## Featured Article

# TESTING DRUGS ON CHILDREN: THE PHARMALOGICAL AND ETHICAL RATIONALES FOR PROVIDING A BETTER STANDARD OF CARE TO PEDIATRIC PATIENTS

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**Children have been dubbed "therapeutic orphans" due to limited labeling of drugs with pediatric uses. The FDA has made strides to combat this with the Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003, which provide incentives and mandates, respectively, for conducting pediatric drug trials. Such studies are necessary for determining appropriate pediatric dosages; the physiological and pharmacological differences between adults and children render it dangerous to estimate doses based on size alone, though this is common practice. The greatest differences exist between adults and newborns/infants, thus more studies must target the latter group. Opposition to pediatric testing can be resolved by applying the Pediatric Pharmaceutical Research Unit model to increase patient recruitment and to utilize more child-friendly techniques, by understanding the financial advantages of pediatric trial, and by ensuring that patients are exposed to minimal risk of physical and psychological harm. Overall, pediatric studies are key in increasing the knowledge regarding pediatric drugs and improving the pediatric standard of care.**

### Introduction

Reacting to the thalidomide tragedy of the late 1950s, the United States Congress passed the Drug Amendments of 1962. These laws required a drug's safety and effectiveness to be established before marketing,[1] in effect mandating clinical trials for all drugs sold in the United States. While this legislation was a milestone in medical history, physician Harry Shirkey found the lack of attention given to pediatric drugs unacceptable.[2, 3] Pediatric testing, unlike adult testing, was not explicitly mandated, and pediatric disclaimers could be added to drug labels in order to circumvent the new legislation. Shirkey called this disclaimer labeling "orphaning," and in turn called children "therapeutic orphans."[2, 3] He believed that the medical field had shirked its responsibility to provide safe and effective treatments for pediatric patients. Significant change would not come for nearly 30 years, with new Food and Drug Administration (FDA) regulations in 1994.

Due to new legislation and increased authority of the FDA over the last decade, hundreds of drugs have been assessed for pediatric use.[4] Doctors can now prescribe many more drugs to children, from antimicrobials to antipsychotics,[4] based on clinical pediatric data and not trial and error guesswork. Pediatric drug trials have paved the way for safer, more effective pediatric medicine. The FDA has made significant progress in getting the medical industry to recognize its accountability to children, but all parties are a long way off from relieving children of the designation as therapeutic orphans. For instance, only five of the 80 most commonly prescribed drugs to newborns and infants are labeled for pediatric use.[5] To achieve drug standard parity with adult dosages, pediatric trials must continue and expand for pharmaceutical products.

In this paper, I will explore the issues of pediatric drug testing. First, I will present a brief history of the legislation regarding pediatric testing and discuss how recent laws have increased testing due to incentive programs and mandates. Second, I will examine the rationale for continued testing, which is that the physiological and pharmacokinetic differences between children and adults make it dangerous to prescribe children drugs that are not listed for pediatric use and to extrapolate data regarding pediatric drug dosages from adult drug trials. In particular, I will emphasize the importance of testing on very young children, including newborns and infants, who stand to gain the most from age-specific data since their physiology is most different from adults. Finally, I will evaluate the arguments against pediatric testing and establish the critical need for testing.

### History of Pediatric Drug Testing

The FDA first targeted pediatric drug testing in 1994 with regulations that "encouraged" drug companies to conduct pediatric studies of new drugs that seemed to have pediatric applications.[6,7] Since the passage of the 1962 Drug Amendments many drugs commonly prescribed to children had never been tested on children in a clinical setting. Even morphine, "which is a standard, necessary pain medication," was given to children despite the fact that its safety and effectiveness was not established.[7] Because of this, doctors have been forced to "blindly grope" for appro-

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priate pediatric drug dosages, notes Dr. Gloria Troendle, a medical reviewer from the FDA.[8] Dr. Paula Botstein, deputy director of the FDA's Office of Drug Evaluation, when the 1994 regulation began, explained:

"Pediatrics textbooks usually give drug dosages, but the source and reliability of the information are seldom specified. Mostly, pediatric doses of drugs that have not been formally studied in children are simply established by experience. Some drugs are used all the time in children. Anesthesia drugs would be a good example. They may not be labeled or approved specifically for children, but children routinely need major surgery. So physicians build up the experience in using the drugs. It's not the ideal way."[7]

Botstein responded to the question of why pediatric regulation had taken so long in a 1995 interview, saying that the new regulation was due to "pediatricians infiltrating the FDA."[7] Pediatricians' increased influence on the FDA, whether by employment or lobbying, forced the administration to pay attention to the overlooked needs of children.

