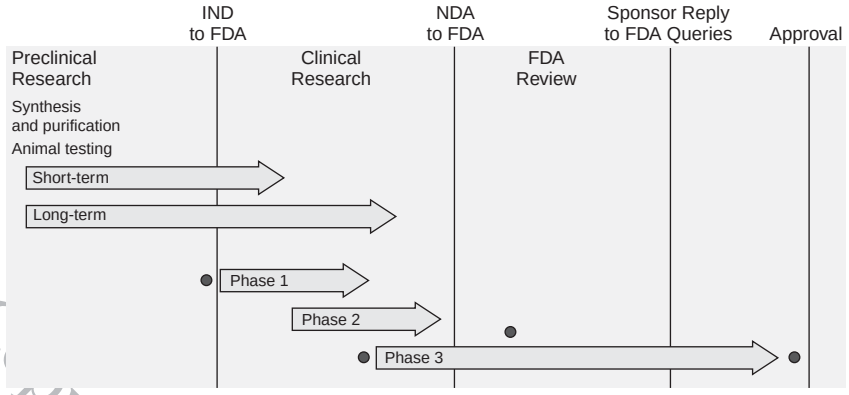
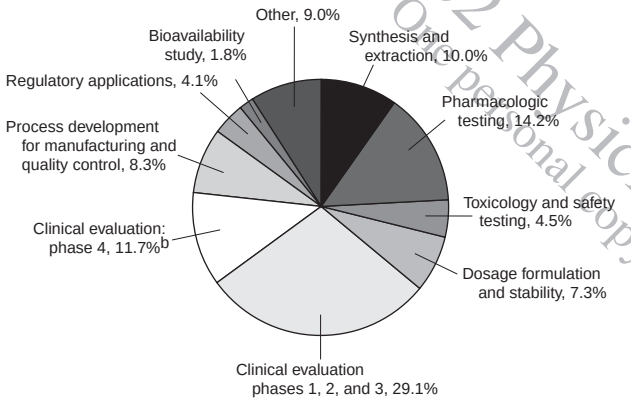
Figure 1. The U.S. Food and Drug Administration (FDA) Approval Process[a]



[a]Adapted from the Center for Drug Evaluation and Research.[2] Abbreviations: IND = investigational new drug application, NDA = new drug application. Symbol: ● = Sponsor encouraged to meet with the FDA.

Figure 2. Allocation of U.S. Drug Research and Development by Function[a]



[a]Data from the Pharmaceutical Research and Manufacturers of America.[3]
[b]Phase 4 consists of postmarketing surveillance and testing and reports to the FDA regarding any adverse side effects or toxicity.

kinetic and pharmacologic properties of the drug and to assess safety and adverse events, typically in a small number (fewer than 20) of healthy adult volunteers. If phase 1 data concerning the drug's safety, pharmacokinetics, and pharmacologic effects are favorable, then a company may elect to proceed with phase 2 trials. Phase 2 trials are designed to provide preliminary data on the efficacy, safety, and tolerability of the drug for a particular indication in a few hundred patients diagnosed with the condition for which the indication will be sought. Unfortunately, during phase 1 and phase 2 trials, many drugs "die" because they are found to have safety or tolerability problems or to be ineffective.

If the phase 2 trials suggest that the drug is effective, safe, and well tolerated for the desired indication, then large phase 3 trials may begin. Phase 3 trials usually include several hundred to several thousand patients and are designed to confirm the efficacy and safety of the drug in the general population for which it is intended. The International Conference on Harmonization (ICH)[6] has defined international technical guidelines and requirements for product registration. The ICH has recommended adequate evaluations of safety be made prior to the registration of an NCE intended for long-term use: short-term exposures should be evaluated in 1500 patients, 6-month exposures in 300 to 600 patients, and 1-year exposures in a minimum of 100 patients.

