NOTE

THE BEST PHARMACEUTICALS FOR CHILDREN ACT OF 2002: THE RISE OF THE VOLUNTARY INCENTIVE STRUCTURE AND CONGRESSIONAL REFUSAL TO REQUIRE PEDIATRIC TESTING

LAUREN HAMMER BRESLOW*

On January 4, 2002, President Bush signed into law the Best Pharmaceuticals for Children Act, which is the government's most comprehensive legislation regarding pediatric research to date. The Act offers pharmaceutical companies a six-month exclusivity term in return for their agreement to conduct pediatric tests on drugs. It also provides public funding and organizes private funding to help conduct pediatric research on those drugs that pharmaceutical companies opt not to test in children. This Note reviews the history of pediatric research and traces the development of the Best Pharmaceuticals for Children Act's unique incentive and public funding structure. The Note contends that, while the Act is comprehensive and promotes important pediatric studies, its incentive structure forces consumers and taxpayers to bear the costs of testing pharmaceuticals in children instead of the manufacturers who research, develop, and market those drugs. Congress should consider mandating pediatric studies in any future enactment of the legislation.

In January of 2002, Congress passed the Best Pharmaceuticals for Children Act ("BPCA"), which was its second major attempt to increase the number of clinical tests performed on pediatric populations.[1] Congress passed the BPCA in response to the modest success of its earlier effort to promote pediatric clinical testing,[2] the pediatric exclusivity provision of the Food and Drug Administration Modernization Act of 1997 ("FDAMA").[3] With both the 1997 and 2002 efforts, Congress has attempted to address the dearth of information about the safety and effectiveness of drugs that children commonly use.[4] Indeed, before passage of

---

* Law Clerk to the Honorable Barbara S. Jones, United States District Judge for the Southern District of New York; Harvard College, A.B., 1998; Harvard Law School, J.D., 2002.

[1] Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C).

[2] *See* H.R. REP. NO. 107-277, at 14 (2001) (explaining that while the incentive had been successful, it was not adequate to address the need for studies in certain drugs such as those with no patent protection or those for neonates); S. REP. NO. 107-79, at 2 (2001) (noting the success of the 1997 legislation as well as the need to augment its provisions).

[3] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305–09 (codified as amended in scattered sections of 21 U.S.C.).

[4] *See, e.g.*, S. REP. NO. 105-43, at 151–53 (1997); S. REP. NO. 107-79, at 1–2 (2002); H.R. REP. NO. 107-277, at 13–14 (2002).

the FDAMA, few drugs were labeled for children, as neither Congress nor the Food and Drug Administration ("FDA") required pediatric testing of drugs, and drug companies rarely labeled drugs for children on their own.[5] A 1994 study found that six of the ten drugs most commonly prescribed to children had no pediatric labeling.[6]

The 1997 pediatric exclusivity provision did not require manufacturers to conduct pediatric clinical testing, but rather offered incentives to manufacturers in order to encourage such testing on a voluntary basis.[7] If a manufacturer agreed to conduct pediatric tests on a drug, it would receive a six-month extension on a pre-existing patent or exclusivity term.[8] Likewise, the BPCA does not require pediatric testing, but it does go a step further than the 1997 legislation, establishing a two-tiered approach to ensure research of drugs used by pediatric populations. Under this approach, a manufacturer may again opt to test its own drug in pediatric clinical trials and thereby earn the additional six-month term.[9] If a manufacturer does not wish to perform such pediatric studies, the BPCA allots funds to enable the FDA to contract for the testing of those drugs for which it believes pediatric studies would be beneficial.[10]

While the BPCA is a strong step forward for children's health, it comes at a significant price. The six-month patent extensions cost consumers hundreds of millions of dollars because of the delay in cheaper, generic drugs reaching the market.[11] In addition to the patent extensions, taxpayers will fund the drug studies that manufacturers refuse to conduct, which average about $3.87 million per drug.[12] For fiscal year 2002, Congress appropriated $200 million to that end.[13] For all other groups besides children—men, women, minority and ethnic groups—no such incentive structure or public funding is used to ensure adequate testing.[14] Instead, under the Food, Drug and Cosmetic Act pharmaceutical companies must complete safety and effectiveness tests on these groups as a condition of marketing their drugs.[15] This Note reviews the history of pediatric testing

---

[5] As this Note will discuss, the FDA began to require pediatric testing in new and already marketed drugs in 1998. *See infra* Part II.B.