While there was an increase in the number of studies in the years following this initial regulation,[7] the FDA developed real authority in moving drug companies away from disclaimer labeling through the enactment of the FDA Modernization and Accountability (FDAMA) Act in 1997.[9] A particularly critical piece of the legislation was the Better Pharmaceuticals for Children Act (BPCA), a section of FDAMA that created a voluntary incentive-based program for drug companies.[10] In exchange for conducting pediatric studies on new and already marketed drugs, drug companies would receive a six-month extension on patent and marketing exclusivity for their drug.[11]

Where the FDA's carrot is market exclusivity, its stick is the Pediatric Rule. The 1998 Pediatric Rule required not-yet-approved drugs as well as already marketed drugs to be studied in pediatric patients. However, in 2000 the Association of Physicians and Surgeons sued the FDA arguing that the Pediatric Rule exceeded the FDA's statutory authority. The rule was suspended, but, following the enactment of the BPCA as an independent piece of legislation in 2002, Congress decided to continue to enforce the rule.[6] The Pediatric Research Equity Act (PREA) of 2003 codified the Pediatric Rule, and both BPCA and PREA were reauthorized in 2007 under the Food and Drug Administration Amendments Act (FDAAA).[9]

The pairing of the FDA's exclusivity incentive and the "pediatric rule" has had marked success in getting drug companies to conduct pediatric drug studies, which provide invaluable information to guide doctors in prescribing appropriate doses of prescription and over the counter drugs (i.e. ibuprofen) for children. The pediatric-related legislation encouraged drug studies that established the safety and efficacy of ibuprofen as an antipyretic and analgesic for children from six months to two years old,[12] whereas previously information was only available for children over two. It was important to expand the pediatric labeling for ibuprofen because it was routinely used in children under two without appreciating possible side effects.

The laws have met with criticism as well. In 1999, the generic drug industry sued the FDA over its incentive program's patent extension and exclusivity,[13] since the regulations apply not only to the product studied in the pediatric trials, but also to "any of the drug company's formulations, dosage forms, and indications" that contain the same moiety.[4] For example, a 1998 study that showed the efficacy of an injectable form of Zantac to be used on premature newborns granted all Zantac products six more months of market exclusivity. This included over the counter Zantac products that are primarily used by adults.[13] In response, a spokesman for the Elizabeth Glaser Pediatric AIDS Foundation, which strongly supports pediatric testing, said, "We went in knowing we were rewarding the drug companies too richly. But our past history shows that was the only way of motivating them."[13] This broad interpretation of BPCA impacted consumers, with the exclusivity rule preventing low-cost generic drugs from becoming available.[4]

Looking beyond the financial burden of the exclusivity rule, the success of its financial incentives shows that money is an important consideration for whether drug companies will conduct pediatric tests. A pediatric study can cost some one million dollars, but a six-month patent extension can yield an average of $50 million in profit.[13] Dr. Ralph Kauffman, director of medical research at Children's Mercy Hospital in Kansas City, Missouri, said, "Once the economic disincentive [of pediatric testing] was removed, the dam broke completely open."[4] As of 2006, more than 100 drugs had been granted exclusivity. As of 2004, 691 pediatric studies had been proposed to the FDA and 298 approved. Additionally, BPCA provides for government funding of pediatric studies in older drugs that are not eligible for patent extensions.[4]

**Pediatric Pharmacokinetics**

The generous incentives program demonstrates how strongly the government and the scientific community support pediatric studies. The main impetus for conducting these trials is to improve the standard of care applied to pediatric patients and consequently their well being. Too many drugs prescribed to pediatric patients do not have scientifically established protocols for how the medication should be used in children. These types of drugs are considered off-label, or used for "an indication, age, dose, or route of administration outside the terms of the product

license."[14]

Prescribing off-label drugs is legal and common, but can be very dangerous for children. Generally, when doctors prescribe an off-label medication, they reduce the adult dosage to fit a child's smaller body.[4] However, children are not tiny adults. There are many significant physiological differences in the way children's and adults' bodies process drugs. Pharmacokinetic (PK) dissimilarities exist in how individuals absorb, distribute, metabolize, and excrete drugs. For example, neonates and infants have different body compositions than adults. Neonates/infants are comprised of 70-80% water, compared to 60% in adults, and adults have greater body fat composition. Therefore, the babies require higher doses of hydrophilic drugs and lower doses of lipid-soluble drugs to achieve necessary serum concentrations. Additionally, the blood-brain barrier is not complete at birth, so newborns can have enhanced central nervous system drug effects due to increased permeability of chemicals across this membrane. These are only two of the many considerations, aside from size, that physicians must be wary of when altering dosages of off-label drugs.[15]

