Pediatric Drug Development and Policy after 1979

As 1980 dawned, there was good reason for stakeholder optimism regarding pediatric drug safety- and efficacy-related issues. In the over-the-counter drug market, protective caps made products safer and aspirin poisoning rates continued to decline. Those with a vested interest in pediatric prescription drugs could look to new scientific and ethical guidelines governing pediatric drug research. And Food and Drug Administration staff affirmed commitment to the 1979 regulation that full clinical trial data supporting claims for children’s dosing and administration accompany any pediatric indication in new drug applications (NDAs).

But the 1979 rule, like the 1938 and 1962 laws, did not require pediatric studies. In other words, companies only had to submit pediatric data if they sought its inclusion on the label. In many ways, the rule was only a reiteration of earlier legislation. The intention of both the 1938 Federal Food, Drug, and Cosmetic Act and the 1962 Kefauver-Harris Amendments was to make sure that directions for use were safe and effective for all groups, including children. The decades-long core issue remained unaddressed: who would pay for all the additional steps necessary to assure pediatric drug safety and efficacy? This variable had never been incidental in the United States, but as the pharmaceutical industry continued to comprise a larger sector of the American economy and health care costs escalated in the early 1980s, it became increasingly important. Given the small pediatric market relative to adults, drug
companies had few economic incentives to invest in pediatric testing. Ever since the first sulfonamides arrived on the market, clinicians had, through trial and error, adapted them for use in children as quickly as possible. As a result, industry leaders correctly wagered that they would continue to do so. As long as every major firm behaved in a similar fashion, there was no competitive disadvantage to this practice.¹

Thus, more than one hundred years after Abraham Jacobi had first argued that children could not be considered miniature adults when it came to therapeutics, they remained, as Harry Shirkey had memorably categorized them, “orphaned” in terms of many of the protections afforded to adults. But as this history reveals, it was not because no one had considered children’s issues. In the late nineteenth and early twentieth centuries, Jacobi himself as well as other pediatric and public health leaders railed against the risks to infants from soothing syrups. In the 1930s, the Philadelphia Pediatric Society convinced the American Academy of Pediatrics (AAP) to seek more pediatric representation to the USP. In the 1940s, Irvin Kerlan and Robert Stormont at FDA prophetically identified the need for more clarity regarding pediatric drugs. In the 1950s and 1960s, Shirkey’s pioneering efforts pressed the AMA, AAP, and USP to work for broad reforms in pediatric drug development, testing, and regulation. Others, including John Nestor, Frances Kelsey, Helen Taussig, Jay Arena, and Leon Eisenberg, strove to spotlight problems surrounding children and drug safety. In the 1970s, researchers such as Allen A. Mitchell and Sumner Yaffe created innovative research and practice initiatives to propel pediatric pharmacology knowledge forward.

All these efforts focused attention on the problem and resulted in some legislative successes. In 1906, fears of soothing syrups and other patent medicines that maimed or killed children helped create the modern FDA. In 1938 and 1962, respectively, robust new laws increased federal oversight of the pharmaceutical industry in the wake of the Elixer Sulfanilamide and thalidomide crises. Yet, by and large, adults benefited disproportionately from these statutes because the laws did not mandate anyone to address children’s issues specifically. And just as had occurred in the past, an analysis in the wake of the FDA’s 1979 pediatric regulation revealed that it, too, failed to reduce the pediatric drug knowledge gap. Despite Marion Finkel’s best efforts to “pressure companies to do pediatric studies of certain products undergoing the approval process,” the regulation remained “voluntary but encouraged.” Thus, only a small percentage of new drug applications submitted to FDA with potential for use in children included pediatric clinical trial data.²

Moreover, by 1980, those who sought more robust governmental oversight of the pharmaceutical industry in the United States knew they faced an uphill battle. Sharp declines in manufacturing in the 1970s and an oil embargo that sent gasoline prices sharply upward stalled the economy. The resulting
recession shook Americans’ optimism and ended the postwar economic boom. Watergate and other political scandals disillusioned many Americans’ belief in governmental solutions. As a result, Ronald Reagan’s small government philosophies resonated with voters in the 1980 presidential election.3

A New Template for Pediatric Drug Development: The Orphan Drug Act

It was in this clinical, economic, and political context that Connecticut mother Abbey S. Meyers began fighting on behalf of her son David. David suffered from Tourette Syndrome (TS), a complex neurological disorder characterized by repetitive movements and vocal tics. As his symptoms worsened in the late 1970s, David’s doctor suggested he try an investigational drug for schizophrenia, Orap (pimozide). Meyers felt very relieved when the drug improved David’s symptoms. But in 1979, McNeil Laboratories, a division of Johnson and Johnson, decided to stop its manufacture. Their tests revealed it was not useful for schizophrenia and that not enough people suffered from TS to make the drug financially worthwhile to produce. As a result, Orap became a drug with only “orphan” potential, a term referring to drugs that might be used in either adults or children, but in numbers so small that their manufacture would not prove profitable. Several companies did make a few targeted products as a philanthropic gesture, but the scale was small and there was no organization to these efforts. Unfortunately, Orap was not one of those drugs. Aghast that David’s treatment had disappeared overnight, Meyers began contacting other parents in the Tourette Foundation. Because it was a small organization, she also reached out to the growing number of advocacy groups for other rare diseases, ultimately uniting them into what became the National Organization for Rare Diseases (NORD).4