[6] Food & Drug Admin., Dep't of Health and Hum. Servs., The Pediatric Exclusivity Provision: January 2001 Status Report to Congress iii, 37 tbl. 7 (2001) [hereinafter 2001 Status Report to Congress].

[7] *See* 21 U.S.C. § 355a (1997) (amended 2002).

[8] *Id.*

[9] *See* Best Pharmaceuticals for Children Act of 2002, 21 U.S.C. § 355a.

[10] Best Pharmaceuticals for Children Act of 2002, 42 U.S.C. § 284m.

[11] 2001 Status Report to Congress, *supra* note 6, at 14–18.

[12] Public Citizen Congress Watch, Patently Offensive: Congress Set to Extend Monopoly Patents for Cipro and Other Drugs 2, *available at* http://www.citizen.org/documents/ACF34F.PDF (last visited Sept. 20, 2002).

[13] Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, § 409i(d)(1)(A), 115 Stat. 1409, 1411.

[14] *See* H.R. Rep. No. 107-277, at 57 (2001).

[15] *See* Federal Food, Drug and Cosmetic Act of 1938, ch. 675, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301–397).

to determine why children have been separated from the mainstream of drug testing and how Congress came to implement a program for pediatric testing.

Part I considers the reasons pharmaceutical companies have avoided pediatric research. It suggests that the pharmaceutical industry avoided pediatric research to dissociate itself from a history of pediatric testing that exploited and abused children. In addition, pharmaceutical companies sought to avoid tort liability that might arise from adverse drug reactions in children, as well as the scientific and ethical challenges specific to pediatric testing.

As Part II recounts, until the 1990s, the government, including Congress and the FDA, allowed pharmaceutical companies to avoid pediatric testing. The FDA's regulations placed only minimal requirements on pharmaceutical companies regarding pediatric testing. The result was that by the late 1990s, few drugs were labeled for children, leading to an unsafe medical environment for children, especially severely ill children taking many drugs.[16]

Part III discusses the FDA's efforts in the 1990s to address the lack of pediatric testing and labeling and reviews its attempt to bring pediatric studies into the mainstream of the Food, Drug, and Cosmetic Act. The FDAMA, however, continued to treat children as a special group of clinical subjects, refusing to mandate pediatric testing by the pharmaceutical industry. It also further separated children from adults by awarding pharmaceutical companies a patent or exclusivity extension for their decision to test in children.

Finally, Part IV addresses Congress's most recent enactment of pediatric testing legislation, the Best Pharmaceuticals for Children Act, which attempts to address many of the weaknesses of its 1997 predecessor, the FDAMA. Part IV concludes by arguing that Congress, under the BPCA, has continued to isolate children from mainstream research, and that this separation is costing taxpayers billions of dollars. Because the voluntary, incentive-based pediatric testing provision is unjust and costly, it should be reformed to allow for more stringent, cost-efficient regulation.

I. The Isolation of Pediatric Research from the Mainstream of Clinical Testing

For much of American history, children were the primary subjects of clinical research.[17] Indeed, until the early 1970s, the government made

---

[16] *See* Tamar Nordenberg, *Pediatric Drug Studies: Protecting Pint-Sized Patients*, FDA Consumer Mag., May-June 1999, at 24.

[17] *See generally* Susan E. Lederer & Michael Grodin, *Historical Overview: Pediatric Experimentation*, *in* Children as Research Subjects: Science, Ethics, and Law 3, 4–18 (Michael A. Grodin & Leonard H. Glantz eds., 1994).

few efforts to regulate pediatric testing.[18] Physicians often abused their clinical freedom, conducting tests on children that were exploitative and dangerous.[19] As a result of this exploitation, pediatric clinical testing acquired a negative connotation, pushing private pharmaceutical companies away from the field of pediatric research and drugs.[20] Other factors, such as the high legal costs of harming children, also turned companies away from research on pediatric drugs.[21] The result of pharmaceutical companies' avoidance of pediatric medicine was that by the 1990s few marketed drugs had been tested for safety and effectiveness in children.

