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Improving Drug Therapy for Pediatric Patients: Unfinished History of Pediatric Drug Development

Robert M. Ward, MD, FAAP, FACCP, DABCP

ABBREVIATIONS American Academy of Pediatrics Section on Clinical Pharmacology and Therapeutics (SOCPT); Best Pharmaceuticals for Children Act (BPCA); Committee on Drugs (COD); Food and Drug Administration (FDA); Food and Drug Administration Act of 2007 (FDAA); Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); Federal Food, Drug and Cosmetic Act (FDCA); FDA Modernization Act of 1997 (FDAMA); Office of Pediatric Therapeutics (OPT); Pediatric Pharmacy Association (PPA); Pediatric Research Equity Act (PREA); Pure Food and Drug Act (PFDA); Pediatric Trials Network (PTN); United States Pharmacopoeia (USP); Written Request (WR)

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Protection of children from medication toxicity and providing evidence of effectiveness have long been the goals of studies of drugs in infants, children and adolescents. Ideally, the first child studied with a newly approved medication will receive that drug in dosages based on well-controlled studies with well-studied appropriate formulations in similar aged patients with similar disorders that established efficacy similar to what was required in adults. With motivation to achieve what is best for children, we have come a long way, but the progress is incomplete.

In the 1800's, the beginning of modern pharmacopeia's emerged in the U.S. and Europe.[1] These specified how to create medications by pharmacists who were skilled chemists. In the U.S., the first pharmacopoeia was published in 1820 and this was supplemented by legally protected Patent Medicines that often made outrageous therapeutic claims. A single product, such as Dr. Roger's Syrup, might be labeled effective for everything from a viral URI to tuberculosis (consumption in those days).[2] In reality the primary ingredient was often ethanol which was readily dispensed and contributed to abuse by alcoholic adults and caused toxicity in children. Even cocaine toothache drops could be purchased over the counter for treatment of children.

After over 25 years of appeals to Congress, Dr. Harvey Wiley, Chief of the Department of Chemistry of the Bureau of Agriculture, achieved passage of the 1906 Pure Food and Drug Act (PFDA), known in Washington as Wiley's Act.[3] Enactment of this law coincided with the publication of Upton Sinclair's description of the unsanitary conditions in the meat packing plants in Chicago in *The Jungle* which supported the inclusion of foods in this law. The PFDA required food to be unadulterated and free from "putrid" ingredients. Similar to today, there were a lot of disagreements within Congress about the need for this law and how to implement it. The PFDA, signed by President Theodore Roosevelt, prohibited manufacture, sale, or interstate transportation of adulterated, misbranded, poisonous, or deleterious foods, liquors, drugs, and medicines based on its label. Supporters of this law included women's groups interested in protecting children. SEC. 4. Specified "That the examinations of specimens of foods and drugs shall be made in the Bureau of Chemistry of the Department of Agriculture, or under the direction and supervision of such Bureau." This Bureau was under the review of Harvey Wiley, PhD. SEC.6. provided, "That the term "drug," as used in this Act, shall include all medicines and preparations recognized in the United States Pharmacopoeia (USP) or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals." Violators could be fined up to $500 and imprisoned for up to 1 year. In SEC 8. The Fourth provision indicated a drug was misbranded, "If the package containing it or its label shall bear any statement, design, or device regarding the ingredients or the substances contained therein, which statement, design, or device shall be false or misleading in any particular". Although this act initiated the power to evaluate the accuracy of the label for a drug undergoing interstate commerce, it did not establish the Food and Drug Administration (FDA), contrary to some descriptions of this act. That would come later. It also did not require pre-emptive inspections before marketing.