When a mother who lived in the district of powerful California Democratic Representative Henry Waxman faced a problem obtaining an orphan drug for her child, she contacted Meyers, NORD’s president. Meyers, the self-proclaimed “housewife from Connecticut,” seized an opportunity.5 She organized a group of parents who, in 1980, convinced Waxman, chair of the House Commerce Committee, to convene a hearing focused on orphan drugs. Meyers testified eloquently, using arguments rich with themes of both gender and social class that garnered media attention:

As a mother, when I realized that my son could no longer get Pimozide, I was devastated. Without medication . . . he could not write, feed, or dress himself. I panicked. I began to study drug policy in foreign countries in order to find a way to smuggle the drug into the United States. I, a law-abiding, middle class mother began to contemplate breaking the law in order to circumvent the needless
suffering of my child. I learned that the practice was not new and that if I were affluent I could easily get this drug from Mexico. But I was not affluent.6

Meyers saw the issue starkly, as good versus evil. She implored the committee “in the name of my children” and “millions of others like them” to intervene on their behalf with legislation to protect them from “profit margins and red tape.”7 Meyers’s words and the way in which she framed the issue as corporations versus children captured attention on and off Capitol Hill. It is unlikely, however, that her efforts would have gotten very far without Waxman’s deft legislative hand, which guided an orphan drug bill through Congress and the quiet leadership of the FDA’s Marion Finkel. Finkel and her colleagues at FDA had been studying problems related to orphan drugs for years. She bolstered Meyers’s emotional testimony with concrete policy recommendations.8

The drug industry had refused Waxman’s offer to testify. After the hearing’s negative publicity, companies scrambled to undo Meyers’s characterization of them as greedy and unfeeling toward desperately ill children. The industry made sure that their interests were well represented in subsequent Capitol Hill discussions. But the drug industry had little interest in an orphan drug law. At one 1981 hearing, for example, Louis A. Engman, president of the Pharmaceutical Manufacturers Association, argued that the private sector could effectively address the issue, and was already doing so.9 But the bill Waxman introduced not only featured savvy activist parent Abbey Meyers, it attracted celebrity attention. Television star Jack Klugman’s brother suffered from a rare disease and the actor reached out to Meyers. At her urging, Klugman subsequently testified on Capitol Hill and devoted two episodes of his popular TV show Quincy to orphan drugs. With effort, the bill passed both houses of Congress just before Christmas 1982. Nonetheless, it appeared that President Reagan planned to ignore the bill until Congress adjourned, killing it using a legislative procedure known as a pocket veto. The Orphan Drug Act arrived on Reagan’s desk just before Christmas. According to Meyers, in an effort to appeal to the president’s emotions and reach out to him directly, NORD purchased a large advertisement in the Palm Springs, California, newspaper (close to the southern California ranch where the president spent his holiday) and the Washington Post. Warded to make him feel like “Scrooge” by ignoring those “doomed to an early death” or suffering from “painful and disabling sicknesses,” the advertisement begged him to not to ignore the bill.10

In January 1983, Reagan quietly signed the Orphan Drug Act into law despite his professed antipathy for governmental expansion and to the dismay of the pharmaceutical industry. The statute created a new FDA branch, the Office of Orphan Products Development, with Finkel as its first director. The law offered incentives for companies that invested in drug development for conditions afflicting only small numbers of people, subsequently defined
as fewer than 200,000 individuals each year. It also offered lucrative rewards in an attempt to generate industry interest in developing and manufacturing orphan drugs, among them tax credits for research-related expenses. Importantly, the Orphan Drug Act also authorized an exclusive right to market the drug for seven years.11

No one anticipated the financial windfall the Orphan Drug Act would afford to manufacturers. Health and Human Services Secretary Margaret Heckler had suggested that the law would make developing drugs for rare conditions financially feasible, but admonished that it would “make nobody rich.”12 She could not have been more wrong. The exclusivity provision protected the producer of an orphan product from competition, but was silent on what it could charge. This meant that companies retained a seven-year monopoly on their drug and could set the price at whatever they chose. As a result, the profits for some orphan drugs reached a billion dollars. Newly created biotechnology and niche drug companies raced to develop orphan drugs.13

While the drugs were often expensive and generated enormous profits for some companies, the Orphan Drug Act also meant that, for the first time, children with rare conditions such as pediatric genetic metabolic disorders lived healthier lives.14 Given that many such diseases were genetic or congenital anomalies, children benefited disproportionately from the law. Because so many of the orphan drugs focused on children, the Office of Orphan Products Development became the central place for discussions regarding pediatric drug-related issues within the agency in the 1980s. Finkel’s successor Marlene Haffner noted, soon after she became its director in 1986, that she and her office “view[ed] the problem of the inadequate study of products for pediatric indications as an orphan issue.”15