During the drug development process, the FDA encourages periodic discussion with the sponsoring company prior to decision-making. Once phase 3 trials have provided sufficient data on safety and efficacy, an NDA is submitted, and the FDA begins the review process. The ultimate goal of this process, which may take a few months to several years, is for the FDA to approve the United States Package Insert (USPI, "label") so that the new drug may be marketed in the United States.

The regulation of drugs in the United States began with the Food, Drug, and Cosmetic Act of 1938. Under this act, pharmaceutical manufacturers were only required to prove their products were safe. It was not until the passage of the Kefauver-Harris amendments in 1962 that the basic criteria for new drug approvals were changed to require that "drugs must be demonstrated by well-controlled studies to be effective for their intended uses as well as safe."[1] Ironically, while the Kefauver-Harris amendments were enacted as a result of the disastrous epidemic of infant malformations produced by thalidomide, the provisions of the amendments primarily benefited adults. In September 1996, the American Academy of Pediatrics testified to Congress that, despite efforts by the FDA to encourage pediatric labeling, "Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer in the labeling that they are not

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approved for use by children," although many of them "are widely used to treat illness in children."[1] Such arguments convinced both the FDA and Congress that additional efforts were needed to promote pediatric drug studies and pediatric labeling. Congress responded with Section 111 of the 1997 FDA Modernization Act (FDAMA), which allowed the FDA to grant an additional 6 months of marketing exclusivity when a pharmaceutical company conducted and submitted pediatric studies of a medication in response to a written request from the FDA.[7] Often referred to as the "carrot" by the FDA, the pediatric exclusivity provision of FDAMA was so successful at encouraging industry-sponsored pediatric studies that it was recently renewed via the 2002 Best Pharmaceuticals for Children Act.[8] In addition to implementing the pediatric exclusivity provisions of FDAMA, the FDA sought to promote pediatric drug studies and labeling by publishing a number of new regulations and guidance. The most important of these was the 1998 "Pediatric Rule."[9] The "Pediatric Rule," sometimes referred to as the "stick" by the FDA, requires a pediatric assessment in clinical trials, including applications for drugs with a primary pediatric indication. Other important regulations and guidance published in recent years by the FDA address the design and conduct of pediatric clinical trials,[10] including trials of psychoactive drugs[11] and ethical issues.[12] Atomoxetine, a novel treatment for ADHD, is one of the first NCEs submitted to the FDA for a primary indication in the pediatric population under these new regulations and guidance.

Psychotropic Drug Development

Consistent with practices in the rest of the pharmaceutical industry, prior to the mid-1990s, premarketing studies (phases 1 through 3) of psychiatric medications were conducted almost exclusively in adults. As a consequence, FDA-approved labeling was for adult indications, such as depression, and the only pediatric labeling was usually a disclaimer about the lack of studies in children and adolescents. A few postmarketing pediatric studies were conducted for pediatric cases of the primary (adult) indication for the drug (e.g., childhood depression) or for child-specific indications (mental disorders usually first diagnosed during childhood, for example, ADHD). Many were small, single-site, investigator-initiated trials with limited or no support from industry and not intended to provide information for pediatric labeling. Upon the implementation of the pediatric exclusivity provisions of FDAMA and the "Pediatric Rule" in 1997 and 1998, a change began to occur in psychiatric drug development. Companies still pursued adult psychiatric indications first, but increasingly adult studies were followed by large, multisite, well-controlled pediatric trials. The pediatric trials were based on written requests from the FDA and were designed to evaluate the safety and efficacy of psychotropic medications for pediatric cases of the primary (adult) indication. While this represented progress in pediatric psychopharmacology research, clinical trials of psychotropic medications for child-specific indications, such as autism, continued to receive limited industry support. It was not until the industry began to develop new treatments for ADHD, such as atomoxetine, that extensive phase 2 and phase 3 clinical trials were conducted with children and adolescents.