Later came in the 1930's when the azo dye prontosil was found by Gerhard Domagk to be metabolized into

a potent antibiotic, sulfanilamide, that could effectively treat streptococcus, pneumococcus and gonococcus.[4,5] Sulfanilamide was considered a wonder drug that decreased mortality dramatically and is credited with saving Winston Churchill's life when he developed pneumonia. Unfortunately, sulfonamide was virtually insoluble in water and was formulated and dispensed only in tablet form. Children who could not swallow a tablet were not able to be treated until an astute chemist found that sulfanilamide could be dissolved in diethylene glycol. It was tested only for taste and was then sold by the Massengill company as Elixir of Sulfanilamide-Massengill. In particular, it was not tested by the Council of Pharmacy and Chemistry of the American Medical Association to determine its safety and the solution was unknown to the Food and Drug Association of the U. S. Department of Agriculture. Sales by traveling salesmen began in September 1937 and by the following month over seventy deaths were reported to the American Medical Association.[6] Patients died with anuria after treatment with this new solution of sulfanilamide. One death even occurred after a patient changed from tablets to the elixir. In total over 100 deaths were attributed to the Elixir of Sulfanilamide-Massengill, and the majority were children. Findings at autopsy were all similar with hepatic and renal necrosis which could be duplicated in animals treated with diethylene glycol or the Elixir of Sulfanilamide, but not by treatment with sulfanilamide.[7] Geiling and Canon were assisted in these studies by a young pharmacology trainee, Frances Oldam Kelsey, who would play a major role in the next major phase of FDA regulations.[4]

Diethylene glycol was already known to be toxic, but the only legal power to remove the elixir from the market was the 1906 Pure Food and Drug Act that made it misbranded, because an "elixir" was considered to be an ethanolic solution.[8] As pointed out in a report by the Secretary of the Department of Agriculture, "Had the product been called a "solution," rather than an "elixir," no charge of violating the law could have been brought."[9] Dr. S. E. Massengill testified, "I have broken no laws" and was fined $16,500, but Harold Watson, the formulation chemist committed suicide.[10]

It was clear that more stringent controls on pharmaceuticals were needed. The Federal Food, Drug and Cosmetic Act (FDCA), P.L. 75–717, was approved June 25, 1938.[11] This law established quality standards for food, drugs, medical devices, and cosmetics manufactured and sold in the United States to be established before they undergo interstate commerce. The U.S. Food Drug and Cosmetic agency now assumed prospective regulatory authority for the first time. Oversight and enforcement of these standards were vested in the Secretary of Health and Human Services. Several provisions described how this oversight should be carried out to protect patents while insuring the products were safe for their intended use in patients. Many more regulations and laws followed to strengthen consumer protection in the use of medications.[12]

In 1962, similar to discussions today, Senators Kefauver and Harris were conducting hearings concerning the high costs of drugs. At the same time, a severe congenital malformation syndrome was occurring in many countries, but primarily in Europe with phocomelia (seal like limbs), along with malformations of the ears, heart and intestinal tract. Dr. Helen Taussig who spoke fluent German traveled to Europe, investigated these cases, and wrote a thorough description of these disorders.[13,14] Thalidomide was being marketed in 46 countries and sold over the counter, although that was later changed to requiring a prescription, due to a polyneuritis.

In the U.S. Richardson-Merrell Pharmaceuticals had applied for FDA approval of thalidomide in 1960 when companies were allowed to sell drugs 60 days after submitting their request to the FDA if they showed that their drugs were safe as long as the FDA did not object.[15] The company had distributed 20,000 tablets to physicians for research purposes. Dr. Frances Kelsey, who had trained in pharmacology and medicine, was one of 7 review officers at the time. She was assigned thalidomide for review. Dr. Kelsey had read a British study of neurological side effects and found that there were limited data backing up the company's claims of safety and even some falsified reports. Astute pediatricians in Germany presented cases at medical conferences and suggested a relationship between the multiple malformation syndrome and a new sedative medication often taken during pregnancy, Distaval, also known as thalidomide in the United States. Despite threats of lawsuits, Dr. Kelsey refused to approve it without more data about the outcomes from the treatment of pregnant women in the U.S. with the tablets distributed for research.

Confirmation that the multi-malformation syndrome involving flipper-like limbs was caused by thalidomide and the limited protection by current laws led to the next phase of drug regulations. Kefauver and Harris who had been trying to strengthen FDA regulations pivoted their hearings and amended the 1938 FDCA to require both safety and efficacy be demonstrated before new drugs could be marketed in the U.S.[16] Implementation of these Kefauver-Harris Amendments in 1962 led to the usual requirement for 2 randomized controlled studies demonstrating safety and efficacy before approval of new drugs.