**American Childhood in the 1980s:**
**New Fears Concerning Protection**

By the 1980s, American children and families were also experiencing the effects of broad and deep changes in the social and economic landscape over the course of the previous decade. While indigent and working-class mothers had always worked outside the home, a majority of middle-class mothers now did so as well, by necessity as the United States moved from a manufacturing economy to one more focused on services, which lowered the wages of many, or by choice, as a result of second wave feminism.16 Rising divorce rates also altered traditional notions of family life. Partly because many parents were busier, children’s lives became more structured and some worried that they suffered as a result. During the 1980s, fears about children’s safety and protection escalated in the United States. While the numbers of “missing children,”
for example, were relatively few, their stories were featured again and again on television and in books and magazines, stoking anxiety.17

At the same time, all children now received more scrutiny for behavioral and learning disorders than in the past. This was due, in part, to legislative mandates. The 1967 Early and Periodic Screening Diagnostic and Treatment Act screened Medicaid-enrolled children for developmental conditions. The 1975 Education for All Handicapped Children Act mandated that every American child receive a free education appropriate to his or her needs. Taken together, the numbers of children diagnosed with learning disabilities, behavioral conditions, and mental illness began to rise. As their incidence escalated, inpatient psychiatric hospital stays by children quadrupled relative to earlier decades. Managers of the new for-profit private psychiatric units quickly realized that children’s length of stay averaged 50 percent longer than those of adults, making them lucrative customers.18

Children and parents in the 1980s faced a number of other crises that further heightened anxiety about American youngsters’ well-being. Aspirin became linked in the early 1980s to Reye’s syndrome, a terrifying brain disorder that caused profound neurological dysfunction and was often fatal.19 The pediatric antipyretic market supremacy afforded to St. Joseph Aspirin for Children was challenged in much the way it had been by the rapid rise in aspirin poisoning in young children in the 1950s. In 1981, the Centers for Disease Control recommended warning labels advising against aspirin’s use in children. The aspirin industry responded by employing all the tactics it had developed to delay safety caps. It fomented confusion about the problem, challenged the science based on technicalities, argued that warning labels did not serve children well, and funded its own “consumer” groups to fight against the parent-founded National Reye’s Syndrome Foundation and AAP campaigns.20 The resulting stalemate lasted five years. The aspirin industry finally lost the scientific and legislative battle in 1986. After warning labels were placed on every bottle advising against aspirin’s use in children, the incidence of Reye’s syndrome declined dramatically. Unfortunately, however, the delay resulted in the death of almost fifteen hundred children, and probably permanent cognitive disabilities in many more.21

The AIDS epidemic brought another unanticipated risk to children. Although the numbers of children afflicted by the disease relative to adults were always very small in the United States and concentrated in a few cities, it raised frightening new fears. Misinformation abounded about the likelihood of disease transmission from casual contact with body fluids such as saliva. Like adults, children suffering from AIDS had few treatment options beyond supportive medical and nursing care. But in 1987 the FDA approved the anti-retroviral drug Zidovudine (azidothymidine), also known as AZT. Children were, however, orphaned once again because the drug had been tested only
in adults and, as such, was not approved for use in pediatrics, even for dying youngsters.\textsuperscript{22}

Activists had successfully hastened the drug evaluation process so adults could gain access to experimental antiretroviral drugs. Whether this course of action was in the best interests of children with AIDS weighed heavily on families, clinicians, and the FDA. Old questions emerged. While physicians could legally prescribe the drug to children, how could they be sure youngsters got a dose that was large enough to be effective but not so high as to be toxic? Could any of the ample adult data regarding the drug be extrapolated to children? And how should issues surrounding proxy consent be addressed? That many of the infants and children who stood to benefit from (or be harmed by) experimental AIDS medicines hailed from indigent minority backgrounds complicated the problem, as did the fact that a large number resided in hospitals or foster homes as wards of the state because one or both parents had died from the disease. The legacy of past experimentation in vulnerable populations loomed large in these debates.\textsuperscript{23}

\section*{A Home for the Therapeutic Orphan}

It was in this context in 1990 that representatives from the FDA and the National Institute of Child Health and Human Development (NICHD) once again came together with members of the pharmaceutical industry, the AAP Committee on Drugs (COD), and other leading stakeholders. The Institute of Medicine-sponsored conference signaled “renewed interest in finding solutions to the longstanding difficulties in making drug therapy as available to children as to adults, and in eliminating the barriers to drug testing in the pediatric population so that children are not therapeutic orphans.”\textsuperscript{24} This gathering differed from earlier ones. First, there was less finger pointing than in the past as to whether industry, FDA, or academic medicine was to blame for the situation. Second, attendees were encouraged by the Orphan Drug Act’s success at stimulating drug companies to invest in treatments even if the targeted population was small. Third, pediatric-specific drug development barriers and costs were more frankly and openly discussed than at past meetings. Finally, the conference was held in the context of the urgency surrounding how best to balance issues of risk and protection with regard to antiretroviral therapy for HIV positive children.\textsuperscript{25}

Paula Botstein, FDA pediatrician and deputy director for medical affairs, worked on pediatric issues in the 1980s and 1990s. She and her colleagues were trying to shift FDA thinking from the agency’s all or nothing approach that mandated full pediatric clinical trials before approving a pediatric indication to one that allowed waiver of a complete trial in certain instances.\textsuperscript{26} Just as it was wrong to assume children were just small adults and that dosing
was always proportional, so, they reasoned, was it incorrect to ignore adult data if evidence "exists to show that the course of the disease and the drug response are sufficiently similar in adults and children to permit extrapolation." Botstein was part of a group that created a pilot initiative allowing, in certain instances, for adult research to be considered in place of full pediatric trials.

