The Need for Pediatric Drug Development

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Therapeutic tragedies in pediatric patients contributed to formulation of the legal requirement that new medications had to be carefully studied before they could be approved for interstate sale.[1] Despite this, the majority of pediatric patients who require treatment are prescribed medications that are either not approved for pediatric use or contain incomplete directions for pediatric use in the approved product label.[2,3]

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Sulfanilamide Elixir Exposes the Risk of Limited Medication Regulations

In 1938, development of a liquid formulation of sulfanilamide, an antibiotic effective against streptococcus, staphylococcus, syphilis, and gonorrhea, allowed oral dosing of pediatric patients who could not swallow the sulfanilamide tablets.[4] Unfortunately, the solvent used to dissolve sulfanilamide was sweet tasting, raspberry flavored diethylene glycol, an industrial solvent that was not then recognized as a toxin. Reports of nausea, vomiting, renal failure, and hepatic dysfunction, with a 30% mortality rate followed the geography of the salesmen's routes through Oklahoma, Louisiana, and New York. Despite more than 100 deaths, there were no existing laws restricting manufacture of this formulation, Massengil Elixir of Sulfanilamide, except that the term elixir was reserved for ethanolic solutions.[4] Mr Samuel Massengil was fined $26 100 for selling a misbranded medication. The chemist who developed the solution committed suicide. In 1938, this tragedy led to passage of the Food, Drug, and Cosmetic Act (FDCA) that required approval of all new drugs through a New Drug Application, disclosure of all active ingredients, and evidence that the drug was safe when used according to the directions on the label. Proof of efficacy was not required, so broad therapeutic claims could be advertised. The Agency was given only limited regulatory powers, and medications could be marketed if no objection was raised within 60 days of the New Drug Application.

Thalidomide, Nearly a US Disaster

Thalidomide was once considered a popular sleep aid and treatment for nausea during pregnancy. It was marketed over the counter in Germany in the 1950s, until it was associated with neuritis, and then a prescription was required in 1961.[5,6] Thalidomide was widely marketed in Europe by many names.

In 1961, a dramatic increase in a rare, disfiguring, congenital anomaly, phocomelia, was discussed at medical conferences in Europe. Thalidomide during early pregnancy was the suspected cause of this multiple malformation syndrome that included severe shortening of the extremities, malformations of ears, heart, intestines, and other structures, depending on the embryologic stage at the time of exposure.[7,8] Thalidomide was being evaluated for approval in the US at that time with over 2 500 000 doses distributed in the US. Dr Frances Kelsey delayed Food and Drug Administration (FDA)

AAP	American Academy of Pediatrics
BPCA	Best Pharmaceuticals for Children Act
CPD	Committee on Drugs
CTSA	Clinical and Translational Science Awards
CYP	Cytochrome
FDA	Food and Drug Administration
FDAMA	FDA Modernization Act of 1997
FDCA	Food, Drug, and Cosmetic Act
ISPCTN	Institutional Development Awards States Pediatric Clinical Trials Network
INC	International Neonatal Consortium
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
PREA	Pediatric Research Equity Act
PTC	Pediatric Trials Consortium
PTN	Pediatric Trials Network
T2D	Type 2 diabetes
WR	Written request

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approval initially because of the polyneuritis and neuropathy observed in England and Germany, but later because she had heard of the association of phocomelia with thalidomide.[5]

Kefauver-Harris Amendment to the FDCA Changes FDA's Role in Drug Oversight

Congressional hearings begun by Kefauver and Harris in 1959 were focused on the high price of medications. With the identification of thalidomide induced severe congenital anomalies, they changed direction and extended the powers of the FDA. For the first time, the FDA was given a major regulatory role in protecting US citizens from ineffective medications. New provisions included a requirement for Good Manufacturing Practice, requirement for filing an application with the FDA before starting testing (Investigational New Drug application), and the authority to remove marketing approval if new evidence showed a lack of safety or effectiveness. Congress required that new drugs must be demonstrated to be not only safe, but also effective based on well-controlled, scientific clinical trials before they could be marketed. Pediatric tragedies served as the genesis of this Congressional requirement, yet the actions and efforts that followed were focused primarily on drug development for adults.

