

Pediatric Pharmacotherapy

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Recent changes in the policies requiring the inclusion of pediatric-specific dosing information on labeling for newly-marketed medications have increased interest by pharmaceutical manufacturers in pediatric research. As a result, health care professionals involved in the care of infants and children are more likely than ever to become involved in investigational drug research. The purpose of this article is to provide a brief review of the regulatory processes involved with the approval of a medication by the United States Food and Drug Administration and to highlight those areas affecting research in children (1-6).

The Food and Drug Administration (FDA) is mandated by Congress to ensure the safety and efficacy of all new medications. In 1938, Congress passed the Food, Drug, and Cosmetic Act, which created the agency we now know as the FDA. This act, requiring pharmaceutical manufacturers to provide evidence of the safety of all new medications, resulted from a national tragedy. During the previous year, more than 100 people had died from ingesting sulfanilamide elixirs that contained ethylene glycol (1,4). In 1962, the Food, Drug, and Cosmetic Act was amended to require evidence of efficacy as well as safety. These new regulations, the Kefauver-Harris Amendments, also required investigators and manufacturers to notify the FDA prior to testing a new medication in human subjects (4). Although these measures are often taken for granted, governmental regulation of medication safety and efficacy has been in existence for a relatively brief period of time.

New Drug Development

The process by which the FDA gauges the safety and efficacy of new medications can be divided into five discrete phases. These phases encompass pre-clinical studies and research development (pre-clinical phase), clinical research (phases 1, 2, and 3), and post-marketing surveillance (phase 4). The pre-clinical phase includes initial identification of the drug as well as in vitro studies and tests conducted in animal models to establish pharmacological characteristics. In recent years, the use of computer simulations has revolutionized much of the pre-clinical evaluation process (7). Phase 1 clinical trials begin the period of investigation in humans. These trials establish initial dosing, pharmacokinetic, and toxicity information. Most of the studies during phase 1 are conducted in 20 to 100 healthy volunteers. Phase 2 trials are generally larger and involve patients who might benefit from treatment with the new drug. Aside from establishing efficacy, these trials often reveal adverse effects as well. Phase 3 trials enroll even larger numbers of patients to ascertain specific information such as equivalency to standard therapies or the incidence of an adverse effect in a larger population. Phase 4 post-marketing data is gathered from a variety of sources and includes reports of adverse effects, inspections of manufacturing facilities, and studies to expand or refine dosing information (1,2). The sponsor, typically a pharmaceutical manufacturer, submits data to the FDA at two separate intervals during the new drug development process. After the completion of the pre-clinical phase, the sponsor submits data to the FDA by filing an investigational new drug application (IND). The IND contains all data gathered on the medication up to that time along with the proposed plans for studying the drug in humans. A panel made up of FDA staff has 30 days from the time that an IND is filed to determine whether clinical studies will be allowed. The FDA review panel may allow testing to begin or require the sponsor to provide more information before proceeding. It has been estimated that only one

out of every five drugs given an IND will eventually reach final approval for marketing (2).

At the end of the phase 3 trials, the investigator submits a new drug application (NDA). A NDA provides a compilation of all data supporting the safety and efficacy of a new drug. As with the IND review, a panel of FDA personnel is formed to review each application. The average time for processing a NDA is 24 months and some applications may be up to 100,000 pages in length (2). This extensive review process often involves both FDA staff and an advisory committee which can recommend approval or suggest further testing of a new drug. Advisory committees are composed of expert consultants in academic and clinical practice as well as consumer representatives. Several UVA physicians have served on FDA advisory committees.

Throughout the IND/NDA review process, the FDA uses a classification system to describe new medications being investigated. A basic knowledge of this system may be useful to clinicians participating in new drug research. The classes are presented below (2,6).

Chemical Types

- Type 1- New Molecular Entity
- Type 2- New Ester or Salt
- Type 3- New Formulation
- Type 4- New Combination
- Type 5- New Manufacturer
- Type 6- New Indication
- Type 7- New NDA for Drugs Marketed Prior to 1962

Therapeutic Potential

- Type P- Priority Review, Therapeutic Gain
- Type S- Standard Review
- Type AA- AIDS Drug
- Type E- Drug for a Life-threatening Illness
- Type F- Drug Involved in Fraud Policy Violation
- Type G- Previous Type F Drug with New Validation
- Type N- Nonprescription Drug
- Type V- Orphan Drug

A drug under investigation may be described by more than one of these types. For example, a new therapy for patients with AIDS might be classified as a Type 1-AA.

Expedited Review

In 1987, the FDA introduced new steps to expedite the review of medications for the treatment of serious or life-threatening diseases (1-3). This change in policy came about as limitations in the current treatment of AIDS became apparent. These policies, however, apply to more than just AIDS therapies. The FDA has provided examples of other diseases which might be applicable. Life-threatening conditions include advanced cases of AIDS or severe combined immunodeficiency disorder, advanced congestive heart failure or emphysema, recurrent sustained ventricular tachycardia or fibrillation, advanced metastatic cancer, bacterial endocarditis, and subarachnoid hemorrhage. Some examples of serious conditions include: Alzheimer's disease, advanced multiple sclerosis or Parkinson's disease, certain forms of epilepsy or diabetes, as well as advanced stages of other chronic illnesses (3).

