Children and Drug Safety

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The Growth and Development of the Therapeutic Orphan, 1961–1979

By 1961, Harry Shirkey was the nation’s most strident and recognized advocate for children’s drug policy. That year he suggested that the United States Pharmacopeia (USP) work with the American Academy of Pediatrics (AAP) Committee on Drugs (COD) to address pediatric drug safety.¹ His proposal coincided with a time when rhetoric trumpeting U.S. investments in child well-being was arguably at its most vocal. The largest generational birth cohort in American history, the baby boomers, showed no signs of slowing down. More and more children were being born every year, an ever larger percentage of the population of the United States. In 1940, for example, youngsters under the age of eighteen years made up less than one-quarter of the population; by the early 1960s they comprised more than one-third.²

Beyond their numbers, proclamations regarding Americans’ commitment to children’s well-being symbolized strength and power to the rest of the world. The Golden Anniversary White House Conference on Children and Youth convened in 1960 personified this ideology. Like its predecessors, held roughly a decade apart since 1909, the conference drew together experts from the worlds of science, health care, politics, and culture. Conference leaders extolled the ways in which new drugs, especially antibiotics, had improved children’s lives. The progressive, linear narrative accompanying scientific
discussions in the three-volume manifesto arising from the conference and pediatricians' first-hand reports signaled that the decade of the 1960s would bring even more positive change to the lives of children and families.3

The nation’s new president, John F. Kennedy, himself the father of two very young children and a third that did not survive its premature birth while he was president-elect, added to the spotlight on children by professing a robust governmental commitment to children. Soon after his January 1961 inauguration, and at the urging of his sister, Eunice Kennedy Shriver, President Kennedy proposed the first National Institutes of Health (NIH) branch dedicated to a life stage—the National Institute of Child Health and Human Development (NICHD), which would focus its attention on the developing child. One acknowledged aim of the new institute was to generate more pediatric-related research and provide funding to train children’s specialists.4

By the early 1960s, the impact of the explosion of new drugs—resulting in a much more pharmaceutically oriented disease economy for both children and adults than in the past—was readily apparent. A staggering 90 percent of the medications physicians now prescribed had not been available just two decades earlier.5 Analysts estimated that more than four thousand prescription products had come onto the market in the years between 1951 and 1961. Seventy cents of every dollar spent on drugs in 1961 went toward an agent not available ten years earlier. Pediatric products were central to this rapidly growing economic sector, because of children’s growing numbers and their symbolic importance to the postwar American ideal.6 Newborns and premature babies were now not the only subcategory within pediatrics who metabolized drugs uniquely, according to research. In the case of toddlers and the cardiac drug digitoxin, for example, evidence suggested that children sometimes required as much as a 50 percent higher dose than adults based on body weight.7

Nevertheless, little consensus existed, even among elite pediatricians, that more federal oversight of the drug industry specific to children was desirable. At the 1961 Conference on Perinatal Pharmacology, Charles D. May, the influential editor of Pediatrics and a member of the AMA Council on Drugs, expressed his sympathy for the drug industry. His primary fear was that too much regulation might cause manufacturers to “panic” and “take drugs off the market,” thereby making new agents unavailable to children.8

Another AAP subgroup, the Committee on the Fetus and the Newborn, supported Shirkey and disagreed with May, taking a vocal stance in the wake of the gray baby syndrome crisis. Under the chairmanship of William A. Silverman, who was now a national leader of the new pediatric subspecialty known as neonatology, the committee pushed for more “extensive preclinical investigation than is being carried out at the present time,” because “there is increasing awareness” of the necessity of making “more than a quantitative
distinction between infants and children. The fetus and the newborn infant often behave so differently as to warrant consideration as separate categories of the human species.” Silverman’s adrenocorticotropic hormone (ACTH) research on retinal damage in premature infants receiving oxygen a few years earlier had turned him into an activist for better research into their needs.9 The warnings from the Committee on the Fetus and the Newborn proved horrifyingly prescient within a few short months when the Washington Post broke the thalidomide story, bringing it to the forefront of legislative debates in 1962. The tragedy also ended the unbridled optimism for a boundless future of health improvements from an ongoing stream of new wonder drugs that had begun with the sulfonamides in the late 1930s.10

**Thalidomide and Its Aftermath: A New Era of Safety for Children?**

A tranquilizing and antinausea agent widely employed in Europe and Japan, thalidomide had been under consideration for FDA approval since September 1960, but a newly hired FDA physician and pharmacologist, Frances O. Kelsey, stalled the application.11 Under the 1938 law, the FDA had sixty days to review a new drug application. If the agency took no action during that time frame, the product was automatically approved. Kelsey reviewed the submission, concluding that the supporting evidence for thalidomide was weak. She decided to use an FDA loophole that delayed an incomplete application until the distributor supplied the requested information. She waited until two days before the end of the sixty-day review period to send a letter demanding additional toxicity data from the William S. Merrell Corporation of Ohio, which hoped to become the U.S. distributor of thalidomide under the brand name “Kevadon.”12

Although Merrell and her superiors pressured her to approve the drug, Kelsey refused to buckle and sent five more such letters requesting more data. She grew more worried about thalidomide, particularly after meeting in February 1962 with John Nestor. Nestor informed her that one of his professors from Johns Hopkins, pediatric cardiologist Helen Taussig, had just returned from Germany, where she had consulted on what appeared to be an epidemic of congenital heart defects and other anomalies.13 Kelsey and Nestor traveled to Baltimore to learn what Taussig had found. Taussig’s report convinced Kelsey that the many defects, most notably the frightening long-bone malformation known as phocomelia (Greek for “seal limb”), that she observed in hundreds of German children could be attributed to fetal exposure to thalidomide. Kelsey contacted Merrell to warn them about Taussig’s finding. Although the FDA had not yet approved thalidomide for sale in the United States, she knew that under the 1938 law drugs could be administered to
patients without FDA approval so long as they were labeled as investigational and the company maintained records of its studies. Her fears that at least a few pregnant women in the United States had been prescribed thalidomide were confirmed when she learned that more than 1,000 physicians had been supplied with the drug.14

When reports of Taussig’s investigation reached Estes Kefauver and his staff, they leaked the thalidomide story to the media. Kefauver saw the chance to attract attention to his concerns regarding the U.S. drug industry, and he made sure Taussig testified on Capitol Hill.15 Taussig herself saw the thalidomide crisis as an opportunity to broaden the political discourse beyond Kefauver’s primary focus on advertising, increased competition, and stronger antitrust rules to more explicit protections governing drug safety in pregnant women, fetuses, infants, and children. Moving quickly, Taussig presented findings from her German trip to the academic pediatricians who comprised the American Pediatric Society (APS) conference, and she contacted leading pediatricians all over the country, asking them to mount a letter-writing campaign to pediatric organizations and the FDA in support of more stringent monitoring of the pharmaceutical industry.16

But despite the thalidomide crisis, some American medical leaders still disagreed about the need for new legislation. Philip S. Barba, associate dean at the University of Pennsylvania medical school, for example, explained to Taussig in July 1962 that he remained “fearful of writing things into laws.”17 Well-known physician Morris Fishbein, editor of Medical World News and former editor of the Journal of the American Medical Association (JAMA) even wrote a letter to the New York Times attacking those who testified at the Kefauver hearings as “mavericks” and “scientific Leftists.”18 He took Taussig to task by name, claiming that her call to test drugs in pregnant animals before their approval would escalate costs. He also derided her as not “qualified as an expert in drug research, development, or promotion, or in the laws regulating these activities.”19 Since brokering decisions about drug efficacy traditionally fell within medicine’s province, both Barba and Fishbein probably worried that increasing the government’s authority would ultimately supersede or replace that of physicians.

Fishbein was no match for Taussig’s sophisticated media strategy, however, as she announced warnings about thalidomide specifically and spoke out on the need for pediatric drug safety in general in numerous radio, television, magazine, and newspaper interviews, speaking out in ways that Kelsey and Nestor, as government employees, could not do publicly. At the same time, she worked closely with Kefauver and his staff to add what she hoped would ensure broader and more meaningful safety protections for fetuses, infants, and children into the bill.20 One of her most effective tools was showing legislators pictures of thalidomide-maimed children. She riveted them with a gendered
appeal, not as legislators but as American fathers: “I am quite sure that if any of your wives had given birth to a child with this type of malformation, you would want to exert all the influence you possibly could to prevent the occurrence of another similar tragedy.”

Once she had policymakers’ attention, Taussig argued for new protections for children: “[S]afety and efficacy go together. . . . [A] drug cannot be assumed to be safe for infants and children because it is safe for adults. . . . [I]t is not sufficient to merely state in tiny print somewhere at the end of the advertisement of a drug: ‘Warning: this drug may not be safe for children (or for pregnant women) because this aspect has not been tested.’ . . . [S]afe should mean safe for all ages and all groups of people.”