The most significant PK differences are observed during the neonatal/infancy stages as compared to adulthood. Physicians must be conscious of the level of organ maturation as well as the slower rates of metabolic processes. This latter consideration affects the half-life of a drug, since it stays in the body for a longer period of time. Therefore, a baby needs a lower dose of a drug over a longer interval than its body size might suggest, in order to prevent toxicity.[16] While variability for drug half-life does exist between individuals at the same developmental stage, the range of newborn to adult variability ratios "exceeds the 3.16-fold factor commonly ascribed to inter-individual PK variability."[17] The substantial differences between these age groups highlight the need for more pediatric drug testing, specifically in the youngest of patients. In fact, adverse reactions to drugs untested in children are a major cause of death and injury in children less than two years old,[18] which demonstrates how vital pediatric testing is for this age group. With the development of neonatal intensive-care units and survival of premature babies there is a dire need for safe and effective treatments. One recent success for premature infants involves pulmonary surfactants, which treat respiratory distress syndrome in preemies whose lungs are underdeveloped at birth.[7]

However, it is especially difficult to design studies around infants and newborns. Obstacles include recruiting a sufficient number of babies for the study, adequately measuring pain and quality of life in children so young,[19] and the ethical issues surrounding the inability of children to be informed of their participation in a trial. While researchers must take these issues into consideration, the complexity involved in altering doses for this age group makes clinical trials a necessity in order to reduce the unknown risks of using untested drug therapies.

On the whole, the appreciable differences between pediatric and adult patients' physiology and pharmacokinetics make it inappropriate to extrapolate drug data from adults to children. Requiring doctors to guess about doses, safety, and effectiveness of drugs due to lack of information makes children vulnerable to unknown side effects and adverse drug reactions. While BPCA and PREA have made great strides toward encouraging pediatric studies, 75% of the drugs found in the Physician's Desk Reference and 27% of those in the Harriet Lane Handbook, which is used specifically in pediatric practice and lists older medications, are still not labeled for pediatric use.[15] Increased pediatric labeling would provide evidence of the safety, efficacy, and age-dependent dosing indications in infants, children, and adolescents. It would also help protect physicians from malpractice suits that involve off-label drug use. Furthermore, increased labeling would make the drugs on-label, so insurance companies would potentially cover the cost of many additional medications.[2, 15]

### Arguments Against Testing

Despite the advantages offered through increased pediatric studies, many individuals oppose testing drugs on children. The arguments against pediatric testing fall into three main categories: logistical issues, financial issues, and ethical issues.

First, the logistical issues generally relate to methodology and the difficulty of designing and completing clinical trials using children. On a practical level, pediatric studies are prone to recruitment problems.[14,19] In 2002, Patient Quest, an agency that recruits patients for clinical trials, claimed that over half of "[their] studies are in crisis mode due to failed patient recruitment efforts."[20] This problem is due to many factors. First, the pool of potential subjects is inherently small. Most children who participate in trials have the disease in question, and there are relatively few children with any specific disorder. Scientists also need to study different age groups and different formulations of drugs for proper control and variable conditions, but that requires even more division among the few subjects.[14, 21] A small sample size reduces a study's statistical power, so the researchers, the drug company, and the FDA will have more difficulty in identifying whether the study's conclusions can be applied to a wider population or are significantly affected by chance and small numbers.

The only area of pediatrics that does not have a recruitment problem is oncology. An important element of this is the high level of collaboration between researchers and the prevalence of multicenter trials. Applying these two aspects of research to other fields of pediatric medicine could alleviate some of the recruitment problems, since subjects from multiple study sites can be included in research data.[19] This kind of infrastructure does exist in the form of the Pediatric Pharmaceutical Research Unit (PPRU) Network, which was established in 1994 and now includes 13 pediatric research centers supported by the National Institute of Child Health and Human Development.[4] The PPRU focuses on "delineat[ing] the effects of childhood development on the pharmacokinetics of drugs, the influence of age-specific changes in drug disposition and pharmacodynamics, and the interplay between disease states and stages of development." The network attracts pediatric subjects because of its combined outpatient capabilities. Its many sites working together can "ensure prompt recruitment for clinical trials" and shortened study periods.[22] Adding more facilities to the network would further improve its ability to conduct large trials and contribute information about pediatric pharmacology to drug companies and to the FDA.