A. Pediatric Testing in the Nineteenth and Twentieth Centuries

One barrier to pediatric testing is the negative connotation associated with it as a result of a history of abuses in the field. Some of the earliest medical testing was performed on orphans and the children of physicians, rendering them the unprotected "guinea pigs" of a burgeoning field of medicines and vaccines.[22] The legal status of children contributed to their vulnerability to medical exploitation. Before the twentieth century, the law offered little protection to children, classifying them as chattel, property, and extensions of their parents.[23] Thus, childhood was not only dangerous because of rampant disease[24] but also because children had no legal recourse from abuse or abandonment, be it at home or under the care of a physician.[25]

In the 1870s, public outrage regarding the treatment of children led to the creation of organizations dedicated to children's rights.[26] At the same time, medicine and medical societies began to recognize the needs of children as distinct. Children's hospitals began to open in major cities,[27] and in 1873, the American Medical Association ("AMA") established a separate division for women and children.[28] It would be almost

---

[18] *See* Kurt R. Karst, *Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry*, 49 AM. U. L. REV. 739, 747 (2000).

[19] *See generally* Leonard H. Glantz, *The Law of Human Experimentation with Children*, *in* CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW 103, 103 (Michael A. Grodin & Leonard H. Glantz eds., 1994) (providing a historical overview of pediatric testing).

[20] *See infra* Part I.

[21] *See infra* Part I.

[22] *See generally* Glantz, *supra* note 19, at 103 (providing a historical overview of pediatric testing).

[23] *See id.* at 103; Marvin R. Ventrell, *Rights and Duties: An Overview of the Attorney-Child Client Relationship*, 26 LOY. U. CHI. L.J. 259, 261 (1995).

[24] Lederer & Grodin, *supra* note 17, at 4–5.

[25] *See generally* Jill Elaine Hasday, *Parenthood Divided: A Legal History of the Bifurcated Law of Parental Relations*, 90 GEO. L.J. 299 (2002).

[26] *See, e.g.*, Ventrell, *supra* note 23, at 263.

[27] *See* Lederer & Grodin, *supra* note 17, at 6.

[28] Anne M. Dellinger, Book Review, 21 J. HEALTH POL. POL'Y & L. 159, 160–61

fifty more years before the independent American Academy of Pediatrics was founded in 1930 to specifically promote children's welfare.[29]

While pediatric drug testing did lead to the eventual advancement of children's health, the means used to achieve that end exploited the vulnerability of children.[30] In fact, the development of vaccines for diseases such as smallpox and measles can be credited to physicians who used their own children and institutionalized children as subjects.[31] Children were inoculated with potential vaccines and then purposefully exposed to virulent strands of disease.[32] In the late 1800s, Alfred F. Hess, drector of the Hebrew Infant Asylum of New York, explained that using institutionalized children as research subjects was a great benefit to science because "the standardized conditions in the asylum approximated those 'conditions which are insisted on in considering the course of experimental infection among laboratory animals, but which can rarely be controlled in a study of infection in man.'"[33]

These experiments were often performed without parental consent, and activists began to protest against medical abuse that occurred when poor parents brought their children to public hospitals.[34] Nonetheless, well into the twentieth century, physicians continued to use children when testing drugs to treat diseases such as tuberculosis, scurvy, and rickets.[35] For example, Saul Krugman, a researcher associated with New York University, conducted hepatitis testing in severely mentally retarded children at Willowbrook State School from the 1950s through the 1970s.[36] While Krugman ostensibly obtained parental consent, these consents were later criticized for being coerced and uninformed.[37] Krugman had enticed parents to consent to the tests in exchange for a promise to aid their children's entrance into a better care facility.[38] Technological advances in medicine did not spare children either. Researchers used X-rays

---

(1996) (reviewing SUSAN E. LEDERER, SUBJECTED TO SCIENCE: HUMAN EXPERIMENTATION IN AMERICA BEFORE THE SECOND WORLD WAR (1995) and CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW (Michael H. Glantz & Leonard Grodin eds., 1994)). Despite its interest in pediatric medicine, the AMA remained one of the strongest opponents of regulated medical research. William Williams Keen, the President of the AMA at the turn of the eighteenth century, adamantly resisted any regulations, arguing that claims of abuse were exaggerated. *Id.* The AMA did not change its position until after World War II. *Id.*

[29] Lederer & Grodin, *supra* note 17, at 6.