The cumulative efforts of Kelsey, Nestor, and Kefauver yielded talking points for the FDA leadership. In June 1962, the director of its Bureau of Medicine, Ralph G. Smith, gave a speech at the National Meeting of the Drug and Allied Products Guild, wherein he warned: “[E]xperts in the field of pediatrics have pointed out that infants and children may react to drugs differently from adults. . . . It is no longer considered safe to derive children’s doses from safe adult doses by age or weight formula. Safety of new drugs for infants and children must be shown by actual use in the various age groups.”

Just as agency staffers had warned companies the previous year in *F-D-C Reports*, the FDA was trying to get the drug industry to undertake, or at least voluntarily underwrite, pediatric testing. But some senators wanted government to play a stronger role than simply encouraging industry from the sidelines. As legislators delved deeply into the pharmaceutical industry during the Kefauver hearings, their concern at the lack of communication between different branches of the federal government increased. Minnesota Democrat and pharmacist Hubert Humphrey, for example, expressed shock on the Senate floor that his staffers had found a complete lack of “basic collaboration” regarding issues of fetal drug safety between the Children’s Bureau, NIH, and the FDA.

By the time President Kennedy signed the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act in October 1962, Kelsey was a national heroine, and the FDA received sweeping new responsibilities, involving it in all phases of the drug development process. Both pediatricians and politicians were optimistic that the new law would improve pediatric drug safety. The FDA now supervised all clinical testing for any new drug, setting standards that affected every aspect of drug company operations, such as, for example, the type of records they needed to maintain and the manufacturing guidelines they needed to follow. Other significant changes governing the drug approval process included new informed consent provisions for clinical trials that the FDA deemed “adequate and well-controlled.” Manufacturers filing a new drug application also needed to supply evidence of a drug’s efficacy; that
is, the drug had to “have the effect it purports or is represented to have . . . for the use intended.” In other words, a company that applied for FDA approval needed not just data that the drug was safe, but also evidence to support its curative or ameliorative effect on the condition it was prescribed to treat.

Harry Shirkey convened an urgent ad hoc meeting on October 28, 1962, at the American Academy of Pediatrics annual conference. Gathering just eighteen days after President Kennedy signed the Kefauver-Harris Amendments, the twenty attendees included many of those who had campaigned actively for the new legislation, such as John Nestor and Helen Taussig. Multiple AAP subcommittees sent representatives to the meeting, as did the Pharmaceutical Manufacturers Association (PMA), a drug industry trade organization. The mood was celebratory as Shirkey led the group in crafting recommendations they believed necessary to implement the new law, such as mandatory testing in pregnant and infant animals before human clinical trials could begin; stronger pediatric pharmacologist representation in FDA decision-making; development of protocols for clinical testing that incorporated the metabolic and physiological specifics of the developing child; and procedures for assuring pediatric clinical drug trials prior to FDA approval.

Ongoing congressional hearings were scheduled for March 1963 in order to investigate existing FDA procedures for a broad range of drug-related issues—including those concerning pregnant women, neonates, and children—in the wake of the new law. Hubert Humphrey prepared exhaustively for his leading role, one that drew on the pharmaceutical knowledge he possessed and most legislators lacked as well as his deft political skills. He requested written summaries about pediatric drug-related issues from stakeholders such as the AAP and invited comments from a number of scientists, pediatricians, drug researchers, and FDA thought leaders. Humphrey asked them all to address the same questions, which reflected his belief in the power of government to effect positive change:

Has the U.S. Government, including the Food and Drug Administration, done all that it should have done in cooperation with your profession and the pharmaceutical industry in the interest of the well-being of infants and children? If not, what should it have done earlier? Whether or not the past record was satisfactory, what should the Federal Government be doing now and what should it do in the future with respect to drug safety and efficacy?

Humphrey also wrote to Surgeon General Luther Terry in early March 1963, expressing his frustration and “deep personal feelings” that a research grant application that aimed to investigate the effects of drugs on newborns, particularly premature babies, had not been funded by the NIH, and warning that he intended to spotlight this decision at his forthcoming hearings.
He proclaimed in the letter, “[t]o me, it is shocking that as of March 1963 in this, the leading medical Nation on earth, funds have been so lacking that this indispensable concept”—that is, the study of drugs in children—“is still only in the proposal stage.”

As the hearings began on March 21, Humphrey called an eager John Nestor to Capitol Hill, asking him to explain publicly the insider’s perspective he had already provided to Humphrey’s staff in great detail. Nestor’s remarks unequivocally set the hearing’s tone: “In the past, adequate recognition has not been accorded to the problem of drug therapy in infants and children. There has been a failure to recognize that the metabolism and action of drugs often differ both qualitatively and quantitatively in this special group.” Nestor began his testimony by explaining the informal manner in which he became an FDA consultant. “Upon reading in a medical magazine of the problems of FDA in obtaining and retaining qualified physicians,” he made an appointment with the FDA commissioner and “offered my services.” Believing that the agency sought his “frank and open” opinion, he accepted a position, but he quickly became disenchanted:

Unfortunately, although my frankness was acceptable before I was hired, after joining the organization I found that any medical opinion that raised issues that involved reappraisal of past decisions, past policies, or past commitments to the pharmaceutical industry would be challenged—not in a healthy scientific atmosphere, but rather, with indifference, disapproval, or even hostility. This, unfortunately, was frequently the case with drugs for pediatric use.

Pointedly reminding the congressmen that he was the first board-certified pediatrician ever hired by the FDA, Nestor appeared to hold nothing back, excoriating the agency’s operating procedures in general and citing a number of instances in which he alleged incompetence. He painted a damning portrait of the FDA regarding pediatric policies, claiming that staffers involved in pediatric-related decisions lacked an appreciation of the latest scientific research relevant to children. As such, they possessed “a failure to recognize that the metabolism and action of drugs often differ both quantitatively and qualitatively in this special group” and a “disregard of the long- and well-established medical principle that infants and children often react differently to disease and drugs than do adults.”

Moreover, according to Nestor, the FDA did not seem concerned about its ignorance regarding children, stipulating that “the standard the FDA aspired to” with regard to children was “perfunctory and meager”:

Applications were approved for [pediatric use] . . . despite the fact that the testing had been carried out in only a few children and very few infants in many
instances. There seemed to be a general disregard for the need to establish the safety of the use of the drug in the pediatric age group. What may be regarded as an “established” drug and therefore, not a “new” drug in adult medicine is often a new type of treatment for adults and children, raising all the questions of rationale, risks, and usefulness.35

In other words, he was trying to explain in lay terms that children and adults often received the same drug for different purposes; for example, antihistamines were used for treating allergies in adults and for treating colic in infants. Nestor concluded by hinting at fraudulent activity on the part of industry, which, he claimed, was ignored by a complaisant FDA.36

Charles May, now professor of pediatrics at New York University School of Medicine and former editor of *Pediatrics*, followed Nestor’s testimony and provided his views as an expert with outsider status relative to governmental processes. May was much less inflammatory than Nestor and, interestingly, said nothing about his 1961 remarks at the Conference on Perinatal Pharmacology, in which he had voiced weak support for any new regulation. Perhaps as evidence of just how tepidly he supported the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, however, he put the blame for the lack of data about newborns and pharmacology not on industry or government regulations, but on pediatricians who had not “given sufficient attention” to the problem.37

Although May’s testimony was surely a relief to FDA leadership, the damage from Nestor’s accusations required a response. Agency commissioner George P. Larrick sent a letter to Humphrey that same afternoon, rebutting each of Nestor’s charges. With regard to Nestor’s claim that FDA staff not only ignored children but lacked a basic understanding of how they differed from adults, Larrick cited multiple cases to demonstrate the reverse. For example, he provided the text of a speech in which Bureau of Medicine director Ralph G. Smith detailed the latest understanding of newborn physiology and pharmacodynamics. Larrick particularly faulted Nestor for not making clear that almost every one of the instances he cited had occurred before the Kefauver-Harris Amendments became law. But none of this seemed to matter to a furious Senator Humphrey. He responded to Larrick’s rejoinder with his own “Initial Rebuttal to the Rebuttal.”38

The focus of the hearings now turned away from the past and toward considerations for the future, such as how best to evaluate drugs according to the new rules for safety and efficacy, as well as the pressing need for more qualified investigators to undertake pediatric drug research. Witnesses and congressmen expressed considerable optimism about the new NIH branch, the NICHD, and its potential role in training the investigators necessary to generate new science as well as to teach clinicians about pediatric pharmacology.39
Alaska Senator Ernest Gruening, a doctor who had worked as a journalist before he entered politics as a New Deal reformer, emphasized two issues he felt needed to be addressed immediately. First, the NIH had no obstetricians and only one pediatrician on its grant-making staff, and, second, with the exception of poison prevention and treatment, not one of the 6,200 hospitals involved in the FDA system for reporting negative drug outcomes was a children’s hospital. Gruening believed that the answer to children’s underrepresentation in pharmaceutical development lay in the NICHD’s potential to expand the science and increase the number of researchers necessary to address these issues. He expressed his hope for such a plan when introducing Stanford University biochemist and pediatrician Norman Kretchmer, who had recently published an editorial in *Pediatrics* in which he had championed these very thoughts. Kretchmer did not mince words when it came to accountability for safety and efficacy. He argued that the “responsibility is on the manufacturer to take particular care to comprehend and document the entire range of action of a drug when it is to be used in the treatment of the young infant.” Provocatively, he dryly suggested that if pharmaceutical companies took the money they put into advertising and used it to support clinical pharmacology, they would have ample funding to assess drug effects for infants and children.