ADHD Treatments Then and Now

Historically, all of the medications approved by the FDA for the treatment of ADHD were stimulants. Amphetamine was synthesized in 1931,[13] and the field of child psychopharmacology began in 1937 when Bradley[14] described the beneficial effects of Benzedrine, a racemic mixture of amphetamines, on children with minimal brain dysfunction, a historical description for ADHD. Methylphenidate was synthesized in 1944 as an alternative to the amphetamines.[15] Both the amphetamines and methylphenidate were originally approved as safe and marketed under the Federal Food, Drug, and Cosmetic Act of 1938, and both were used for the treatment of "minimal brain dysfunction" in the 1950s and 1960s.[16] These drugs were subsequently approved as safe and effective following the passage of the Kefauver-Harris amendments in 1962. Pemoline was synthesized in 1962[17] and approved for the treatment of minimal brain dysfunction in 1975.[18] The current labeling of these drugs is often based on data that were required as part of their original approvals, and dates back to that time. Over the intervening years, the FDA has implemented additional requirements for establishing the safety and efficacy of NCEs as part of the approval process.

Recently, several medications have been introduced for the treatment of ADHD. These products are extended-release formulations of the amphetamines or methylphenidate (Adderall XR, Concerta, Metadate CD, Ritalin LA) or a single stereoisomer of methylphenidate (Focalin). None of these new medications was an NCE. As a result, these medications were treated much like generic medications and were able to base much of their applications to the FDA on the original applications that had led to the approvals of the amphetamines and methylphenidate. Because of this, the preclinical and clinical data required for these new versions of the stimulants were less extensive than those required for an NCE.

DEVELOPMENT OF A NEW PEDIATRIC DRUG: ATOMOXETINE

Atomoxetine is a nonstimulant that is being considered for approval by the FDA for the treatment of ADHD. Atomoxetine is a highly specific inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other neurotransmitter receptors or transporters. Atomoxetine is the first NCE developed for the treatment

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Table 1. Additional FDA Requirements for a New Chemical Entity (NCE) for a Primary Pediatric Indication[a]

Most safety and efficacy studies conducted with children and adolescents
Meet ICH exposure requirements with pediatric patients
Developmental toxicology studies using immature animals
Pharmacokinetic studies and pilot studies in adults before in children
Some pharmacokinetic studies in children

[a]Abbreviations: FDA = U.S. Food and Drug Administration, ICH = International Conference on Harmonization.

of ADHD since pemoline. To our knowledge, atomoxetine is also the first treatment for a chronic, nonfatal, primary pediatric indication to go through the modern FDA process requiring efficacy and safety data in children, which has presented some unique challenges to the sponsor in attempting to obtain FDA approval.

Challenges to the Development of a Medication With a Primary Pediatric Indication: FDA Requirements

As part of the new pediatric regulations and guidance, the FDA now requires that sponsors seeking approval for an NCE for a primary pediatric indication conduct most safety and efficacy studies in children and adolescents (Table 1). In the case of atomoxetine, this meant that the number of human exposures required under ICH guidelines (1500 acute exposures, 300 to 600 exposures for 6 months or more, and 100 exposures for a year or more)[6] had to be in children and adolescents. This makes atomoxetine somewhat unique in the world of psychopharmacology, because, unlike with many other medications, there are far more atomoxetine data available from studies with children and adolescents than with adults.

The FDA recognizes that the toxicology of drugs used to treat chronic childhood disorders must be evaluated not only in traditional adult animal models, but also in systems that test for developmental toxicity. Because atomoxetine was being studied as a treatment for ADHD, a chronic disorder that often requires long-term treatment in developing children, the FDA required that the sponsor conduct preclinical toxicology studies in immature animals. These studies, which we believe are the first of their kind in the field of psychopharmacology, examined the effects of chronic atomoxetine exposure on physical, sexual, neurologic, and behavioral development in several species, primarily rats and dogs.