Notwithstanding the AIDS and Reye's syndrome epidemics and societal angst concerning children's well-being, by the early 1990s American children were, as a group, healthier than ever before. Pediatric morbidity and mortality rates continued to decline, although disparities according to race, social class, and ethnicity persisted. Better chemotherapeutic regimens for cancer, improved surgical techniques for congenital anomalies, and more sophisticated medical and nursing care made it easier to save ill and injured children and those born very prematurely. But improved survival rates meant that there were larger numbers of medically fragile and chronically ill youngsters than in the past. As a result, more children received more drugs relative to earlier decades. In 1994, the FDA codified the pediatric waiver, debuting what became known as the Pediatric Rule. This regulation requested that industry include pediatric data when submitting a new drug application and strove to make it easier for them to do so by permitting extrapolation from adults in certain instances.

So long as evidence suggested that a disease's course and a drug's effects were similar in children and adults, data from adult clinical trials could be cautiously considered for children, especially when accompanied by all available pediatric pharmacokinetic and safety data. The new guideline was launched with great optimism and fanfare. Health and Human Services Secretary Donna E. Shalala celebrated its promise stating "taking care of our children is our top priority. . . . These measures promise the kind of quality medical care our children deserve." FDA commissioner pediatrician David A. Kessler, affirmed the agency's commitment to youngsters. "We have a duty to our children," he professed. "We can get the information we need to treat our children safely and effectively if we think creatively and are willing to commit resources to the challenge."

At about the same time, the NICHD launched an effort that everyone hoped would make it easier to build a national pediatric pharmacology database. Sumner Yaffe, now director of the NICHD Center for Research for Mothers and Children inaugurated a federal funding structure to create Pediatric Pharmacology Research Units (PPRUs). Located in academic medical centers, PPRUs linked drug companies to pediatricians and their patients. The inability to access child subjects was a factor companies had identified as inhibiting pediatric drug development. Shortly afterward, the National
Institute of Mental Health (NIMH) replicated Yaffe’s initiative, funding Research Units in Pediatric Psychopharmacology (RUPPs) to facilitate psychoactive drug research in children. The pediatric population was an increasingly attractive one for companies that manufactured mood-altering agents. There had been a sharp rise in costs for child mental illness in the 1980s, as the numbers of inpatient beds and pediatric lengths of stay increased. Insurers in the 1990s responded to financial pressures by turning toward a managed care model for psychiatric treatment. Drug therapy was much cheaper than a hospital stay.34

Unfortunately, however, despite the government’s request for a voluntary effort on the part of industry and the NICHD- and NIMH-funded research units to facilitate access to children and investigators, only a few drug companies initiated pediatric drug studies. Stakeholders within the FDA and AAP became convinced that a drug company mandate was the only way to assure that every new application for any drug that might be used in children included relevant pediatric information. The agency issued this requirement in 1998. In an effort to generate more pediatric data for agents already approved by FDA, government also offered a lucrative incentive. Six additional months of patent protection before another company could compete by making a similar generic product stood to be worth billions of additional revenue on a blockbuster drug.35

While the idea of patent extensions for voluntarily undertaking pediatric research proved popular with drug companies, the mandatory Pediatric Rule was less so. Those who opposed the regulation framed their concern in the language that supporters on all sides of pediatric drug regulation had long done: child protection. Henry I. Miller, for example, a representative of the conservative Hoover Institution at Stanford University, argued that mandating pediatric testing as part of a new drug application to FDA was not only “unnecessary,” it was “inimical to free market forces.”36 Such action was, he stipulated “detrimental to kids” because it stood to make it more expensive to develop new drugs and take longer to bring them to market.37 Instead, he suggested (without acknowledging that this practice had represented the status quo for decades) the drugs should be tailored to adults but contain labels that stressed the product had not been tested for safety and efficacy in children. Miller also recommended that FDA “publish a list of such drugs,” so that “parents and physicians could exert moral and economic pressure on drug companies.”38 He either did not know or deliberately obfuscated the fact that attempts had been underway in one form or another without success to do just that ever since the Philadelphia Pediatric Society drew attention to the lack of pediatric dosing information in the 1930s. When the FDA’s authority to create the Pediatric Rule was successfully challenged in federal court, Congress,
with input from the FDA and AAP COD, crafted new legislation to give the agency the statutory power to do so. While many drug companies remained opposed to pediatric legislation, some in industry now looked to capitalize on children’s market potential in recognition that new regulation was forthcoming. As Ronal Keeney reminded her colleagues in the trade journal *Pharmaceutical Executive*, “half the world’s six billion people are under the age of 15. Clearly there is a vast market opportunity for pediatric products.”

All this effort culminated in the 2002 Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Together, the laws provided a clear “carrot” and “stick” and created an Office of Pediatric Therapeutics within FDA to centralize all efforts related to children. The BPCA “carrot” continued patent extensions in an effort to encourage drug companies to generate pediatric data for drugs FDA had already approved. The PREA “stick” mandated pediatric data for a new drug application in which the medication might be used in children. By 2006, the statutes had resulted in 115 label changes updating pediatric information, twelve new pediatric formulations of drugs already on the market, and adverse effects information in more than fifty agents. In 2012, President Barack Obama signed legislation making these laws permanent. Since then, the numbers of drugs carrying pediatric information on their labels has continued to expand.