These new FDA laws had an unanticipated chilling effect on studies of drugs in children. Some argued it was totally unethical for children to participate in clinical studies and become the human equivalent of a test animal. Others were concerned about the costs and difficulties of conducting studies in children who could not consent for themselves. As new drugs were approved, pediatric patients were seldom included in clinical trials. Without children's participation in clinical trials, no pediatric prescribing information was generated for inclusion in the label for the new medication. Instead, pediatric prescribing often occurred with nothing more than anecdotal experience. Prescribers had no formal guidance in the use of medications for pediatric patients and had to rely on the familiar text in many approved labels, "safety and effectiveness of [add a drug name] have not been established in pediatric patients."

Importance of a Drug Label

The emphasis this report places on labeling of drugs for children reflects the high data-driven bar required to achieve labeling by the FDA. The study design must undergo review by the local institutional review board as well as the FDA for scientific validity and ethical appropriateness. The study must conform to the present federal guidelines for Good Clinical Practice. Finally, all the data undergo careful scrutiny by monitors to confirm the data's accuracy before review both by the sponsor and by the FDA. Thus, the information contained in a final approved product label implies that the data supporting that information and/or a given claim meets rigorous scientific, regulatory, and clinical standards. The dearth of approved pediatric product labeling for medications used routinely to treat children reflects a failure to meet these standards.

Pediatric Patients, Therapeutic Orphans

Just 5 years after the FDCA amendments to require demonstration of safety and efficacy for approval of new drugs, Dr Harry Shirkey described children as "Therapeutic Orphans," because the 1962 legislation allowed their exclusion from testing of new drugs.[9] Wilson[10] provided objective measures of how few drugs were labeled for pediatric patients in 1975 based on a review of the 1973 Physician's Desk Reference where he found that 78% of drugs lacked adequate pediatric labeling. Part of the problem, according to Wilson,[11] was the paucity of people trained in pediatric clinical pharmacology. Of the first 231 people certified by the American Board of Clinical Pharmacology, only 19 (8%) expressed an interest in pediatrics. Thus, the cadre of highly trained, specialized professionals capable of both championing and actively contributing to pediatric drug development was insufficient to adequately impact this problem.

First Guidelines for the Evaluation of Drugs in Infants and Children

The discipline of pediatric clinical pharmacology was emerging and defined itself based on characterization of the impact of maturation, growth, and development on drug disposition and action. This effort was led in the US by Drs Sumner Yaffe, Bernard Mirkin, Ralph Kauffman, Sanford Cohen, Lester Soyka, Jacob Aranda, John Wilson, and several others who worked to increase pediatric studies of drugs. In December, 1970, the Drug Research Board of the National Research Council of the National Academy of Sciences evaluated the status of Clinical Pharmacology and acknowledged the lack of studies to support pediatric therapeutics and of pediatric experts to conduct clinical trials.[12] They stated, "If the abyss of ignorance surrounding pediatric therapy and the introduction of new drugs into children is to give way to a scientific approach, it will be necessary to develop a national program with this as a clear goal and with appropriate support mechanism." They concluded "The need for clinical pharmacologists within the specialty of pediatrics is particularly great. The development of pediatric pharmacology requires special attention." This need remained unmet until 1994 when the Pediatric Pharmacology Research Units were established and funded by the National Institute of Child Health and Human Development (NICHD).

Several years before the Pediatric Pharmacology Research Units were established, the American Academy of Pediatrics (AAP) began efforts to support studies of drugs in children and to counter the claims that participation of children in clinical trials was unethical. The AAP Committee on Drugs (COD) started detailed discussion of how to conduct pediatric studies. They authored a report for the FDA in 1974, "General Guidelines for The Evaluation of Drugs To Be Approved for Use

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