While pediatric trials were essential to the development of atomoxetine, under FDA guidelines, some clinical research could not be conducted in children. This was especially true of phase 1 trials examining the safety and pharmacokinetics of atomoxetine. Such phase 1 trials are usually conducted in "normal volunteers," healthy individuals without the condition for which a drug is targeted, and these studies are necessary for drug development and approval. For a drug intended to treat ADHD, such as atomoxetine, it might be argued that the appropriate normal volunteers for phase 1 studies are children. However, FDA ethical guidelines[12] essentially prohibit giving an experimental medicine to a normal child because this type of study offers no possibility of direct benefit to the child, while exposing the child to more than minimal risk. An alternative approach was devised in which typical phase 1 trials of atomoxetine were conducted in normal adults to provide safety and pharmacokinetic data. Next, a proof-of-concept trial was conducted to test the efficacy of atomoxetine for ADHD in adults. This was accomplished via a double-blind, placebo-controlled, crossover trial with 22 adults with ADHD.[19] In this trial, treatment with atomoxetine was associated with a significant reduction in ADHD symptoms by the second week of the study, suggesting that children with ADHD could benefit from treatment with this medication. This pilot study paved the way for a small open-label study in children, which also found the drug to be safe and effective, and which provided safety and pharmacokinetic data in pediatric patients.[20,21] The safety and pharmacokinetic data obtained from these studies in adults and children were then compared in order to establish that the results of other phase 1 studies in adults could be extrapolated to the pediatric population.

The approach of studying atomoxetine in adults first and then in children was also used to answer several additional questions about atomoxetine. For example, atomoxetine is metabolized primarily via the cytochrome P450 2D6 (CYP2D6) pathway.[22] Most individuals have functioning copies of the CYP2D6 isozyme and are described as extensive metabolizers. Approximately 5% of the population lack the CYP2D6 isozyme and are described as poor metabolizers. The plasma half-life of atomoxetine is approximately 5 hours in extensive metabolizers, and 24 hours in poor metabolizers. As a result, patients who are poor metabolizers are exposed to higher plasma levels of atomoxetine than patients who are extensive metabolizers. To determine if atomoxetine could be administered without regard for the patients' metabolic status, it was necessary to carefully evaluate the drug in poor metabolizer patients. In order to minimize the risk to pediatric patients, phase 1 studies were conducted in adult poor metabolizer volunteers to establish safe dosing guidelines before dosing independent of metabolic status was introduced in phase 3 pediatric clinical trials.[23]

Non-Regulatory Challenges to the Development of a Primary Pediatric Medication

There are several other factors that complicate the study of a new psychotropic drug in children. Pediatric psychopharmacology is a relatively new area of specialization in medicine. A limited number of clinicians regularly treat pediatric patients with psychotropic medications, and an even smaller number of clinicians have formal psychopharmacology research training and experience. Of this elite

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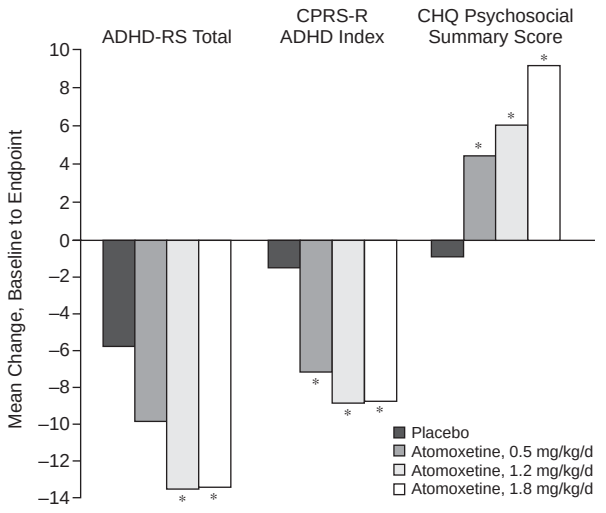
group, still fewer pediatric psychopharmacologists have the necessary resources and staff required to conduct a large, registration-quality study of psychotropic medications in children. Because of the increase in industry-sponsored studies in response to the FDA's pediatric initiative, as well as an increase in pediatric psychopharmacology studies funded by the National Institutes of Health (NIH) and other sources, there is competition for the limited number of established pediatric psychopharmacology research sites. Furthermore, within those research sites there are often several ongoing pediatric studies sponsored by a variety of institutions that compete for the same groups of patients. This competition is most problematic in the case of less common or rare disorders, such as childhood schizophrenia; but even for more common conditions, such as ADHD, a competition between studies may create difficulties at some sites.