**Conclusion**

There are parts of this story where it can be argued that, despite fits and starts, pediatric drug development fits the progressive, triumphalist narrative common among those who wrote about the history of health care until the social history transformation of the 1960s. As a nurse who has observed children near death from overwhelming infection thrive after receiving the correct antibiotic, for example, I cannot help but marvel at what I witnessed. The history of pediatric pharmacotherapeutics is replete with heroic clinicians and researchers who advocated for children’s interests, undertook important research, and reconfigured clinical practice at particular moments in time and in ways that made children healthier and saved lives. At the same time, within the FDA and other branches of government, again and again policy entrepreneurs strove to use all the tools available to them to protect children. They deserve recognition and praise for their efforts.

But the past, like the present, is freighted with nuance and contingency. The history of pediatric drug development and testing is also a messy one, full of florid rhetoric regarding children’s importance to American society, followed by little or no effective action. It is further complicated by the fact that the people and events in this book cannot be removed from the cultural, scientific, and ethical contexts in which children became ill, parents sought advice
and care for them, health care providers practiced, investigators undertook research, and drug companies developed medications. As such, there are no easy “lessons” that can be mapped directly onto today’s concerns.

Nonetheless, the story does suggest a few conclusions worth contemplating. Competing agendas resulted in missed opportunities to act on children’s behalf. In the 1930s, the AAP, for example, identified the problem of children and drug safety but also used the issue as a tool through which to seek legitimacy for the organization. Its approach led the American Medical Association to conclude that the AAP was trying to develop a rival power base for drug-related issues and to conflict rather than action on behalf of children. In the early postwar era the AAP and Children’s Bureau battled one another for finite resources instead of working together on common issues such as pediatric drug safety. Pediatric drug research also advanced the academic careers of the physicians involved. Horace Hodes, Julius Richmond, Leon Eisenberg, and William Silverman, for example, benefited from testing drugs on children, but in many instances so did the children who received the medications. Pharmacotherapeutics improved ill children’s lives and reduced pediatric mortality in the postwar era. But hindsight was often the only way physicians knew whether their experiments would be celebrated as an effective treatment for an almost universally fatal condition—as Hodes’s bacterial meningitis sulfonamide research at Sydenham and Sidney Farber’s and Emil Freireich’s cancer research was—or whether they would yield important information but have no statistically significant effect—as Silverman’s research into retinal damage in premature babies treated with ACTH showed.

Yet, in at least some instances, we can measure and adjudicate the morality of early postwar pediatric drug experimentation. Silverman carefully drew on all the data at his disposal to design his studies. When his trial revealed that the babies who received ACTH had no less retinal damage from oxygen than untreated infants, he was surprised because preliminary animal research suggested a different outcome, as had his clinical observations. Richmond’s case is a particularly resonant example of the power of the context in shaping practice standards. One of the twentieth century’s most venerated pediatricians, he served as the first director of Project Head Start, the acclaimed 1960s federally funded enrichment program for disadvantaged children, and as surgeon general during the Carter administration. Richmond subsequently taught at Harvard Medical School, which endowed a chair in his honor. How can his activism on behalf of children be reconciled with what today seems like disregard for the risks to healthy newborn babies to whom he administered sulfonamides to ascertain more pharmacokinetic information? It is illogical to believe that Richmond callously put children in harm’s way in 1950, only to commit himself to the nation’s most vulnerable youngsters a little more than
a decade later. Rather, his history provides a potent reminder of how invisible and unacknowledged clinical norms and ethical values can be, both to practitioners and to the public. Like most physicians in the early postwar period, Richmond believed it was his responsibility to balance issues of risk and protection for individual children, and many Americans agreed.41

Like Richmond, Hodes, Eisenberg, and Silverman were young men when they undertook the pediatric drug research that launched their academic careers. They, too, subsequently played significant roles in addressing research-related pediatric ethical and social justice issues. Many years later Hodes oversaw the AAP Pediatric Research, Informed Consent, and Medical Ethics (PRIME) committee; Eisenberg became a civil rights activist and later used his perch as chair of social medicine at Harvard to press for more rigorous ethical standards in research and practice. Silverman talked freely and wrote prolifically about the challenges inherent in balancing issues surrounding risk and protection. Their trajectories can be viewed through the lens, not just of shifting research and consent standards, but of their evolving personal and professional development.42

The benefit and risk calculus for children also changed over time, further clouding issues of risk and protection. In 1940, despite a paucity of information about sulfonamide dosing and metabolism in children, it made sense for Hodes to expose children critically ill with bacterial infections to the drugs and, through trial and error, to try to save their lives from almost universally fatal infections. But clinical decision making became more complicated in the wake of penicillin and broad spectrum antibiotics. Once a drug that works fairly well is available for children with a specific condition, for example, when is it worth trying a newer, potentially better agent about which much less is known? The growing appreciation in the postwar era for infants’ and toddlers’ physiological differences from older children and adults complicated this question even more. It also made the need for more drug research both more urgent and more challenging.