[30] Ann E. Ryan, Note, *Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 23 FORDHAM INT'L L. J. 848, 852–53 (2001).

[31] Lederer & Grodin, *supra* note 17, at 5.

[32] *Id.* at 4–9.

[33] *Id.* at 6 (quoting A. F. Hess, *The Use of a Series of Vaccines in the Prophylaxis and Treatment of an Epidemic of Pertussis*, 63 JAMA 1007 (1914)).

[34] *Id.* at 12.

[35] *See id.* at 15.

[36] Ryan, *supra* note 30, at 854.

[37] *Id.* at 854 n.47.

[38] Lederer & Grodin, *supra* note 17, at 17–18.

on children to learn more about digestion and metabolism,[39] and physicians experimented on children to determine the effectiveness of surgical procedures such as vivisections.[40]

Other vulnerable groups such as African Americans and the elderly also suffered from exploitation.[41] It was the public exposure of this abuse that finally sparked sufficient public outrage to instigate legal change in the regulation of clinical studies.[42] In the *New England Journal of Medicine* in the late 1960s, Henry K. Beecher reported on twenty-two cases of clinical abuse in various age groups.[43] He highlighted two now-infamous studies: the Tuskegee study, in which black men were infected with syphilis over the course of forty years, and a cancer study conducted on elderly patients at the Jewish Chronic Disease Hospital.[44] At the same time, the American public and the international community increasingly accepted a definition of human rights that included control over one's body, which incorporated the right to decide whether to participate in a clinical study.[45]

In the 1970s, the Department of Health, Education and Welfare (now the Department of Health and Human Services ("HHS")) finally responded to the call for clinical standards by issuing new rules on the testing of human subjects.[46] Children did not benefit from this surge in public support for protective clinical guidelines, however, since the rules applied primarily to adults. Then in 1974, Congress enacted the National Research Act,[47] which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission") to create standards for the testing in children.[48]

It was another four years, however, before the National Commission made recommendations for pediatric clinical standards.[49] HHS reviewed

---

[39] Ryan, *supra* note 30, at 853.

[40] Lederer & Grodin, *supra* note 17, at 11–12.

[41] *See, e.g.*, *id.* at 16.

[42] *See* Notice of Publication of the Executive Summary of the Report, "Ethical and Policy Issues in Research Involving Research Participants," by the National Bioethics Advisory Commission (NBAC), 66 Fed. Reg. 45,998, 45,998 (Aug. 31, 2001).

[43] Lederer & Grodin, *supra* note 17, at 16.

[44] *See id. See generally* Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354 (1966); HENRY K. BEECHER, RESEARCH AND THE INDIVIDUAL: HUMAN STUDIES (1970).

[45] *See generally* Robert Mittendorff II, *Primum Non Nocere: Implications for the Globalization of Biomedical Research Trials*, FLETCHER F. WORLD AFF., Summer 2001, at 239, 241–42.

[46] *See* Protection of Human Subjects, 30 Fed. Reg. 18,914 (May 30, 1974) (codified at 45 C.F.R. pt. 46).

[47] National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974).

[48] *See* Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589, 20,590 (Apr. 24, 2001) (to be codified at 21 C.F.R. pts. 50 and 56).

[49] Protection of Human Subjects, Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 43 Fed. Reg. 2084 (Jan. 13, 1978).

these recommendations and published a notice in 1978 stating that it would start making rules regarding pediatric studies;[50] it did not publish final rules until 1983.[51] The rules, while establishing strict guidelines and protections for child subjects, applied only to children tested in studies funded or supported by HHS.[52] An earlier FDA proposed rule to govern all pediatric testing, public and private, had been withdrawn.[53] Some regulations addressing adult clinical testing, however, gave the FDA some measure of control over private testing in children. For example, the Internal Review Boards ("IRB's"), which are required for all clinical studies to oversee relevant ethical and research activities,[54] were required to remain especially cognizant of vulnerable groups such as pregnant women, children and those mentally incapable of consent.[55]

The FDA also worked with The American Academy of Pediatricians ("AAP") to promulgate guidelines for private studies in 1977.[56] It was not until 2000, however, that Congress enacted the Children's Health Act of 2000 that required HHS to create rules specifically for testing children in private as well as public studies.[57] The final rules promulgated pursuant to the Children's Health Act of 2000**,** extended the rules governing HHS studies using children to any pediatric studies, public or private, within the jurisdiction of the FDA.[58] Despite these recent improvements in the regulation of pediatric studies, however, such studies have been left with

---

[50] Protection of Human Subjects, Proposed Regulations on Research Involving Children, 43 Fed. Reg. 31,786 (July 21, 1978).