Humphrey also presented data that documented a meager $3.7 million in current NIH funding for twelve pediatric drug-related studies. Although he did not say so for the record, the former pharmacist surely saw a glaring issue in investigations receiving NIH support. The majority of them focused on a narrow population. One study, for example, looked at the way growth hormone affected developmentally disabled children; another focused on pediatric cancer treatment. None of them studied metabolism, distribution, absorption, excretion, and other metrics for the drugs most commonly used in children, information increasingly referred to by the term *pharmacokinetics*.

Finally, Humphrey introduced into the congressional record a number of letters to the government from parents and doctors. Some of these expressed heartfelt gratitude to Kelsey, but others detailed the worrisome side effects of drugs their children had taken. One parent, for example, explained a reaction her ten-year-old son experienced as a result of Compazine. “His eyes became fixed in his head. He couldn’t move them. His facial muscles became rigid. His body began to twist and pull until he had no control.” The letter writer assumed her son was allergic to the medication, but later found a magazine article that acknowledged this potential side effect from the drug. Upset that no one had informed the family, she beseeched Humphrey to “help make this fact known so that parents may become aware of the harmful effects of these drugs.” Letters such as these provided the evidence Humphrey wanted to
show that the American parents demanded more governmental oversight of drug industry practices.

**The Birth of the Therapeutic Orphan**

Shirkey increasingly saw his job as getting all stakeholders for pediatric drugs to “communicate the same message” to industry and policymakers. In an effort to accomplish this aim, he added membership on the AMA Council on Drugs to his USP and AAP appointments. “When anything came up, I brought those three together and made them work it out,” he wrote. The AAP executive board had endorsed Shirkey’s request to broaden the COD charge to one that encompassed all issues surrounding children’s drug testing, safety, policy, and physician education.

In the wake of the Kefauver-Harris Amendments, Shirkey was at first optimistic that structural changes in pediatric drug development and regulation would be forthcoming. Within the year, however, he saw ominous signs that the legislation might not protect children in the ways he hoped it would. He noted disappointedly that drug companies circumvented the additional pediatric drug safety information the law mandated by adding labels that declared, “This drug is not indicated for children.” Because this practice became the norm, individual companies were not at a competitive disadvantage. Without a specific requirement that anyone systematically gather new evidence through a clinical trial or critique already extant pediatric data, by 1964 Shirkey felt children were being left out of the safety and efficacy improvements already benefiting adults. He described this phenomenon with a memorable, Dickensian phrase—*therapeutic orphan*—which would become his mantra in his critique of American pediatric drug policy.

The FDA acknowledged the problem Shirkey was working so hard to publicize at one of its meetings in 1965. In response to a request from the AMA Council on Drugs for how to indicate on a drug label the lack of pediatric data, eight FDA staffers drafted a statement: “This drug ordinarily should not be used in children since safety and effectiveness information on its use is not available.” The FDA, however, took no further action, most likely because at that moment the agency faced a much broader problem than pediatric drug safety. The Kefauver-Harris Amendments assigned the FDA the daunting task of overseeing an efficacy review, determining whether the thousands of drugs brought to market since the 1938 Federal Food, Drug, and Cosmetic Act had the effects their manufacturers claimed. In 1966 the agency contracted with the newly created Drug Research Board of the National Academy of Sciences to plan a review of each drug. Over the next three years, the thirty panels of the Drug Efficacy Study Implementation (DESI) program analyzed
evidence surrounding 4,000 drugs in the hopes of quantifying their therapeutic utility.

Although pediatricians served on a number of the panels and Harry Shirkey played a leadership role because of his appointment to the study’s Policy Advisory Committee, the DESI initiative added little new information specific to children. Operationally, the thirty panels were organized by drug class (such as anti-infective) or organ system (such as cardiovascular), rather than by life stage or other classification. Pediatricians were dispersed through the various panels, making conversations about children difficult. More problematic, however, was that the quality of scientific data for pediatrics just did not exist. It was already clear to Shirkey by 1966 that participants lacked a “firm body of knowledge upon which to base a scientific opinion” about pediatric efficacy in a meaningful way as mandated by the 1962 Kefauver-Harris Amendments. Ultimately, the vast majority of research in the published literature or the drug houses that met DESI requirements included adult subjects only.

To generate the necessary evidence to appraise pediatric drug efficacy using randomized trial data, the few available investigators encountered formidable barriers. No one was really sure how to design a study with meaningful endpoints in a child, an evolving physiological target. Under what circumstances could adult data be extrapolated to children? Which animal models translated to humans? Were drug studies needed for each pediatric subpopulation (premature babies, newborns, toddlers, preschoolers, school-age children, adolescents)? What was the best metric to use in terms of dosage calculation? Should the scientific template be predicated on percentage of adult weight, on body surface area, or on an entirely different model? Given the paucity of scientists or clinicians with the necessary training, who was qualified to develop, conduct, and analyze the investigations?

The NICHD had initiated a developmental pharmacology program to address the scientific issues regarding the fetus, infant, and child, but the institute leaders acknowledged that it would take years for the investment to pay off. Stakeholders could not even agree about pediatric pharmacology’s place within the medical specialty substructure, a decision with both philosophical and reimbursement implications. If, for example, pediatric pharmacologists were situated in medical school clinical departments, revenue streams from grant funding accrued there, and not in the basic science departments that often trained investigators and designed the studies. Finally—and critically—who should incur the cost burden of pediatric drug development? Government? Industry? Parents? Insurers? Hospitals? Medical schools?

Furthermore, the tensions within traditional sources used to guide clinical practice—medical journals—became increasingly suspect as pediatricians scrutinized advertisements in these journals with a more critical eye, using the 1962 safety and efficacy criteria. Journals needed advertising to stay
in business, but advertisements did not go through the peer review process the way scientific articles did, and problems ensued. For example, in a 1966 letter to the editor in *Pediatrics*, pediatrician Arthur Eidelman expressed his dismay that the journal had accepted an advertisement from Merck and Company. The promotion claimed that the steroid Decadron (dexamethasone) was a useful therapeutic for croup. Eidelman argued that the journal’s acceptance of an advertisement “implies de facto endorsement by the Academy of the safety (if not the efficacy) of the particular product or mode of therapy.” He complained that the copy did not explain the drug’s utility for different types of croup (e.g., viral vs. bacterial), and he was upset that it had not noted that Decadron’s use was “still controversial.”56 Finally, he criticized the fact that the journal’s editors had accepted the paid promotion because “What is obviously needed. . . is a large, well-controlled, double-blind (and probably inter-hospital) study to clarify its efficacy in the management of the different types of croup.”58

A somewhat chastened editorial response by Clement A. Smith did not disagree with Eidelman’s charges, yet he attempted to reassure readers that advertisements were carefully vetted. According to Smith, *Pediatrics* had turned down twenty-five drug- and food-related advertisements and forced twenty-eight others to change their language. He conceded, however, that the journal’s system was “not infallible” and that in this instance an error may have been made.59 Smith reminded readers of the journal’s policy warning pediatricians to make clinical practice decisions based on “scientific reports . . . rather than from other sources.”60 In other words, *Pediatrics* tacitly recommended that its subscribers read advertisers’ claims with a skeptical eye. There is no evidence that Eidelman’s complaint—or others like it—made their way to the FDA for follow-up.

Another challenge to the traditional practice of physician-determined estimations of risk versus benefit analyses as the primary criterion for children’s participation in a drug trial, was the mandate included in the Kefauver-Harris Amendments that stipulated informed consent for all research subjects, although exactly what that meant was still under debate. Moreover, the ethics surrounding human experimentation were not confined to the United States. In 1964 the World Medical Association, a group of national medical organizations, published research principles known as the Declaration of Helsinki. These guidelines distinguished between therapeutic and nontherapeutic research, stipulated that all research undergo independent ethical review, and mandated informed consent. With regard to children, the declaration supported the rights of parents to enroll their child in a research study, without restrictions. In other words, a parent’s consent absolved investigators of ethical concerns, even if the study brought risk to an individual child, such as a study undertaken to increase scientific knowledge that brought no potential for
benefit to him or her. By the mid-1960s the FDA required that companies and researchers secure patients’ consent before they received an investigational drug. Researchers, however, found a loophole that they could use if they so chose. The FDA Statement of Investigator form required consent “from subjects, or their representatives, except where this is not feasible or, in the investigator’s professional judgment, [doing so] is contrary to the best interests of subjects.” This qualifier effectively permitted investigators to substitute their own judgment for parents whenever they chose.