There are other important barriers to the recruitment of patients for pediatric clinical trials. Understandably, parents are often reluctant to enroll their children in an investigational drug trial, especially when there are limited pediatric data available for the drug being studied, as was the case early in the development of atomoxetine. As pediatric data are accumulated for an investigational drug, it becomes easier to reassure parents concerned about safety issues. However, recruitment does not necessarily become easier, because parents often are concerned that their child may be randomized to placebo rather than active treatment during a phase 3 trial. One way to address this concern is to offer all children who complete an acute, double-blind, placebo-controlled trial the opportunity to roll into an open-label extension study in which they are assured of receiving the investigational drug.

In an era of managed care and restricted formularies, medical economics is another challenge to the successful development of any new drug. While the FDA "only" requires evidence of safety and efficacy for approval, the agency and those who pay for health care are also interested in the effect of any new treatment on the quality of life and functioning of patients, often referred to as health outcome measures. Historically, industry-sponsored ADHD trials of the stimulants have not included such measures of health outcomes. Nevertheless, such data were thought to be important to the development of atomoxetine, so it was decided to include a health outcomes assessment, the Child Health Questionnaire (CHQ), in one of the phase 3 pediatric trials. The CHQ is a general pediatric instrument, not specific to ADHD, that measures a number of psychosocial items such as family activity and the child's emotional state and level of self-esteem. The trial selected was an 8-week study of 297 children and adolescents with ADHD that compared 3 doses of atomoxetine (0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day) to placebo.[23] The primary efficacy measure in this study was the ADHD Rating Scale IV (parent version, ADHD-RS). Secondary efficacy measures included the CHQ and the Conners' Parent Rating Scale-Revised (CPRS-R). The results of this trial (Figure 3) demonstrated not only that atomoxetine was superior to placebo at reducing the core symptoms of ADHD, as measured by the ADHD-RS and the CPRS-R ADHD Index, but also that atomoxetine improved the quality of life and social/family functioning of children and adolescents with ADHD, as measured by the CHQ.

Figure 3. Efficacy of Atomoxetine in Attention-Deficit/Hyperactivity Disorder (ADHD)[a]



[a]Data from Michelson et al.[23] Abbreviations: ADHD-RS = ADHD Rating Scale, CHQ = Child Health Questionnaire, CPRS-R = Conners' Parent Rating Scale-Revised.
*$p < .05$ vs. placebo.

CONCLUSION

The current FDA requirements for the approval of a new drug are appropriately rigorous and present a challenge to the development of NCEs for primary pediatric indications. Atomoxetine, a novel medication for ADHD, was one of the first NCEs developed under the stringent new FDA pediatric regulations and guidelines. Additional challenges to the development of NCEs in pediatric psychopharmacology include ethical issues in pediatric studies, a limited infrastructure to support clinical trials, difficulties in patient recruitment, and an economic need for health outcomes data in a medical specialty with little background in collecting such information.

Drug names: amphetamine (Adderall), fluoxetine (Prozac and others), methylphenidate (Concerta, Ritalin, Metadate, and others), pemoline (Cylert and others).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, atomoxetine is not approved by the U.S. Food and Drug Administration for the treatment of attention-deficit/hyperactivity disorder.

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