In 1962, Dr. Kelsey was awarded the Distinguished Civilian Service Medal by President John F. Kennedy. In 2010, the FDA initiated the Frances O. Kelsey Award for Excellence and Courage in Protecting Public Health and selected Dr. Kelsey as the first recipient at age 96.[17]

Implementation of the Kefauver-Harris Amendments improved the quality of new medications, but this benefit for adults did not extend equally to children. By 1968, Dr. Harry Shirkey, a leader in pediatric drug dosing pointed out that pediatric patients were abandoned

from inclusion in the studies leading to approval of new medications by the 1962 amendments and described children as "Therapeutic Orphans". [18] A few years later, Dr John Wilson evaluated the labels of 2000 approved medications in the 1973 Physicians' Desk Reference and determined that 78% lacked pediatric prescribing information in the label.[19] Several reasons for not studying medications in the pediatric population were proposed, including: it is unethical to study children; studying children is too hard; pediatric studies are too expensive. Despite efforts to increase pediatric studies to provide reliable data for dosing, efficacy and safety, the review by Wilson in 1973 and again in 1999 showed no increase in pediatric labeling.[19,20]

In 1970, the FDA contracted with the American Academy of Pediatrics to develop a framework for the study of drugs in the pediatric population. The responsibility for this work was delegated to the Committee on Drugs (COD) which was being chaired by Sumner Yaffe, MD, who was in the middle of the longest period of leadership (10 yr) of the COD. By 1974, the COD had written, "General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children." [21] This 40 page treatise included a broad range of topics from ethics to analytic techniques. Chapters described developmental changes in drug metabolism as well as pharmacologic changes during pregnancy. Ages for study were defined for neonates, infants and adolescents. Although this was very thorough and well written, it had little effect on the frequency of pediatric drug studies.

A few years later in 1977, the COD published one of the strongest statements about the need to study drugs in pediatrics, "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations."[22] "The Committee believes that it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children. Furthermore, it is not only ethical but also imperative that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who may need them."

In 1979, the FDA implemented a requirement that medication labels must contain a "pediatric use" section to describe how to use the medication to treat pediatric patients. The main result was the inclusion in the label that, "Safety and effectiveness in pediatric patients have not been established." Overall, this effort was relatively ineffective.

The continued lack of pediatric prescribing information in medication labels led the FDA to enact the 1994 Final Pediatric Rule which requested pediatric study and labeling if the drug was known to be used widely in pediatrics.[23] One of the major provisions was allowing extrapolation of efficacy from adults to children without additional study if the disease process was similar in both populations. This would reduce expenses and duration of studies leading to labeling. The Rule also allowed labeling to be based solely on published randomized, well-controlled trials that met the standards of the FDA. Unfortunately, 77% of the changes submitted were inadequate to increase pediatric labeling and led instead to the familiar disclaimer, "Safety and effectiveness in pediatric patients have not been established." To avoid delaying new treatments for adults, the FDA requested post marketing studies in pediatrics, but of 71 studies requested by 1991, only 11 studies were completed by 1997.[24] Inclusion of pediatric prescribing information in the label of newly approved drugs, decreased from 9/17 (56%) in 1991 to 6/30 (20%) in 1998. Off-label prescribing remained the predominant basis for pediatric therapy.

The FDA began to explore legislative solutions to create incentives for pediatric studies similar to what they had done for orphan and generic drugs in the form of market exclusivity. Market exclusivity is protection from competition provided by the FDA for a specific use of a new drug (new molecular entity) which may run during patent life. (Patent protection is completely separate protection provided by the Patent Trade Office and lasts 20 years.) Because the market for pediatric indications was quite small, the FDA considered applying market exclusivity for all uses of a new molecular entity not just for the pediatric indication. Questions arose about how much exclusivity would incentivize companies to undertake pediatric studies and what types of studies would provide optimal pediatric benefit. This led to the FDA Modernization Act of 1997 establishing Pediatric Exclusivity which differed from existing market exclusivity by extending existing market protection for an extra 6 months for all formulations and all uses of the active moiety.[25]

The FDA Modernization Act of 1997 (FDAMA) was bipartisan legislation signed by President Clinton on November 21, 1997, intended to increase the study and labeling of drugs in the pediatric population. A Guidance indicating how to qualify for exclusivity was published in July, 1998. A drug could qualify for this exclusivity if "additional pediatric information may produce health benefits in the pediatric population", a relatively low bar. This voluntary process required that the studies must conform to the FDA's Written Request (WR) that outlined the studies needed and they had to be completed before current market exclusivity expired. The WR could specify the pediatric population(s) by age and numbers to be studied as well as what indications to be studied. For some drugs, the pediatric indications were completely different from the indications in adults. FDAMA would sunset in 5 years unless it was renewed.