All these issues—lack of qualified investigators, research design, consent, funding for pediatric drug research, and advertising debates—needed to be considered in the context of tectonic shifts in health care economics occurring in the mid-1960s. More American families had health insurance through private employer-sponsored plans. The elderly and indigent could look to new public programs, Medicare and Medicaid. The old, largely self-pay or charity-supported health care model in which patients often participated in research or acquiesced to medical care without question was waning.

A signal that ethical norms in the United States were in transition arrived in 1966 when Harvard anesthesiologist Henry Beecher published a damning critique of contemporary biomedical research ethics. In his article, Beecher described twenty-two research studies from the mainstream medical literature that he judged ethically troubling, four of which included children. One article Beecher condemned was emblematic of the type of research undertaken in earlier decades by Hodes, Richmond, Finland, and other investigators. The article, published in the prestigious New England Journal of Medicine, explained that Wyeth Laboratories had funded Howard E. Ticktin and Hyman J. Zimmerman, George Washington University medical school faculty members, to study the effects of the antibiotic Triacetyloleandomycin (TriA) on institutionalized “mental defectives” or “juvenile delinquents” at the Laurel, Maryland, Children’s Center. The participants, some as young as thirteen years old, were healthy except for their acne. The study was undertaken to “determine the incidence and type of hepatic dysfunction” from TriA. More than half of the fifty patients in the study experienced signs of liver problems from the drug, at which point they were subjected to an invasive liver biopsy; several individuals required more than one such procedure. Liver function tests eventually returned to normal in all subjects.

As soon as Beecher’s critique was published, he began receiving letters from physicians. While not drug-related, one exchange between Beecher and a young pediatrician at the University of Rochester medical school reveals how difficult it could be to initiate a dialogue about ethical concerns. The pediatrician, Evan Charney, told Beecher about an episode that had been troubling him since his training days at Boston Children’s Hospital three years earlier. In
1963 he had written to A. Ashley Weech, editor in chief of the *American Journal of Diseases of Children*, expressing concern about a recent study in which newborn female infants were restrained, had a catheter placed in their umbilical vein, and received an intravenous infusion for a study of newborn water balance. Charney pointed out that this experiment was undertaken to generate knowledge, not to benefit the children enrolled. As such, he believed the study “a debatable case of medical judgment which requires careful scrutiny.”

Charney included his back and forth correspondence with Weech in the materials he sent to Beecher. Weech replied to Charney explaining that he would not publish his letter because it might “do a great deal of harm to the scientific reputations of a group of young men.” Weech also commented in a patronizing tone that when he was a junior doctor like Charney, he, also, was “too young at the time” to understand the importance of some investigations. Instead of publishing Charney’s critique, Weech offered to contact the lead physician on the study, T. C. Panos at the University of Arkansas. Weech subsequently forwarded to Charney his correspondence with Panos, in which the latter acknowledged the difficult balance between risk and protection. Nonetheless, Panos agreed with Weech about Charney’s concerns and motivations: “[T]here is the danger . . . of confusing ethics with self-righteousness.”

In Beecher’s reply to Charney, he made clear that Panos’s research was just the type of study he had been criticizing. He bluntly told Charney that the *American Journal of Diseases of Children* should be “downright ashamed of itself for the attitude it took.”

### National Conferences on Pediatric Pharmacology, But Little Progress

Progress on pediatric drug safety seemed stalled. Clinicians could rely only on their own judgment or the published literature. For example, in 1967 the FDA investigated the case of an eight-year-old child who had died from an Eli Lilly and Company drug used to treat parasitic infections. The doctor prescribed the drug, Delvex (dithiazanine iodide), according to the unnamed resource he consulted. Delvex had not received FDA approval for use in children, so there were no FDA-sanctioned pediatric dosing guidelines. The suggested dosage published in the manual was most likely predicated on clinical trial and error and, in this case, proved fatal to a child. Worse yet, the paucity of pediatric drug knowledge was becoming normalized in the pharmacology literature. For instance, Louis S. Goodman, the renowned professor of pharmacology at the University of Utah, authored many editions of a definitive textbook, *Pharmacological Basis of Therapeutics*, with Yale University medical school pharmacologist Alfred Gilman. The authors’ notes and correspondence for the volume throughout the 1960s—a period in which there was a tremendous expansion...
of knowledge in other areas of pharmacology—barely mention pharmacokinetic issues specific to children. Discussions regarding how to move forward on children’s drug safety and efficacy issues now pervaded research, clinical practice, industry, FDA, and NICHD discourse. The National Academy of Sciences, FDA, NICHD, and the National Institute of General Medical Sciences (NIGMS), which oversaw pharmacology research training programs, decided to sponsor an invitational conference in 1967 in an effort to help the FDA “fulfill its responsibility . . . [and] . . . approve recommended dosages for drugs and directions for their safe use” in the pediatric population. By bringing together academic pediatricians, industry, and the FDA, the conference leaders aimed to promulgate a set of regulations governing children and drugs.

If Harry Shirkey attended the conference, no documents record his participation. In fact, his name does not appear in the list of attendees invited, a curious omission for a pediatrician with his credentials. Perhaps he was absent because he was then serving as a visiting professor at Honolulu’s Kau keolani Children’s Hospital, far from the conference site and planners in Washington. Perhaps the organizers at the FDA found Shirkey’s term therapeutic orphan unnecessarily inflammatory or confrontational, and expected his participation to follow suit. Or perhaps tensions among the few pediatrician-pharmacologists on the national scene had become heightened. A reorganization of the AAP Committee on Drugs (COD) resulted in Shirkey’s chairmanship going to Harvard-trained Sumner Yaffe, a pediatrician at the State University of New York at Buffalo medical school. Finally, it may have been that Yaffe’s basic science research training and experience (as well as his close affiliation with NICHD) embodied the pedigree the conference conveners sought.

The meeting began optimistically and ambitiously, with the stated goal of addressing issues of safety and efficacy that the FDA could use to quickly generate a regulatory template. When Eli Lilly and Company’s Charles N. Christensen spoke for the drug industry, however, he offered a sobering perspective. First, he sought to mute expectations, explaining that instead of presenting an “ideal” program as organizers had requested, he wanted the group to consider what was “practical” instead. He argued that “before we get to the question of how to do it [study pharmacokinetics in the developing child], we must consider, are we going to do it?” Christensen did agree with the broad statement that “we need more and better evaluation of drugs in infants and children.” His solution, however, left all the control and decision-making about how and whether to test with industry, advocating for an advisory group to consult with drug companies and the FDA “[i]nstead of a stringent set of ‘this you must do for every drug’ rules.” Christensen also stressed what industry saw as a barrier to complying with the Kefauver-Harris Amendments as the
law related to children: too few trained researchers and a lack of pharmacokinetic guidelines.

Physician Charles F. Weiss, representing Parke Davis and Company, agreed with Christensen, characterizing what he saw as an “emotionalism” surrounding pediatric experimentation that heightened the risk for industry and investigators. He believed the stakes were high, that the negative public relations consequences of a study that harmed children would likely be worse than for other groups. On the other hand, Weiss pointed out, because children occupied a symbolic place in the United States as deserving innocents who needed protection, there could be a payoff in public goodwill for any company that successfully developed a new pediatric medication. Weiss also acknowledged that children could serve as evidence of companies’ beneficence, noting that charities do not “put up the picture of an old alcoholic or prostitute on its posters to get money. Instead they use the picture of a little child in braces.”

Pediatrician Charles U. Lowe from the University of Florida medical school outlined the objectives for the final panel, one that considered ways in which the media could aid “in convincing the public about the need to enroll children in drug studies in order to generate the necessary data.” But this session, too, revealed that there would be no easy resolution to how best to move forward on issues concerning pediatric drug knowledge. Panelist Mildred Spencer, medical editor for the Buffalo Evening News, reminded attendees that their access to research participants was likely to decline in the wake of Medicaid because the indigent could no longer be pressured to do so in exchange for charity care. She ominously synthesized the challenges ahead, ones that could not be fixed easily by a public relations campaign:

The public today has taken the attitude, and it is my attitude, that nothing should be done on someone else’s child that we would not want done to our own children. . . . The press cannot create a climate of favorable public opinion for you. We tell the story. The reaction of the public depends on what you do. . . . It may be that [institutionalized mentally retarded] children are not as valuable as the future citizens the drugs may save, but I do not think the public is going to accept using them as test subjects. And I do not think anything the press can say will make the public accept it.