But even according to the research ethics of the era in which they undertook their research, some investigators’ studies are, like Richmond’s sulfonamide research, less justifiable. Elmer H. Loughlin, Louverture Alcindor, and Aurele A. Joseph, for example, administered the broad spectrum antibiotic Terramycin (oxytetracycline) to indigent Haitian children for a protracted period of time simply to see how it affected their growth. Samuel O. Sapin’s, Ephraim Donoso’s, and Sidney Blumenthal’s intrusive and risky digoxin experimentation on healthy infants posed a high risk to those babies. Lauretta Bender expressed few qualms about exposing children to mood-altering agents and LSD for protracted periods of time. Her research questions were often vague and not designed to answer a specific question. Bender rejected the idea of the randomized trial, despite sturdy evidence that it provided robust
information. The metrics she drew upon to base her conclusions that children improved after treatment with psychopharmaceuticals were rarely defined.

A close analysis of the historical record with regard to pediatric drug research from the 1930s through the 1970s also suggests another professional group whose research participation deserves more attention—nurses. As Silverman’s anecdote in Chapter 3 about the nurse whose interventions confounded his attempts at randomization shows, nurses participated in almost every aspect of drug research. They usually administered the drugs and tracked children’s responses and adverse reactions. And they almost surely reassured parents and educated them about their child’s treatment protocol. Historians and bioethicists have largely ignored nurses’ participation in drug research. Perhaps scholars are loath to attack a professional group that they perceive as lacking agency. Nurses have struggled for autonomy and societal recognition and, as such, may fear that a full accounting of their profession’s participation in twentieth-century research does not serve their twenty-first-century agenda for more political clout and professional autonomy. It is true that nurses had significantly less power than physicians. Moreover, many of those caring for children at the hospital bedside in the early postwar era were nursing students. But, like physicians, nurses practice under a code of ethics. Although the early codes focused more on professional conduct, they articulated nurses’ duty to patients. Surely the nurses administering sulfonamides to Richmond’s patients or those participating in the hepatitis studies at Willowbrook should have known that their actions could not be easily reconciled with their profession’s ethical guidelines. In any case, American nursing has yet to grapple with its participation in what many today consider unethical drug experimentation.43

But if the lessons are subtle in some places, in others the uses—and abuses—of child protection rhetoric are hard to ignore and can serve as a stark example of the ways a weakly regulated drug economy failed children. In the 1950s, manufacturers of broad spectrum antibiotics implied through their promotional materials that they created pediatric formulations not for profit, but out of beneficence, despite evidence to the contrary. Sometimes industry also used the issue of child protection disingenuously. Nowhere is this more evident than the case of children’s aspirin. The aspirin industry co-opted the child protection rhetoric to defend its action (and inaction) on aspirin poisoning in young children, and many died as a result. From the mid-1950s to the early 1970s, aspirin manufacturers confounded every attempt to mandate safety caps and standardize pill size to prevent poisoning, parental confusion, and dosing error. On numerous occasions, industry representatives obfuscated or outright rejected the overwhelming evidence that aspirin poisoning represented a significant threat to young children. When denying the existence of aspirin poisoning in young children became impossible because of insurmountable evidence, companies blamed parents for inadequate supervision of
their youngsters and, in the audacious case of Maurice L. Tainter, toddlers and preschoolers themselves.

While Plough, Inc. did fund Jay Arena’s safety cap research after aspirin poisoning rates in children skyrocketed, his company’s executives continued to publicly fight increased regulation. They subsequently used the company’s voluntary investment in the safety cap to try to fend off a mandate and as proof that it cared about children’s well-being. Parents, health care providers, public health officials, and FDA officials who argued for new aspirin-related laws were no match for manufacturers’ stance that youngsters’ best interests were served by growing up in a nation unfettered by safety caps and other common sense mandates such as a standardized dosage for children’s aspirin. As a result of industry opposition, it took almost two decades to legislate a solution to the problem of children’s aspirin poisoning.

The history of low dose flavored aspirin also reveals the ways in which its invention, marketing, and research into the subsequent problem of aspirin poisoning in young children was freighted with notions of gender, race, and social class. Advertisements in magazines such as Parents emphasized white middle-class families and showed boys and girls playing with toys that reinforced stereotypes. African American and other minority children were underrepresented in early aspirin poisoning research. Safety cap tests gathered information about parents’ marital status, presumed proxies for social class or morality. It is an exemplar of the ways these variables suffuse American life and research in often unacknowledged ways.