FDAMA was essentially an experiment to increase pediatric studies and labeling. In the FDAMA Evaluation on September 1, 2001, a little over 3 years after its implementation, the FDA had issued 157 WRs for 332 pediatrics studies, awarded exclusivity to 25 products

leading to 12 pediatric label changes.[24] Many more studies and label changes were pending at the time of the 2001 report. "In general, the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."[24]

FDAMA was considered a success, but it came at a cost. According to Pharmacy Times, a pharmaceutical trade periodical, 6-month sales in 1997 for "block-buster" drugs ranged from over $402 Million for Augmentin to over $1.1 Billion for omeprazole (issue no longer available). Even noting that these figures are for sales, not profits, it was clear that added profits could easily pay for pediatric studies, estimated at $5-10 Million/study. But this did not apply to all drugs receiving PEDIATRIC EXCLUSIVITY. Nine of 33 drugs receiving exclusivity were not listed in the top 200 for sales. For some of these the costs of the pediatric studies likely exceeded sales.

If FDAMA was considered the carrot for pediatric studies, the 1998 Final Rule was considered the stick. The 1998 Final Rule was proposed on 8/15/1997 and approved on 12/2/1998 to fill the gaps that the voluntary law, FDAMA, would leave.[26] This Rule, written by the FDA, may require studies of new drugs if: 1) they provide a significant benefit over existing labeled therapies for a relevant pediatric population; 2) the absence of labeling could pose a significant risk to pediatric patients; 3) they are indicated for a condition in which few products are labeled for pediatric use. The 1998 Final Rule included the provision from the 1994 Final Rule that efficacy could be extrapolated to children if the disease is sufficiently similar in children and adults. Studies could be limited to dose, kinetics and safety. Each relevant age group had to be studied, which represented a big gain for newborns. It even provided that new formulations might be required which was often a pediatric challenge for drugs developed as tablets or capsules for adults. Waivers were possible if: a new formulation was required and could not be developed; if the drug was not an improvement over existing therapy; if it was unsafe for pediatric patients; and if study was impractical because of small pediatric populations.

Approval of the 1998 Final Rule was followed quickly by lawsuits questioning the FDA's authority to require companies to conduct studies. On 10/17/2002, Judge Henry Kennedy in the District, wrote: "The Pediatric Rule may well be a better policy tool than the one enacted by Congress; it might reflect the most thoughtful, reasoned, balanced solution to a vexing public health problem. The issue here is not the Rule's wisdom. The issue is the Rule's statutory authority, and it is this that the court finds lacking."[27] The 1998 Final Rule was overturned, but Congress was coming to the rescue of pediatric studies. The next year in 12/2003, Congress passed the Pediatric Research Equity Act (PREA)[28] reinstating almost all of the provisions of the 1998 Final Rule, but the differences from the voluntary process leading to Pediatric Exclusivity that had been renewed in 2002 as the Best Pharmaceuticals for Children Act (BPCA)[29] need to be noted. PREA could only require pediatric studies of the indication being proposed for adults. But PREA maintained the requirement for studies "if they are likely to provide a health benefit" to children.

BPCA reauthorized the 6-month exclusivity incentive for studies that fulfill the FDA WR before current market exclusivity expires. It added neonates as a special population needing study based on the number of studies that continued to stop at a lower age limit of 6-12 months. It required racial and ethnic representation in studies and established the Office of Pediatric Therapeutics (OPT) in the Commissioner's office. Every award of exclusivity required a 1-year follow-up safety report to the FDA Pediatric Advisory Committee that was established by the OPT.