In the wake of the conference, the AAP COD developed a formal liaison relationship with the FDA and an advisory role to the Pharmaceutical Manufacturers Association. Committee membership doubled and the group began meeting more frequently, publishing an ongoing commentary about pediatric drug-related issues in Pediatrics. Additionally, Sumner Yaffe successfully convinced the AAP executive board that there was need for a new workgroup, the Section on Pediatric Pharmacology, which would address educational issues
pertaining to drugs. The COD, however, would remain the official AAP voice for drug policy. The revamped COD now included a place for industry representation and added two of the more vocal attendees at the recent conference, Charles H. Christensen and Charles Weiss. Even though Shirkey had left the COD, he remained an ex officio presence because of his affiliation with the AMA Council on Drugs. An FDA representative, medical officer Jean Lockhart, filled the final committee position.85

All the issues present at the 1967 conference resurfaced in May 1968, when infant formula maker Ross Laboratories sponsored a pediatric pharmacology symposium. The Ross meeting began with frustration and finger-pointing, unlike the positive tone that characterized the start the previous year. Conference chair Alan K. Done of the University of Utah medical school opened the gathering by expressing his frustration that “concern and talk” about pediatric drug safety had not, as yet, yielded “progress and practical solutions.”86 Next, neonatologist William A. Silverman posed a blunt question that signaled his impatience with the status quo: “What is the FDA doing to stimulate research in pediatric pharmacology?”87 Daniel Banes, FDA associate commissioner for science, responded reluctantly that the agency’s primary role was, thus far, that of a “gadfly to induce industrial firms and universities to conduct research” because it lacked grant-making authority.88

When it was his turn, C. Joseph Stetler, president of the Pharmaceutical Manufacturers Association, expressed industry’s belief that “needless and arbitrary limitations on drug development” put in place a few years earlier in the wake of the thalidomide disaster made it harder for them to do business.89 Speaking in general terms, and without discussing pediatric issues, he stressed the increased costs companies faced because of the Kefauver-Harris Amendments, the results of which, he argued, were slowing the pharmaceutical development juggernaut that began in the 1940s. The only area in which industry and FDA reached consensus at the meeting was that too many pediatricians refused to undertake the necessary clinical research, even with drug company sponsorship. Shirkey did attend the Ross conference and spoke eloquently about the growing “unreality” of the situation.90 He also pointed out the way physicians were put “in a very difficult legal position” because “drugs which ultimately will be used in infants or children” include instructions “stating they should not be so used.”91 A second conference ended with no real consensus or forward movement.

The FDA received a number of queries around this time from individual pediatricians whose concerns over the impasse echoed Shirkey’s. For example, Melissa A. Warfield, medical director of the Children’s Hospital of the King’s Daughters in Norfolk, Virginia, sought guidance about the antiemetic drug Tigan (trimethobenzamide hydrochloride), specifically about the label’s “Not for use in children” warning. Given that her institution cared for children from
birth through eighteen years, how should she interpret this guideline for her hospital’s formulary? In internal memoranda, FDA staffers debated the definition of a child in the context of Warfield’s letter. In his reply to Warfield two months later, B. Harvey Minchew, acting deputy director of the FDA Bureau of Medicine, suggested that she consider that Tigan was approved for use in those over the age of twelve years. He indicated his displeasure that the manufacturer had not provided more precise data, pointing out that the FDA “generally recommend[s]” that companies do so. He also reminded Warfield of her right to use drugs off-label, meaning that a doctor could prescribe the drug for a purpose or a dosage he or she chose. The physician, he noted pointedly, had the right to use “commercially available drugs in a manner which his knowledge and experience indicate to him is in the best interest of his patient.”92 Although no further correspondence between the two exists, it is probable that this delayed reply, one that put the onus of deciding safety and efficacy back on Warfield, did not provide the guidance she sought.

In 1968, in a speech at Harry Shirkey’s Children’s Hospital in Birmingham, Alabama, FDA commissioner James L. Goddard publicly and frankly acknowledged the agency’s frustration about therapeutic orphans. Situating the agency’s work in the context of increased funding for maternal and child health services proposed by President Lyndon B. Johnson that year, he informed those in attendance of the FDA’s general efforts in the approval, monitoring, and regulatory processes for drugs. Goddard expressed his concern that the FDA was not receiving investigational plans from drug companies for children. But he also articulated the agency’s limitations. “Unless such data is submitted to us,” he said, “it is not legally possible for the FDA to permit anything else [other than a label stipulating the drug has not been established as safe for children] on the label of a marketed drug other than that prohibitive clause.”93 He asked his audience of pediatricians to take ownership of the problem because he was “loath to believe that all the tough questions must be passed on to the Government for final answers. Surely this issue of drug use in children—the prohibition in the labeling being based on the void in the clinical back-up—surely this issue can be examined and resolved by physicians themselves.”94 Goddard had admitted that the problem might seem “insoluble,” although he did try to end optimistically, claiming he remained “confident” of a solution, one that accounted for children’s “moral, ethical, and medical issues.”95 He assured the group he believed that children—“who are now receiving such comprehensive attention in health” from President Johnson’s Great Society programs—should not “be literally deprived of useful drugs.”96 Undoubtedly Shirkey, if not others, could hear that Goddard’s speech sounded remarkably similar to one ten years earlier by prior commissioner Paul B. Dunbar: celebratory, focused on generalities, and lacking operational details.97 In the late
1960s, FDA staffers repeatedly lamented the growing knowledge gap between pediatric and adult pharmacology, but their meetings yielded no concrete plan of action.98 As they had in the past, they debated how to define the age ranges for pediatric categories—for example, neonates, infants, children, and adolescents. But their central question remained as to how the agency should proceed when the drug under consideration held “a clear possibility for use in children” and “data on safety and efficacy are extensive in adults but meager in children”?99

The situation was no better for the AAP COD. Its meeting minutes and discussions in this era are conspicuous for what they avoid—who should pay for pediatric testing? Members spent a great deal of time on the wording of statements about the importance of pediatric testing and drug safety and the merits of particular therapeutic agents, but the critical issue of just who should fund drug testing was never discussed for the record.100 As a subcommittee within the AAP, of course, the COD was not free to advocate independently from its parent organization. Members faced the difficult balancing act of focusing attention on issues surrounding children and drugs without overtaking the agenda of the larger organization. For the AAP executive board, pediatric pharmacology was just one of many issues. At that point in time, for instance, the AAP sought congressional support for pending bills related to child abuse, and for increases in funding for pediatric medical training and social welfare programs.101 By design, the AAP had mandated the COD to advocate but not agitate—a very tenuous position. It could serve as an “authoritative body” in terms of the “science and practice of therapeutics as it relates to the pediatric patient.”102 It could consult with the FDA, monitor legislation, issue commentary on particular drugs, and study drug-related issues, but it could not independently weigh in on potentially controversial, but critical, issues such as who, exactly, should provide funding for and oversight of the process.

As the decade ended, with no concrete outcomes from either of the pediatric pharmacology conferences and little progress within the FDA, Shirkey grew even more worried. In private correspondence in 1969 to Cleveland, Ohio, pediatrician Irwin A. Shaefer, he was so frustrated he romanticized the pre-1962 Kefauver-Harris Amendments era: “Before the drug amendments of 1962,” he complained, “there was some pediatric testing before a drug’s release and its use by a physician for a child.”103 While Shirkey blamed industry, he was also upset with pediatricians for not accepting responsibility to undertake research. He was also irritated with the FDA, explaining to Shaefer the way he had “put this issue squarely” commissioner Herbert Ley at a National Research Council Policy Advisory Committee meeting for the DESI program:

He [Ley] had mentioned the poor data which comes from industry. I enlarged this to suggest that he expand his criticism to us in the “scientific community”
Development of the Therapeutic Orphan

It is also likely that Shirkey was increasingly discouraged by the confusion surrounding consent and pediatric research. Henry Beecher spotlighted the pediatric specific issues regarding informed consent and research ethics for children as part of his ongoing critique of medical ethics. He and lawyer William J. Curran published their analysis of legal precedents, risks, benefits, and, ultimately, their recommendations for children in a 1969 *JAMA* article. Beecher and Curran believed that parents and older children should have a great deal of deciding power with regard to participation in research, a position subsequently challenged by Princeton University religion professor Paul Ramsey and NIH lawyer Edward Rourke. Ramsey and Rourke wanted to limit children’s participation in any research deemed nontherapeutic for that child, even if they and their parents gave permission, arguing that exposing youngsters to risk without direct benefit to them was simply immoral. Pediatricians, too, were divided on this issue.

The FDA’s informed consent guidelines in the late 1960s gave parents full consenting authority for any research, medication, or treatment, therapeutic or nontherapeutic, a stance with which the COD appears to have been in full accord since it published the guidelines in *Pediatrics* in 1969 with positive commentary. The FDA rules allowed physicians to abstain from informing a parent, guardian, or child if he or she thought it best. If, for example, the physician deemed it “impossible or ‘not in the child’s best interest’—a situation which the attending physician must determine with great care,” he or she could order the drug be administered without permission. In other words, it fell within the purview of physicians to determine when, and in what circumstances, parents and children should be brought into the discussion.