[51] Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814 (Mar. 8, 1983) (codified at 45 C.F.R. pt. 46).

[52] *Id. See also* Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects, 46 Fed. Reg. 8366, 8367–68 (Jan. 26, 1981) (codified at 45 C.F.R. pt. 46).

[53] Protection of Human Subjects; Proposed Establishment of Regulations, 44 Fed. Reg. 24,106 (Apr. 24, 1979); Withdrawal of Certain Pre-1986 Proposed Rules; Final Action, 56 Fed. Reg. 67,440 (Dec. 30, 1991) (codified at 21 C.F.R. ch. 1). *See also* Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589, 20,590 (Apr. 24, 2001) (to be codified at 21 C.F.R. pts. 50 and 56) (explaining that only if a study was funded or conducted by HHS would the clinical guidelines apply).

[54] Circumstances in Which IRB Review Is Required, 21 C.F.R. § 56.103 (2002).

[55] Criteria for IRB Approval of Research, 21 C.F.R. § 56.111 (2002); IRB Membership, 21 C.F.R. § 56.107 (2002).

[56] Karst, *supra* note 18, at 747.

[57] Children's Health Act of 2000, 42 U.S.C. § 284h. Congress was prompted to enact this bill in light of the increased enrollment of children in clinical testing that resulted from the pediatric exclusivity provision of the Food and Drug Modernization Act as well as the 1998 final rule. Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589 (Apr. 24, 2001) (to be codified at 21 C.F.R. pts. 50 and 56). As will be discussed in Part III, the pediatric exclusivity program and the 1998 final rule encouraged and required, respectively, manufacturers to research new drugs as well as already marketed drugs on children, thereby increasing the number of studies that included pediatric populations. *See* 21 U.S.C. § 355a. *See also* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[58] *See* 21 C.F.R. §§ 50.51–56, 56.109, 56.111 (2002).

a scarred reputation. It has become difficult to separate the notion of pediatric testing from unethical medicine. Accordingly, it is not surprising that pharmaceutical companies have opted to avoid pediatric testing.

B. Liability in the Courtroom: The Costs of Harming Children and Fetuses

Risk of tort liability is a second barrier to adequate pediatric pharmaceutical testing. Drug manufacturers often cite the risk of liability as one of the most important reasons that they avoid a certain area of drug manufacturing.[59] In particular, manufacturers have faced great liability due to vaccines and drugs that have adversely affected children, including fetuses.[60] In the case of vaccines, the degree of liability was so extreme that Congress had to intervene to protect vaccine manufacturers in order to ensure a steady and safe vaccine supply.[61]

The advent of vaccines and the subsequent national vaccination program has been considered one of the greatest public health programs in American history.[62] State governments,[63] with the strong endorsement of the federal government, mandated childhood immunizations for a variety of diseases before entrance into public school.[64] Indeed, government-mandated vaccines saved millions of children from death, painful disease, and disability.[65] Nonetheless, even when functioning as approved by the FDA, vaccines will predictably injure and kill a certain percentage of children.[66] In the 1950s and 1960s, companies faced product liability litigation as a result of adverse effects of vaccines in children.[67] By the 1970s and early 1980s, the crisis came to a head, as manufacturers claimed that they would not be able to maintain the vaccine industry if the federal government did not protect them from liability.[68] Between 1980 and 1985, plaintiffs sought $3.5 billion against vaccine manufacturers; the number of manufacturers of the diphtheria, tetanus, pertussis

---

[59] *See, e.g.*, Shawn Pogatchnik, *Contraceptive Studies at Standstill, Study Finds*, L.A. TIMES, Feb. 15, 1990, at A24.

[60] *See infra* text accompanying notes 61–82.