There are two mechanisms for providing new therapies for these patients: expanding patient access during clinical trials and accelerating the testing/review process. Within the scope of expanding patient access to investigational medications, there are two pathways: treatment INDs and parallel track use. A treatment IND allows the investigator to provide the drug to patients who have a life-threatening disease for which there is no satisfactory alternative therapy already available. The investigator must be in the process of conducting standard clinical trials throughout the duration of the treatment IND. A treatment IND is typically granted while a drug is in phase 3 trials (1). This process is familiar to many clinicians as "compassionate use" availability. The development of the treatment IND system was done to formalize the use of investigational drugs outside protocols and to provide a mechanism for collecting and analyzing this additional patient data.

Information regarding the availability of investigational drugs under the treatment IND program is published in the [FDA Drug Bulletin](#) and in a monthly column from the FDA in [JAMA](#). It is recommended that clinicians interested in obtaining a drug through this system contact the sponsor directly (1).

The parallel track is a similar mechanism to the treatment IND, but allows use of the medication in a controlled fashion even earlier in the development period. The regulations allowing this method of review were formalized in 1992. In the parallel track method, patients may receive treatment during the period when phase 2 trials are being conducted. The purpose of this system is to allow patients who do not qualify for inclusion into phase 2 trials to have access to new therapies. As with the treatment IND system, the use of a parallel track is reserved for serious or life-threatening disease states where there are few or no therapeutic options available. Surfactants were originally studied under a parallel track plan.

Unlike the above methods for expanding access during the usual approval process, the system for accelerated approval is designed to get the new product on the open market more quickly. While the average length of time from the discovery of a new therapeutic entity until marketing averages eight to nine years, the accelerated programs can reduce that time to three to four years (1).

There are two methods for accelerating approval: the use of surrogate markers to determine efficacy and the use of telescoped trials. Surrogate markers might be used when the ultimate outcome of therapy will not be known for a prolonged period. For example, a reduction in mortality may be the desired outcome for a new AIDS therapy, but changes in CD4+ count or the frequency of infections may be acceptable substitutes to assess benefit more rapidly. "Telescoping" of clinical trials involves the enrollment of larger patient populations during phase 1 and phase 2 trials, often eliminating the need for phase 3 trials. Didanosine (DDI) was one of the first drugs to reach the market in the United States after an accelerated FDA approval process.

There remains considerable controversy over the correct emphasis on expeditiously reviewing new therapies and making them available to seriously ill patients in contrast to the need to protect society as a whole. There is justifiable concern regarding the potential for the release of ineffective or unsafe therapies. In the original Cardiac Arrhythmia Suppression Trial (CAST), several antiarrhythmics were found to suppress premature ventricular contractions, a surrogate endpoint for fatal arrhythmias in patients following myocardial infarction. Further investigation, after the acceptance of these agents by many clinicians, revealed that the mortality rate in the medically-treated patients was more than twice that of the controls. The risk versus benefit of these new FDA policies will only become apparent as more drugs are marketed after expedited review.

Flexible Trial Designs and Pediatric Labeling

When the new regulations regarding the requirements for pediatric labeling information were announced in January 1995, the need for studies conducted in children became apparent. The new regulations state that all NDAs submitted to the FDA must now contain information on pediatric use. If a sponsor does not include pediatric information, a specific explanation of why the drug should not be used in children must be provided. In addition, currently marketed drugs that are used in children but do not carry pediatric (FDA-approved) labeling must undergo reassessment under a supplementary NDA prior to December 1996. As most health care professionals are aware, the traditional method of drug development has focused on testing in healthy adult volunteers followed by experience in patients expected to benefit from the new therapy. Even therapeutic (phase 2 and 3) trials typically excluded patients under 18 years of age. These policies were not only the result of sponsor-driven protocols for drug testing, but also of the FDA's policies regarding the acceptability of trial data. Prior to 1995, most drugs were approved on the results of two or three large-scale comparative clinical trials performed in adults. In response to the need for information about the effects of drugs in unique patient populations, such as children, the FDA has relaxed their criteria for study design to include studies enrolling a variety of patient types. In addition, NDA data may include material

gathered from open-label, noncomparative studies. As a result, it is anticipated that many more pediatric health care providers will be involved in investigational drug research.

In summary, the ongoing changes in the United States Food and Drug Administration reflect an attempt to allow more patients access to beneficial therapies while maintaining the original mandate requiring the establishment of the safety and efficacy of these new medications. The new regulations regarding children should provide significant benefits to health care professionals caring for children, by providing more therapeutic information on marketed drugs and by increased support for clinicians performing research in pediatric medicine.