**Who Speaks for Children?**

In 1970, in an attempt to break the stalemate and stimulate industry to take ownership of children’s drug development- and safety-related issues, Marion J. Finkel, the new deputy director of the FDA Bureau of Drugs, brought stakeholders together to discuss pediatric-related issues. An internist, Finkel joined the FDA in 1963 as part of its post Kefauver-Harris Amendments expansion. She rose through the ranks quickly, and by 1970 she was the agency’s highest-ranking woman. Finkel signaled industry that the FDA might not approve
new drug applications if the product had a potential pediatric use and lacked the necessary pharmacokinetic and dosing information. At a meeting in November 1970, she asked industry, FDA, and COD attendees for guidance regarding whether all drugs needed to be tested in pediatric subgroups such as neonates, infants, toddlers, and older children. The meeting resulted in just one concrete outcome, a decision to convene a National Academy of Sciences advisory group to address pediatric drug research.108

Finkel believed that companies should fund pediatric studies, an idea that received strenuous objection from the PMA representatives in attendance. Eli Lilly and Company’s Charles Christensen warned that such a policy might result in a firm’s deciding against developing a much-needed medication. Such veiled threats did not deter Finkel, whose remarks were publicized in the trade journal *F-D-C Reports*: “We [the FDA] . . . feel that [the therapeutic orphan] . . . situation requires correction. . . . Accordingly, we are adopting the policy that it is possible that an NDA for a drug that would have considerable therapeutic utility in children . . . in the absence of adequate investigational studies in children will not be approved unless the necessary studies are performed.”109

Finkel’s bold stance came as pediatricians’ requests to the FDA were growing more pointed—and exasperated. Pediatrician Robert Warren from Richmond, Indiana, for example, wrote to the agency in early 1971 concerned about the lack of pediatric drug data. “As a practicing pediatrician I am in a position of making a dosage decision which is avoided by those with far more information,” he complained.110 He received a weak response from staffer John W. Winkler, “regretting” there were no data to give him.111 An aghast and angry Warren penned another letter to Winkler challenging the moral logic of the situation in which he found himself: “[M]y basic question . . . was why should a practicing physician decide appropriate dosage [for a child] under the age of three years when neither the manufacturer nor the FDA will give guidelines. . . . Doesn’t the law now require demonstration of effectiveness as well as safety?”112

In an effort to keep the discussion going, in February 1971, Sumner Yaffe and the rest of the COD, joined by industry representatives Charles Weiss, Charles Christensen, and Schering executive John Leer, put together a proposal aimed at convincing drug companies to underwrite pediatric pharmacology centers. After soliciting thirty-two companies for contributions, Leer dejectedly reported that only six had agreed to donate an unspecified amount of money. Unfortunately, those six companies also stipulated that a majority of their remaining twenty-six competitors join them or their offer would be voided. Given this lack of support, Leer and Christensen told Yaffe that funding from industry would not be forthcoming.113
Another conference, this time sponsored by the National Academy of Sciences in November 1971, included all the familiar stakeholders: the COD with its clinical and research knowledge in the form of its pediatrician experts; the NICHD and NIGMS both charged with training investigators and funding research into developmental pharmacology; and industry, the source or financial sponsor of most drug development. The invited guests worked in groups and focused on a set of specific questions, almost all of which were similar to those raised in the past, although the difference this time was that attendees evinced significantly less optimism. Rather than trying to develop a concrete action plan to address pediatric drug development, pharmacokinetic, and efficacy-related issues, participants devoted the bulk of time lamenting the problem. Significantly, no one addressed Finkel’s demand that industry submit, if not fund, pediatric research. A frustrated Harry Shirkey beseeched stakeholders to break the impasse and called for some group to take leadership, if not ownership, of the problem challenging: “Who speaks for children?”

No one, however, replied. Shirkey lost most of his influence the next year when the AMA abolished its Council on Drugs because most of its duties now fell within the purview of the FDA. Refusing to give in, Shirkey led a discussion at one of the council’s final meetings on the many “problems” in generating the necessary pediatric “research and experience.”

Three major conferences, numerous internal FDA meetings, and several attempts to stimulate industry funding and interest in sponsoring the necessary studies had all failed to generate an action plan that addressed the issue of the therapeutic orphan. Although the NICHD was making progress in training pediatric clinical pharmacologists, the numbers were still very small. Moral, legal, and ethical issues surrounding informed consent for drug testing in children remained unresolved. And despite a major expansion in FDA hiring after 1962, by 1972 only eighteen of the 118 medical officers in the agency had pediatric training and just two specialized in pediatric pharmacology. A sign of the discouragement felt by all participants was the resigned comparison Charles Weiss made when introducing a new section for the journal Pediatrics, called “Pharmacology for the Pediatrician,” by comparing the discipline to “an underdeveloped country.”

In this context, FDA commissioner Charles C. Edwards took the stage at the AAP annual convention in October 1972. He began his speech by reassuring pediatricians that the FDA took the therapeutic orphan problem seriously. He referred to the phenomenon as “an anathema to every concept of modern care” and a “dangerous double standard” that needed “immediate attention.” He acknowledged that “between 1969 and 1971 more than half of all systemic drugs approved with a potential for use in children carried a label disclaimer for pediatric use. But many of these drugs are used in children,
and, in too many cases, the physician has no choice” but to risk using them because they might relieve a child’s suffering. Edwards emphasized the joint FDA-AAP efforts and, like his predecessors, shared his optimism that meaningful guidelines for pediatric drug testing were on the horizon. He warned, however, that “although he was not interested in pointing a finger,” in order to be “successful there must be a total effort on the part of the medical profession, industry, and the FDA. To date, we have not had this total effort.” He did not provide details of what a solution would look like, nor any ideas for how it might be achieved.

Pediatric drug safety and efficacy arose again in 1973 at hearings sponsored by Wisconsin senator Gaylord Nelson that focused on a number of drug-related issues, chief among them safety and affordability. While Nelson's efforts would not result in the sweeping changes Kefauver’s had a decade earlier, the senator did pressure industry concerning a number of issues, among them drug costs. When Shirkey testified at the Nelson hearings, he turned the tables on the senator and his colleagues, pressuring them to ensure Edwards fulfilled his recent promise to improve pediatric drug knowledge and safety.

Shirkey demanded that Congress force the FDA to live up to its mandate of assuring drug efficacy and safety for all, including infants and children. He argued that ownership of the “blame and the shame” lay with the “big three”—industry, pediatricians, and government. In his most blunt public statements thus far, he made a series of provocative statements. He began by focusing on the FDA, arguing that the agency had “a legal responsibility, a charge by Congress, not exclusively a charge to protect only the mature. They cannot arbitrate in favor of the needs of adults just because studies in mature subjects are easier and less costly. Time is running out: They must ultimately withhold approval of any New Drug Application in which realistically a potential use for adults and children exists. The FDA must ‘speak’ for children for new drugs.”

He and a surprised Senator Nelson sparred through a series of contentious exchanges, repeatedly interrupting one another. Nelson challenged Shirkey to defend the ethics of withholding drug approval for an agent known to benefit adults until the completion of pediatric testing. Although he did not mention the term “drug lag” by name, clearly his staff had briefed him on the concept. Some industry sympathizers in the medical community had become increasingly concerned about delays in getting drugs to market, arguing that the additional complexity and costs required by the Kefauver-Harris Amendments hampered drug development. As a result, they maintained that the numbers of new pharmaceuticals lagged behind what they would have been without the law. Fears surrounding drug lag pitted two constituencies, children and adults, against one another. Solving the therapeutic orphan problem the way Shirkey,
Yaffe, and others desired almost certainly meant new laws and potentially more complex regulations surrounding the statutes already in place.125

Shirkey showed little patience for Nelson’s worries about drug lag, explaining the “untenable” problem from the pediatrician’s perspective and rejecting the senator’s framing as a children-versus-adults problem:

He has a patient with an illness for which a certain drug has been most efficacious in adults, and let us say the patient is a child 11 years of age. That age we would call a child. Is he to withhold the use of this drug from this 11-year-old when it has been perfectly successful in a 15-year-old? . . . If he withholds a valuable drug, he is a criminal. If he follows the package insert, which says there have not been adequate studies, and then there is an adverse reaction, . . . then he has used a drug which has been clearly contraindicated for the use of children. He is damned if he does and damned if he does not.126

Back and forth the two men sparred:

SENATOR NELSON: But you would not object to marketing a drug that had only been tested adequately in adults if it were a lifesaving . . . new drug entity?
DR. SHIRKEY: Senator, I should think if it is a lifesaving drug, it should be tested in children.
NELSON: But you would then delay its marketing, even though studies showed that it was safe and efficacious in adults and critically important. You would still withhold it from those adults during the period of time you tested it on children.
DR. SHIRKEY: No. I would not withhold it from those adults. I would make certain a drug this valuable was tested on children so that it could be released for the children. . . . This is the thesis of my whole presentation.127

Answering his own question regarding who spoke for children, Shirkey stressed that the way industry did so was clear: “Industry can ‘speak.’ Industry has been ‘speaking’ and financially supporting the present level of drug knowledge for children. I contend this is inadequate.”128 He also presciently warned Nelson that if the government did not provide funding for pediatric testing, then the decision-making about which medications to test in children lay solely with drug companies. In Shirkey’s mind, industry would, as it always had, continue to focus on developing pediatric drugs they believed would be most profitable, not necessarily ones clinicians believed were most needed.129

Finally, in a brilliant attempt to capture the zeitgeist, Shirkey charged that the lack of pediatric drug information represented a form of discrimination against children as a vulnerable minority. He proclaimed the time nigh for “children’s liberation” from a normative practice in which drugs were regularly
approved without pediatric safety and efficacy data. Shirkey’s testimony occurred at a high-water mark for rhetoric in the 1970s surrounding what society owed all American children. His words echoed those of reformers who nested their advocacy in the language used by other political movements, such as those seeking to end discrimination based on race or gender. Their efforts achieved new prominence in 1973, when civil rights attorney and activist Marion Wright Edelman founded the Children’s Defense Fund, a private, not-for-profit advocacy focused on health, education, protection, and other issues affecting child well-being.