Pediatric therapy often continued to utilize off-patent, older medications, including those whose market exclusivity had recently expired leaving them without an incentive for pediatric study. To increase the study of these generic, off-patent drugs, BPCA established a foundation at the NIH to contract for study of off-patent drugs. Initial efforts to fund this with contributions from sponsors were unsuccessful. Later support was appropriated by Congress, but never authorized. Collaborations between NIH and FDA determined which drugs were most in need of study and established a list of these annually. A new challenge developed when off-patent drugs considered for study were suddenly patented again for a new indication or formulation. Because the label belongs to the original innovator company that developed and obtained approval, but which may not still exist, the FDA and NIH developed a process to publish a proposed label in the Federal Register for comment before it was added to the generic medication. These efforts to increase study and labeling of off-patent medications had little effect initially.

In 2010 the National Institute for Child Health and Development funded the Pediatric Trials Network (PTN) at Duke led by Dr. Danny Benjamin. In studies approved by the IRB and with parental permission, investigators could obtain 2-3 small volume blood samples from children being treated with unlabeled medications. The investigators could also collect scavenged samples of extra blood from the clinical laboratory. Using micro-analytic techniques and population pharmacokinetic designs, the investigators defined the pharmacokinetics for these drugs to combine with clinical evidence of safety and efficacy. As of 2/2022, the PTN had established 22 study sites in 44 states and 4 countries that had enrolled over 11,000 patients.(Personal communication with Dr. Danny Benjamin) They had carried out 44 studies in 18 therapeutic areas, published over 97 manuscripts and added pediatric prescribing information to 17 drug labels.

The Pediatric Exclusivity provision has been included in subsequent renewals of the incentive program in

BPCA as part of the Food and Drug Administration Act of 2007 (FDAA)[30] and the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).[31] FDAA was broadened to include study of devices for pediatrics in 2007. The requirement for pediatric studies of new drugs in PREA which was first passed in 2003 was renewed in 2007 and 2012 as part of FDAA and FDASIA, respectively. BPCA and PREA were finally made permanent in 2012 and show that PREA is now the predominant impetus for pediatric studies. In the 25 years since passage of FDAMA, the requirements and incentives for pediatric studies have been a success producing 996 pediatric studies with 572 by PREA only, 162 by PREA and BPCA, 196 by BPCA only, 16 by BPCA, and 50 by the pediatric rule.[32]

Unfortunately, neonates have not benefited to the same extent as other pediatric patient populations. Laughon et al pointed out in 2014, that only a small percentage (7%) of studies for pediatric exclusivity included neonates.[33] More problematic is the finding that a review of over 446,000 NICU patients showed that of the 28 drugs studied in newborns for exclusivity 21 of these 28 were never or seldom (0.013%) used to treat neonatal patients. Participation in clinical trials of medications which are not used in this population violates basic ethical standards. Although neonatal studies are challenging, these critically ill patients remain therapeutic orphans.

Since 1997, pediatric studies have increased to the point that many sponsors plan on pediatric studies early in their drug development program. This increase in pediatric studies generated many more pediatric investigators and study coordinators. Institutional Review Boards have developed experience and expertise in the review of pediatric studies. These expansions have been accompanied by an increase of pediatricians at the FDA to assist in the requested designs of pediatric studies. The experiment that began with the incentive program of FDAMA has been a success, but new efforts are needed to extend that success to neonates and maintain the increased study of drugs in pediatric patients. Members of the Pediatric Pharmacy Association (PPA) have unique knowledge of pediatric pharmacology that can support pediatric studies and help educate pediatricians. The American Academy of Pediatrics Section on Clinical Pharmacology and Therapeutics (SOCPT) would welcome input from members of the PPA through two different levels of participation. Members with a PharmD degree and board certification as Pediatric Pharmacy Specialists can become National Affiliate members with full voting rights and access to leadership roles within the Section. A PPA member just served as the President of the Executive Committee of the SOCPT and others have served on the executive committee of the section. PPA members who don't qualify for National Affiliate membership can still lend their expertise to the AAP as Section Affiliate members. Together, pediatricians and pharmacists can continue the progress in pediatric studies of medications so the first child treated with a new medication receives that medication based on thorough study of dosage, safety and effectiveness.

Article Information

Affiliations. University of Utah Department of Pediatrics, Divisions of Clinical Pharmacology and Neonatology

Correspondence. robert.ward@hsc.utah.edu

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