Once a study has recruited an acceptable number of subjects, researchers must take into account technical issues including how the study is performed, what procedures are used, and how the staff interacts with children. For example, routine testing procedures in adults like drawing blood and collecting urine samples can be difficult in pediatric subjects, especially young children.[19] Non- or minimally invasive techniques must be utilized, and in many cases first developed, to assess PK and pharmacodynamics of children, which then allow scientists to determine accurate dosages to be used in the trials.[14] Another important consideration in pediatric studies is making the subjects feel comfortable, since a clinical research environment can be frightening to children. Excessive stress is placed on pediatric patients from a disease in itself as well as from procedures and doctors. Employing researchers and practitioners that can make a child feel more comfortable may seem like an afterthought, but is an imperative condition for a pediatric study.

Whereas the logistical issues are most relevant to the scientists conducting the studies, the financial issues of pediatric testing are of main concern to drug companies. In addition to the cost of setting up a study, drug companies view pediatrics as a small financial market, therefore less worthy of the time and effort of research compared to more profitable markets.[4] However, more and more children are taking prescription drugs.[19] The annual percentage increase in spending on drugs is higher among children than among adults.[21] Due to the growing market, it would actually be fiscally wise for drug companies to target the pediatric market.

Finally, there are ethical issues. The main concern is that children are a vulnerable population, both physically and mentally. On a physical level, drug studies can be hazardous. In randomized trials, a patient might not receive the drug therapy and his health might not improve. On the other hand, a patient might receive the drug therapy and his health might decline. The question is, "Should children be exposed to these risks of research so that others can benefit?"[11] A pediatric drug study is an opportunity to test drugs on children in a controlled setting, instead of on a case-by-case basis at the will of an under-informed practitioner. While many in the medical and scientific fields believe that the risk of drug trials is less than the risk of remaining ignorant of how drugs function in children, others are appalled that children can be subject to "medical experiments."[23] Because children are inherently vulnerable and do need to be protected, the level of risk accepted in pediatric trials must be less than that in adult trials.[11] For this reason, the FDA requests that pediatric studies are only conducted during Phase III of a study, which is when comparative clinical trials are run and after baseline safety and efficacy are established.[15]

Pediatric studies also run into problems because of the formalities of informed consent. Minors cannot legally give consent, and only children over the age of seven can assent (agree) or dissent (disagree).[4] But, how informed can a young child be? It is difficult to explain the study itself, along with the risks and possible benefits, to an adult, let alone a child of lesser developmental maturity. For this reason, opponents of pediatric studies believe that children are being exploited by the biomedical industry to make a profit.[23] This is a valid concern. Due to a child's inevitable developmental disadvantage, researchers must put significant trust in the parents ability to make responsible choices. However, another issue surfaces regarding the influence of a child's parents when deciding whether to participate in a study. A child who does not completely understand the situation may look to his parents for guidance and agree with whatever they suggest. This is especially true in acute or life-threatening situations when both child and parents are exposed to high levels of stress. In some cases, the family may be unduly persuaded toward participation due to compensation. Whether or not the compensation is intended for the parents, it can act as an incentive for parents to include their child in a study. To counter this, trials should either not compensate families or not inform them of compensation at the outset. Providing a small reward at the middle or the end of the study, and not advertising such compensa-

tion at the beginning, may reduce the occurrence of parents forcing unwilling children into drug trials.[11]

## Conclusion

It is imperative for drug companies to conduct pediatric drug studies in order to establish the safety and efficacy of such drugs in children. The substantial physiological and pharmacokinetic differences between children and adults require adequate drug testing for children, as it is often dangerous to apply clinical data from adult-based studies to children. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, along with other legislation of the past 14 years, have significantly aided this effort by both incentivizing and mandating drug companies to carry out pediatric studies. The medical community has improved its level of patient care due to the new information regarding treating children, and children have likewise benefited because of this more regimented practice of pediatrics.

The technical and practical problems associated with pediatric trials can be solved by putting pediatric subjects at ease, utilizing minimally invasive techniques when possible, and expanding the PPRU Network to deal with recruitment problems. Financial issues are less significant as the pediatric drug market grows every year and the FDA's exclusivity incentive program allows for substantial profits for drug companies. While ethical issues are of concern to all parties, the dilemmas come down to a choice: Would society rather see sick children treated in clinical, scientific settings or at random without guidelines for treatment in their doctor's office? One must also consider that inhibiting pediatric studies would make children's access to drug therapy even more inequitable compared to adults' access. Society wishes to protect children, but limiting a pediatric practitioner's knowledge of drug therapies can only cause more harm to come to these "therapeutic orphans." Increasing pediatric studies and, effectually, knowledge regarding pediatric drugs are important measures in improving the pediatric standard of care.

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