**Child Protection in a New Era: Weighing the Risks and Benefits in Pediatric Drug Development**

The United States in the early 1970s was a nation in cultural transition. Youth unrest and the civil rights, feminist, and antiwar movements were challenging and fracturing the country. At the same time, a number of voices joined the Children’s Defense Fund in urging greater protections for children. But what did that mean in 1973? While child-saving was never a monolithic movement, advocacy on youngsters’ behalf in the first part of the twentieth century had more unity than it did in the second half. Most progressive era child-savers’ efforts centered around problems such as high rates of infant mortality and child labor and for mandatory education and juvenile justice laws. But reformers’ causes were more diverse in the 1970s. For example, to some, child protection meant legislating what had long been considered a social problem, child abuse, resulting in the first federal legislation to address the problem, the 1974 Child Abuse Prevention and Treatment Act. For others, child protection meant making sure all poor children benefited from new Medicaid rules that paid for well-child care and developmental screening. For the increasingly vocal parents of disabled youngsters, child protection included pressuring government to make sure they benefited from a free public education.

For the most ambitious activists, child protection in the early 1970s meant supporting broad legislation that recognized children’s unique needs as a population, such as the 1973 Comprehensive Child Development Bill (CCDB), designed to draw together programs interspersed throughout the health care, education, and social welfare governmental sectors for all children, poor and non-poor. While targeted laws for child abuse and broad access to public education for all children, including those with special needs, proved popular, the notion of a unified, cross-class, federal approach to children’s health and social welfare proved much less so. The proposal received little bipartisan support and some charged it would “Sovietize” American youth. As the president, Richard M. Nixon, emphasized in his veto of the bill, “For the federal government to plunge headlong financially into supporting child development would
commit the vast moral authority of the federal government to the side of communal approaches to child-rearing as against the family-centered approach.”

For Shirkey, child protection meant that children received medications for which there was robust evidence to support a prescribed dosing regimen and rationale for their use. But the politically contentious debates surrounding the CCDB showed the limits of political will for expansive child-focused legislation, especially laws that placed new mandates on American free enterprise. And even if a law did somehow pass, there was little consensus regarding how pediatric drug safety data could be generated without putting some children at risk as part of the testing. All concerned agreed the need for experimentally based data to address the problem, but both scenarios—testing and not testing drugs on children—were fraught with potential problems. Extrapolating dosages from adults was often not accurate and research put at least some youngsters in jeopardy from the testing. Some feared that the most vulnerable, indigent, and especially minority children would bear the bulk of the risk. So concerned was Marian Wright Edelman about the issue of medical experimentation that she made it one of the Children’s Defense Fund’s six areas of emphasis.

In an attempt to address the scientific issues related to pediatric drug testing, members of the COD in 1973 worked through four drafts of the FDA-contracted General Guidelines for the Evaluation of Drugs to Be Approved for Use during Pregnancy and for Treatment of Infants and Children. When the Guidelines were finalized early the next year, they cogently synthesized the state of the science in pediatric pharmacology, even though the recommendations were surely more tentative than the COD chair, Sumner Yaffe, or the workgroup’s consultant, Harry Shirkey, wanted. Although the document affirmed that drugs that had potential use for children should be tested in them for safety and efficacy, the committee had acknowledged the political reality that necessitated striking a balance between what was “desirable” and “necessary” because data “concerning pharmacokinetics which is desirable may not be feasible because of economic considerations or ethical questions.”

Importantly, the Guidelines provided the clarity for pediatric stages the FDA had been seeking for years, defining the neonate, infant, toddler, child, and adolescent. It discussed issues specific to each age group, known toxicities, and challenges to determining efficacy or safety. Finally, the Guidelines outlined research methodological issues as well as those related to experimental design with particular relevance to the pediatric patient.

The Guidelines addressed consent only briefly, in recognition “that the ethics of ‘drug testing’ in minors is currently being debated.” Medical ethics became a national debate when news of the Tuskegee Study broke. Beginning in the early 1930s, the Public Health Service studied syphilis by observing its effects in indigent African American men in Tuskegee, Alabama, who were
neither informed of the nature of the research nor offered penicillin when it became available in the 1940s. In response to the resulting scandal, Senator Ted Kennedy, chair of the Subcommittee on Health of the Committee on Labor and Public Welfare, convened hearings in February 1973 to investigate experimentation-related issues such as how best to balance issues of safety and consent, especially in vulnerable populations.

A number of morally questionable studies spotlighted by the media during Kennedy’s congressional hearings involved the use of institutionalized children as research subjects, leading to a broader discussion of how best to assure the protection of all youngsters in medical experimentation. Research that had not been deemed ethically troubling at the time now came into question. For example, Joan Hodgman’s late 1950s chloramphenicol research, in which a number of babies died after receiving the drug, became characterized as rogue researchers’ misuse of vulnerable subjects.

Early on the hearings’ first day, FDA commissioner Edwards professed his understanding of the need for more pediatric drug-related data. When Pennsylvania senator Richard S. Schweiker pressed him to provide more detail, Edwards deferred to Henry E. Simmons, director of the Bureau of Drugs, who responded cautiously that FDA regulations regarding children were “evolving.” Simmons assured the senator that the FDA intended to mandate pediatric testing for a drug that might be used in children, but neither he nor Edwards provided an action plan for how this would occur. As the hearings progressed throughout the first half of 1973, Congress, Edwards, and the most tireless champion for children’s drug safety and efficacy, Harry Shirkey, discovered that the pediatric drug–related scientific and ethical issues got even more complex, as discussions surrounding pediatric drugs became entangled in the politics of legalized abortion.

**Pediatric Drug Research in the Aftermath of Roe v. Wade**

In January 1973, just a month before the Kennedy hearings began, the U.S. Supreme Court affirmed a woman’s right to terminate her pregnancy for any reason. Although the *Roe v. Wade* decision allowed states to set limits on second- and third-trimester abortions, in all fifty states abortion was now legal during the first trimester (twelve weeks). The dust had not yet settled on the Supreme Court ruling when a complicated question arose: If a woman planned to terminate her pregnancy, could the aborted fetal tissue be studied in an attempt to generate valuable data that might enhance drug pharmacokinetic knowledge? Supporters reasoned that this information could then be used to help the fetuses of those women who planned to continue their pregnancy.
Shirkey quickly realized that legalized abortion further complicated the issue of pediatric drug research. In a 1974 speech in Buenos Aires, Argentina, at the International Congress of Pediatrics entitled “Ethical Limits of Pharmacological Research in Children,” he expressed his frustration at what he saw as the latest challenge to addressing pediatric drug safety. A woman’s right to choose, he said, had created “a great deal of emotionalism about the whole subject of abortion, and fetal research has been swept in with it.” He worried that, as a result, “vital fetal experimentation” might be restricted or banned. He also saw how it could confound pediatric research consent-related issues. After all, he noted, if mothers had the right to terminate a pregnancy, why should there be any limits to their authority in terms of enrolling their already born progeny in research, even if it engendered significant risk to them? Shirkey’s strategy was to try and tease apart the issues surrounding abortion and pediatric drug development. He argued that no matter what one thought about the issue of legalized abortion, “[t]he present status of pediatric pharmacology” represented a “crime against children.”

The discussions on Capitol Hill in 1973 and 1974 involving research protections, informed consent, and fetal tissue research resulted in the National Research Act, which created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. Congress charged the eleven-member panel with developing national guidelines for human experimentation. Although a number of physicians served on the commission, they were also joined by theologians, philosophers, and others from the emerging field of bioethics. Over the next several years, the group engaged in intense discussions regarding how to protect vulnerable populations such as mentally ill and disabled children from exploitation by researchers. They also debated issues such as what age a child might be developmentally capable of providing research participation assent, even if the law gave legal decision-making authority to parents or guardians.