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FDA News

The FDA is currently evaluating changes in the format of medication labeling. These regulations will affect not only bottle and vial labels, but also packaging and product information sheets (package inserts). The proposed format will include a section devoted to new information which will be periodically updated by the drug's manufacturer. In addition, the current sections will be numbered to facilitate referencing. The ordering of the sections also will be changed, with warnings and prescribing information moved to the beginning of the labeling information and less frequently used information, such as pharmacology, will be nearer the end. Recommendations for patient counseling will be found at the end of the document to allow clinicians to more easily copy this information for their patients.

The changes in format were based on the results of a national survey of physicians and several focus groups. A prototype label, using a fictitious new drug, was presented at a public FDA meeting on October 30th. Written comments about the proposed changes will be accepted until January 19, 1996. Copies of the prototype can be obtained by contacting the FDA at 1-800-342-2722, refer to document number 0212 when calling.

Pharmacology Literature Review

Complications of CF

The authors present a brief overview of the current therapies for the complications commonly associated with cystic fibrosis. The article focuses on two aspects of CF, respiratory and nutritional problems. The section on pulmonary issues addresses the use of standard medications, such as bronchodilators, as well as newer therapies like amiloride, dornase alfa (recombinant DNase), and anti-inflammatory agents. Nutritional supplementation with pancreatic enzymes and vitamins also are described. Sanchez I, Guiraldes E. Drug management of noninfective complications of cystic fibrosis. **Drugs 1995;50:626-35.**

Cyclosporine-Norfloxacin Interaction

This report originated as an observation that children with renal transplants who were receiving norfloxacin as prophylaxis for urinary tract infections required significantly less cyclosporine to achieve desired serum concentrations than those not on prophylaxis. The authors then performed *in vitro* studies to confirm their hypothesis that norfloxacin inhibits hepatic cytochrome P4503A4, the enzyme responsible for cyclosporine metabolism. McLellan RA, Drobitch RK, McLellan H et al. Norfloxacin interferes with cyclosporine disposition in pediatric patients undergoing renal transplantation. **Clin Pharmacol Ther 1995;58:322-7.**

Lamotrigine Update

Another extensive review of lamotrigine, a new antiepileptic, has been published, updating readers with new information gathered from clinical experience. Health care professionals working with children who receive lamotrigine may be interested in new information on adverse effects, particularly the potential for severe dermatologic effects. In addition, the authors review the literature regarding the extended use of this medication in children with refractory seizure disorders, including those with mixed seizure types. Fitton A, Goa KL.

Lamotrigine: An update of its pharmacology and therapeutic use in epilepsy. **Drugs 1995;50:691-713.**

Ondansetron Pharmacokinetics

As the use of ondansetron expands beyond the realm of chemotherapy-induced nausea and vomiting, the need for further research in children has grown. The authors of this study evaluated the pharmacokinetics of ondansetron in 21 children undergoing ENT surgery. The patients were divided into two groups: ages three to seven years and ages 8-12 years. Mean clearance values were 0.5 L/hr in the younger patients and 0.39 L/hr in the older children. Half-life values were 2.6 hours and 3.1 hours for the younger and older children, respectively. The authors concluded that the pharmacokinetic parameters observed in both groups of children were similar to adult values. Spahr-Schopfer IA, Lerman J, Sikich N et al. Pharmacokinetics of intravenous ondansetron in healthy children undergoing ear, nose, and throat surgery. **Clin Pharmacol Ther 1995;58:316-21.**

Propofol Use in Intensive Care

While focusing primarily on adult patients, this new review of propofol's use in the ICU includes basic information that may be of interest to pediatric intensive care clinicians as well. The authors have provided tremendous detail in their description of the pharmacodynamic properties of propofol, including not only its beneficial sedative effects but also its adverse effects. Fulton B, Sorkin EM. Propofol: An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. **Drugs 1995;50:636-57.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics committee at their meeting on 10/27/95:

1. Nedocromil (Tilade®), an anti-inflammatory agent used in the treatment of asthma, was added to the formulary. It is available in a metered-dose inhaler. Although approved for children over 12 years of age, nedocromil has been used in younger asthmatic patients. In a recent trial, nedocromil was shown to be as efficacious as cromolyn therapy in 17 children with asthma (J All Clin Immunol 1994;94:684-8.).
2. Nalmefene (Revex®) was also approved for use at UVa. Nalmefene is an opioid antagonist, similar to naloxone (Narcan®), but with a longer duration of action. It is important to note that this product is available in two strengths. It is used in a

- 100 mcg/ml concentration for reversal of opioid anesthesia and in a more concentrated strength of 1 mg/ml for reversal of opioid overdose.
3. Other products added to the formulary include: magnesium gluconate (Magonate®) and stanozolol (Winstrol®), an anabolic steroid. In addition, some medications in current use have become available in new dosage forms. Cyclosporine is now available in a microemulsion formulation (Neoral®) offering improved bioavailability. Sumatriptan (Imitrex®) is available in tablet form.
 4. An injectable form of amiodarone (Cordarone®) was not approved for formulary addition.
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