The candy aspirin case is not just about the forces behind the product’s creation and its unintended consequences. It also reveals something important about the history of children and childhood—that children have more agency and power in the marketplace than is generally recognized. Plough’s St. Joseph Aspirin for Children and all its competitors could not have succeeded if children did not find it more palatable than a bitter pill or liquid. Plough spent considerable time and money worrying about how to appeal to children, and his product’s phenomenal success reveals how children’s choices inarguably shaped the postwar drug economy. Finally, the St. Joseph example also shows how, once branded, a drug can carry significant cultural power. When children’s aspirin was ingeniously renamed “low dose” and marketed as a heart disease preventive agent for older people in the wake of Reye’s syndrome, sales improved. Its iconic imprint on American baby boomers was such that one of their own became a pitchman in 2011, former child actor Ken Osmond (“Eddie Haskell” on the classic 1950s TV show Leave It to Beaver). And the St. Joseph Aspirin website today attempts to evoke nostalgia in baby boomers by reminding them that “your mom gave you St. Joseph Children’s Aspirin when you were a child. You felt better and were reassured that St. Joseph took care of you.”44
When I began this research, several pediatricians suggested informally that no one had really tried to address the issue of pediatric drug safety from a policy or scientific perspective until the latter part of the twentieth century because the issues were considered too complicated. As this book shows, that is not accurate at all. While few devoted their careers to the problem in the way Harry Shirkey and Sumner Yaffe did, this story reveals repeated instances in which leading pediatricians, organizations, Congress, and the FDA attempted to address pediatric drug safety- and efficacy-related issues. While they were successful in describing how and why children did not benefit in the same way as adults from American drug laws, this acknowledgment did little to help children. Since the issue was never one of recognition, the solution lay not merely in trying to raise awareness of it. While that may not have been clear to most stakeholders in 1938, a time when it was uncommon for physicians to prescribe drugs to children, it was certainly evident by 1975, when Caspar Weinberger openly acknowledged that children did not receive the same legislative protection as adults from the post-thalidomide 1962 Kefauver-Harris Amendments.

While not focused on children specifically, youngsters benefited from the early postwar academic, industry, and government partnerships that generated new cancer therapeutics. And just as it invested in cancer drug treatments, the federal government sought to bring organization and leadership to discussions concerning the risks and benefits of mood-altering drugs in children during this time. Although pediatric cancer and child mental illness had little in common, both received focused federal attention because of societal interest in these areas. But with regard to drug safety for agents used much more frequently in American children, such as antibiotics, government seemed to have no vehicle to generate pediatric pharmacokinetic knowledge beyond market mechanisms and informal partnerships between investigators and drug companies.

Although many people recognized the ways in which drug laws disenfranchised children from safety and efficacy provisions benefiting adults, almost everyone tried to balance what was optimal with what seemed feasible. As the Cold War deepened, the importance of distinguishing the United States from its communist adversaries convinced most stakeholders that more robust statutory oversight, in the form of child-specific laws, for a leading industry were untenable. In a country that embraced the rhetoric of the 1930 Children’s Charter, but did not seek an action plan to bring its promises to fruition, and rejected numerous nonpoverty child-related statutes such as the 1949 Children’s Research Act and the 1973 Comprehensive Child Development bill, they were probably not wrong. Given the numbers of children treated with antibiotics or steroids for common pediatric illnesses by the 1950s, more governmental safety and testing regulations for drugs with potential for pediatric
use would have challenged the narrative that limited regulation protected children better than robust governmental oversight. This belief was not new in the 1950s and it endures today. Many Americans remain ambivalent about child-focused legislation because of fears of state intrusion into family life and parental rights. President Obama’s stalled universal preschool initiative is just one recent example of resistance to stand-alone, public investments in child well-being.45

This story also provides an opportunity to study the unintended consequences of regulatory action. The 1938 Federal Food, Drug, and Cosmetic Act did not contain child-specific language. The legislators’ intent is clear from the surviving documentation; they intended drugs used in children to contain the same degree of safety information as for adults. Absent the direct mandate, however, drug companies remained free to determine how they would test new drugs. While the 1962 Kefauver-Harris Amendments added more governmental oversight of industry it, too, was silent on children. The law also made it more expensive to bring a new drug to market, providing yet another disincentive to undertake pediatric testing. It mandated adequate and well-controlled trials in an era when the scientific understanding of how to do so for the pediatric patient was rapidly evolving, presenting another challenge. The law’s well-intended requirement for informed consent created confusion about who should make such decision, which only worsened in the aftermath of Beecher’s article, the Kennedy hearings, and subsequent debates concerning fetal research and legalized abortion.

The consequences of drug laws remain dynamic. Some believe that the market exclusivity afforded to companies that undertake pediatric testing has incentivized them to move research offshore to areas with less regulation, media oversight, and fewer empowered parents. In other words, it is possible that some of the new knowledge benefiting American children has been derived from testing those in the global south. Other analyses contradict this finding, showing robust pediatric research in the United States, except for infectious diseases primarily found in the countries in which drugs or immunizations are being studied.46

Nowhere in pediatric drug development have there been more unintended consequences than in the area of pediatric psychopharmacology. In 1979, most physicians and parents seemed in broad agreement with Leon Eisenberg, who argued that psychoactive medications should be used cautiously and only after rigorous testing. Few could have foreseen that within a generation American children would be awash in prescriptions for behavioral and mood-altering drugs. There is an entire body of literature analyzing this phenomenon. Some suggest that the increase is the result of better case-finding and shifting disease definitions that have broadened the numbers of children who fit diagnostic
categories for a behavioral or mental condition. Others have argued that there is growing willingness on the part of insurers to pay for medication because it is less expensive than psychotherapy. Still others maintain that newer, more effective drugs mean fewer side effects and risks to children and, as a result, a healthier childhood for those who need medication. Finally, some believe that the reason children receive more mood-altering drugs today is rooted in ongoing changes to American society, child-rearing, and childhood. They suggest that the drug industry successfully capitalizes on anxious parents who seek every competitive advantage for their children in an era of growing economic inequality, or a collective forgetting on the part of parents, teachers, health care providers and others that healthy children sometimes act out, need to be disciplined, or cannot sit still in school.47