The AAP moved quickly to ensure that the commission heard the organization’s perspective on all issues related to children and medical experimentation. It created the Pediatric Research, Informed Consent, and Medical Ethics (PRIME) task force, and invited Horace L. Hodes, who now had almost forty years of experience in pediatric medical research, to serve as chair. Although the task force’s mission was broader than just drugs, the COD strove to make that topic the core of PRIME’s efforts. The COD had its own perspective on consent-related issues, and had a powerful vehicle through which to share its voice, given that it was under contract with the FDA to recommend ethical guidelines for pediatric drug research to complement the group’s recently completed research standards. Members saw the rights of vulnerable populations on a continuum, with children needing more protection than, say, prisoners.
In a November 1974 letter to the NIH that summarized the COD’s thoughts regarding ethical standards governing research, Sumner Yaffe stressed that some experimentation on prisoners was “essential” to garnering new knowledge about pharmacokinetics and toxicity that could benefit children.149

Meanwhile, the drug industry sought an alliance with the PRIME task force and the COD in the wake of the Kennedy hearings. In November 1974, Thomas C. Smith, director of clinical pharmacology for Parke Davis and Company, wrote a gossipy letter to the AAP, proclaiming his dismay at the “demagoguery” and “rude and disdainful” manner in which he thought Senator Kennedy had treated the FDA leadership.150 After all, he snidely noted, more governmental oversight was not likely to provide protection to vulnerable populations, since it was the Public Health Service, not the drug industry or the American medical establishment, that bore the guilt for Tuskegee.151 Given the growing challenges to physician authority made manifest by the Kennedy hearings, the company may have hoped a partnership with the AAP would help stave off any new legislation unfavorable to industry. In written documents and testimony before the National Commission, several organizations—the PRIME task force, the COD, and the research-oriented American Pediatric Society—supported the need for protections for children and for clarity surrounding parental proxy consent. However, they opposed what they viewed as a “precedent-shattering” effect on practice if fetal research was banned.152 Rather, physician groups hoped such decisions could be made on a case-by-case basis as a joint decision between parents and physicians.153

In 1975 the National Commission issued its Report and Recommendations: Research on the Fetus, dashing the hopes of physician groups that decision-making would be left largely to them and their patients and families. The recommendations stipulated that fetal research must not carry more than “minimal risk” to the fetus, that is, the risks of daily life.154 They made no distinction between fetuses in which the mother planned to abort and those in which she did not. Although researchers could petition for an exemption for a specific study, this ruling had the effect of shutting down almost all fetal research.

A Collective National Stalemate and Innovation on the Ground

In 1975, 70 percent of the drugs listed in the Physician’s Drug Reference, a major repository of drug-related information, lacked safety, dosing, pharmacokinetic, adverse reaction, or efficacy information for the pediatric patient.155 The government seemed unclear what steps to take next. Caspar Weinberger, secretary of Health, Education, and Welfare, publicly admitted as much in February 1975, when he said he felt “on the horns of a dilemma” because he lacked procedures and consensus on who should pay for pediatric testing “to
insure . . . safety, efficacy, and correct dosage among children.”
Although twelve years had passed since the 1962 Kefauver-Harris Amendments, Weinberger acknowledged that the law was not in practice as it related to children: “There is no way to abide by the Harrison-Kefauver Act [sic] as it applies to drugs for children without first having a clear mandate on the ethical issues of testing drugs on children as subjects.”

And even the bravado that had animated the FDA’s Marion Finkel a few years earlier, when she warned that new drug applications lacking relevant pediatric data might not receive approval, seemed to be waning. In October 1975, she disappointedly informed the COD that, although the agency sought better pediatric data, it lacked the leverage to change the status quo. At the same time, a burgeoning health consumer movement was bringing new challenges to governmental authority. In 1975, for example, the FDA received many letters from parents about situations in which they questioned the safety of drugs they or their children had been prescribed.

The stalemate and “handwringing,” as one COD member called the conversations in early 1976, also impeded a pediatric perspective on broader drug policy issues of importance to many families, given the growing cost of medications in the United States. One potential solution to reining in costs included encouraging companies to compete with one another by formulating and marketing “generic” drugs once a patent expired for a chemical entity. In order for this practice to be safe, however, scientific evidence needed to show that the generic version was bioequivalent, meaning that it possessed enough chemical similarity to the more expensive brand-name drug to work the same way. The COD argued that children’s biological exceptionalism complicated any discussion of generic drugs for children. Ultimately, the committee determined that “the data which would allow the pediatrician to prescribe generically and expect consistent therapeutic results does not exist.” As a result, “until suitable bioavailability data in children are determined, . . . the physician should continue to prescribe the products which have shown significant clinical effectiveness in his hands or in published clinical trials.”

Despite, or perhaps because of, the policy paralysis regarding pediatric drug safety at the national level, intellectually entrepreneurial physicians and scientists were taking action at their individual institutions. The Department of Clinical Pharmacology at Boston Children’s Hospital, for example, secured funding from the Burroughs Wellcome Fund and the FDA to build an evidentiary base for pediatric drugs. Pediatrician Allan A. Mitchell and his colleagues created the Pediatric Drug Surveillance (PeDS) program in 1974. Their efforts began to inform clinical practice almost immediately. Within two years, 1,300 youngsters on the inpatient wards at Boston Children’s Hospital had contributed data about the hundreds of FDA-approved drugs for which pediatric data were lacking. Mitchell and his team also began trials for new drugs, and,
because the National Commission had not yet issued its pediatric report, the hospital continued to follow its own review process in terms of research ethics. It had created its first ethical review board, the Committee on Clinical Investigation, in 1969.164

Mitchell’s prospective epidemiological study engaged nurse monitors to track a large volume of detailed information—adverse effects, toxicity, dose responses, and other pharmacokinetic metrics—on individual children in an effort to develop a comprehensive pediatric drug therapy database, exactly the type of evidence Taussig, Shirkey, Yaffe, and others had been demanding for years. The study was also aided by emerging computer technology, which facilitated the management and manipulation of large amounts of data in ways not possible in the past. The PeDS program’s interdisciplinary nature also proved extremely valuable because the team-based approach allowed nurses, physicians, pharmacologists, and pharmacists to discuss issues related to medication prescription, formulation, and administration across disciplines in ways that synergized knowledge and improve patient care.165 Others began on-the-ground attempts to generate pediatric drug knowledge, as well. For example, Sumner Yaffe left the University of Buffalo in 1975 for the University of Pennsylvania medical school and its affiliated pediatric clinical site, the Children’s Hospital of Philadelphia (CHOP). Drawing on seed money from Johnson and Johnson, Yaffe developed a pediatric pharmacology research program that focused on several different diseases. Each child served as his or her own control for the study of specific drugs to treat the condition.166

Pediatric drug knowledge advanced rapidly in the area of cancer treatment in the 1970s, as the governmental, industry, and academic pediatric partnership for pediatric cancer established early in the postwar era continued to enhance survival rates, especially for those suffering from acute lymphocytic leukemia (ALL). But the pediatric cancer model did not translate well to children suffering from non–life-threatening conditions. Families with extremely ill children often believed new drugs were worth their potential risks. But there was less justification to exposing a child suffering from an ear infection who needed an antibiotic to an untried agent if there was already one available. Often the older drug, while potentially less effective, had a great deal of empirical evidence behind it.167

In 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published Research Involving Children, a report that drew heavily on the work of the PRIME task force as well as the COD recommendations to the FDA. Research Involving Children affirmed the importance of pediatric drug research and described a series of recommended procedures for weighing risks and benefits and for obtaining informed consent from parents and assent from children if they were deemed cognitively able to provide it. Critically, the report also distinguished research from
therapy and included explicit rubrics for doing so. The commission, however, could not reach consensus about one issue: Should children, even with parental consent, be permitted to enroll in a study offering little or no benefit to that particular child? This controversy had divided the pediatric community for at least a decade. Beecher and others had debated the ethics of enrolling healthy children in intervention-based studies. Two commission members, one of whom was the father of two profoundly disabled children, thought doing so was coercive and immoral. Finally, in 1979, the National Commission issued its report, which codified values such as autonomy and individual rights. It outlined three ethical principles to guide research—beneficence, respect for persons, and justice. The report also highlighted pediatric-specific research issues.168

Another hopeful note that year came from an internal FDA study reporting that the number of pediatric drug company-sponsored clinical trials appeared to be on the rise.169 The FDA’s Marion Finkel took this as a positive sign. She, like everyone else, was cheered that the National Commission had promulgated an ethical road map for research and that the FDA had issued scientific guidelines for pediatric drug research based on the work of the COD.170 COD members surely reacted with excitement on hearing Finkel’s proclamation of the new FDA regulation stipulating that any pediatric indications included on the label needed full description and must be accompanied by dosing and administration information based on research in children.

All these developments seemed to indicate that the time might finally be right for pediatric drug knowledge to move ahead significantly. With Sumner Yaffe as its guiding force, pediatric clinical pharmacology had emerged as a recognized medical subspecialty. A number of pediatric pharmacology training programs were in place and plans for two scholarly journals were underway. Under the auspices of NICHD, a new generation of scientists trained as pediatric pharmacologists were rising in the ranks of industry and academia. In 1979, Yaffe, head of the growing pediatric pharmacology unit at Children’s Hospital of Philadelphia, completed the inaugural edition of the first pediatric pharmacology and therapeutics textbook. His introduction celebrated his optimism that the technical, ethical, and scientific issues necessary to assure better and safer drugs for children had been addressed, especially satisfying, he opined, given the year’s designation as the International Year of the Child.171