No matter the reason, the media regularly sounds alarm about the phenomenon in ways designed to stimulate parental and societal concern: “Still in a Crib Yet Being Given Antipsychotics” blares a December 2015 New York Times headline. In this case journalist Alan Schwarz charts the rise of the antipsychotic drug Risperdal (risperidone). Although the drug is not approved for use in children under the age of five years (and then only for a very specific indication, irritability associated with autism), almost 20,000 children under the age of two years old received a prescription in 2014.48 Finally, perhaps no other class of drugs reflects the social class prism through which American society views children than mood-altering drugs. As of 2015, Pennsylvania youngsters insured by Medicaid, for example, are prescribed psychoactive drugs more often than those with commercial insurance. And those in foster care, almost all of whom are very poor, have even higher rates; they are prescribed antipsychotics at three times the rate of other Medicaid-enrolled Pennsylvania children.49

While the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have substantively improved pediatric drug safety and efficacy, challenges remain. In October 2016, pediatrician Dianne Murphy, former director of the FDA Office of Pediatric Therapeutics, reminded Americans how far the nation had come with regard to drug regulation and children: “the biggest accomplishment is that pediatrics is no longer an afterthought in terms of product development, it’s become part of the process of developing therapeutic products.” At the same time, she also cautioned, “we haven’t tackled the really hard stuff yet, such as therapies for neonates.”50 New data continue to emerge regarding old, presumed to be safe drugs for children. On April 20, 2017, the FDA issued a Drug Safety Communication requiring a labeling change for any drug containing the opioids codeine or tramadol. A review of decades of adverse events reports revealed dozens of incidences of breathing problems in children and two dozen deaths between 1969 and
Another problem impacting pediatric pharmacology knowledge and clinical practice is the fact that not all drug study results are well disseminated, and analyses of this phenomenon focus mostly on the adult population. Finally, because the newly generated pediatric dosage formulations receive extended patent protection as a result of the BPCA incentives, they are usually much more expensive than drugs in pill form. The branded liquid form of the generic antihypertensive Lisinopril, Qbrelis, for example, costs 775 times more than the generic tablet. Because it usually requires less investment to create a liquid formulation of an already existing medication than it does to invent a new drug, some argue that reformulation profits are outsized.

Novel techniques for drug development will require fresh approaches to assure pediatric safety and efficacy. If the relatively new field of pharmacogenomics evolves as some predict, we have begun a paradigm shift almost as profound as the beginning of the antibiotic era. The old rubrics for determining drug doses will be retired, as medications for everyone will be tailored to individual needs based on one’s genetic make-up. In January 2015, President Obama committed hundreds of millions of federal dollars to this initiative. Although precision medicine holds great promise, history suggests that it will be more difficult to operationalize than might appear right now. There will be unintended consequences and unforeseen challenges, and progress will not be linear, for children or adults. Most likely, legislators, politicians, and interest groups, as they have in the past, will look for ways to frame their efforts as benefiting children, considered noncontroversial and deserving of investments in their welfare. Many of those initiatives will serve youngsters well. But others may be narrowly focused, grounded in what is considered politically or economically practicable at the moment, using children as political props, rather than what the evidence suggests they actually need. But children benefit most when, in the words of Stephen P. Spielberg, pediatrician, former FDA deputy commissioner, medical school dean, and industry executive, those who care about them think broadly, engage with both scientific and political issues, and “align . . . with all the things going on out there from the molecular to the economic.”

Our actions on children’s behalf also need to be informed by a social justice framework, one that acknowledges our moral duty—and fulfills the nation’s enduring rhetorical promise—to all youngsters. This does not mean that children always need stand-alone laws tailored specifically to them. Mandates for clean water, milk, safe highways, and thousands of other measures benefit children just as they do everyone else. But sometimes there is sturdy evidence that laws need to be tailored to their unique needs. Early in the postwar period, a
preponderance of data suggested that pharmaceutical policy was one of those instances. For decades, however, there was a lack of political will to apply the growing historical and scientific evidence indicating this was the case to policymaking because of drug industry opposition and Americans’ ambivalence regarding government regulation. As a result, in the twentieth century, the most important changes in the way we control our medications were reactive, not proactive, and were built on the bodies of Elixir Sulfanilamide children, aspirin-poisoned toddlers and preschoolers, and thalidomide babies.

As I sit here writing in early 2017, it appears that the United States is headed toward a betrayal of all three precepts—science, history, and social justice—with regard to children and drug safety. The new administration’s professed goal to undo decades of drug laws threatens the knowledge and other gains wrought by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Even if these statutes remain in place, significant changes to the regulatory apparatus in which they are nested may decrease their effectiveness. Adults can make their support for, or opposition to, the president’s agenda known. But children cannot speak for themselves, and ignoring past experience and present knowledge related to children and drug safety neglects our obligation to them and would be an abrogation of responsibility to our nation’s most vulnerable citizens.