[61] Daniel A. Cantor, *Striking a Balance Between Product Availability and Product Safety: Lessons from the Vaccine Act*, 44 AM. U. L. REV. 1853, 1858–60 (1995).

[62] *See* H.R. REP. No. 99-908, at 4 (1986) ("Vaccination of children against deadly, disabling, but preventable infectious diseases has been one of the most spectacularly effective public health initiatives this country has ever undertaken.").

[63] All fifty states and the District of Columbia have such programs. Elizabeth A. Breen, *A One Shot Deal: The National Childhood Vaccine Injury Act*, 311–12 (1999).

[64] Cantor, *supra* note 61, at 1870–71.

[65] Breen, *supra* note 63, at 311–12.

[66] *Id.* at 313–14.

[67] Russel G. Donaldson, Annotation, *Construction and Application of the National Childhood Vaccination Injury Act*, 129 A.L.R. FED 1 (1996).

[68] *National Childhood Vaccine Injury Compensation Act of 1985*: *Hearings on S. 827 Before the Sen. Comm. on Labor and Human Resources*, 99th Cong. 240 (1985) (statement of Robert Johnson, President, Lederle Lab.) (stating that the number of carriers willing to insure Lederle, a vaccine manufacturer, in 1985 dropped from twenty-six to eight).

("DPT") vaccine the most risky vaccine, fell from eight to two, and, by 1986, the national vaccine stockpile fell below the Centers for Disease Control's six-month supply recommendation.[69]

In 1986, Congress passed the National Childhood Vaccine Injury Act ("NCVIA") in response to the looming crisis in the manufacture and supply of vaccines.[70] The Act established the National Vaccine Injury Compensation Program,[71] which was intended to protect the supply of vaccines, while at the same time ensuring that those who bore the costs of the adverse effects of testing were compensated in a timely and equitable matter.[72] To this end, the program sought to limit manufacturer liability while allowing for legitimate claimants to recover compensation through an administrative hearing.[73] Thus, Congress rescued manufacturers from an otherwise financially devastating flow of liability. Given that drug companies faced this kind of liability from a product that was approved by the FDA and actually credited with saving millions of lives, drug manufacturers greatly feared liability from a clinical test gone wrong.[74] They also avoided marketing drugs for children because of the potential risk. The vaccine lesson taught manufacturers that such an incident would be incredibly costly.[75]

Another reason drug companies have avoided testing on children stems from tort liability with respect to women's reproductive systems. Drug manufacturers claim that the legal repercussions of marketing drugs that adversely affect women's reproductive health and their fetuses have served as inhibitors to advancement and improvement of contraceptive drugs and devices.[76] The most commonly cited examples are the cases of Thalidomide, DES, Dalkon Shield, and Bendectin.[77] Indeed, one study found that the primary source of all tort injury recoveries for women came from medical injuries, primarily those from defective reproductive drugs and devices.[78] Bearing out the claims of the industry, the National

---

[69] Cantor, *supra* note 61, at 1858–59.

[70] National Vaccine Injury Compensation Act, 42 U.S.C.A. §§ 300aa-1 to -34 (200).

[71] *Id.* § 300aa-10.

[72] H.R. REP. NO. 99-908, at 12 (1986), *reprinted in* 1986 U.S.C.C.A.N. 6344, 6353.

[73] *See id.* at 6348.

[74] *See, e.g.*, *Consumerists Say Approvals No Product Safety Guarantee*, CHEM. MARKETING REP., May 21, 1990, at 9.

[75] *See, e.g.*, *Liability Nightmare*, NAT'L REV., Aug. 23, 1985, at 15.

[76] Cindy Skrzycki & Michael H. Gallagher, *The Risky Business of Birth Control*, U.S. NEWS & WORLD REP., May 26, 1986, at 42.

[77] *See generally* Sylvia A. Law, *Tort Liability and the Availability of Contraceptive Drugs and Devices in the United States*, 23 N.Y.U. REV. L. & SOC. CHANGE 339 (1997); Thomas Koenig & Michael Rustad, *His and Her Tort Reform: Gender Injustice in Disguise*, 70 WASH. L. REV. 1, 38–40 (1995).

[78] *See* Koenig & Rustad, *supra* note 77, at 53 (arguing that the "vast majority of mass torts leading to punitive damages awards affected products used exclusively by women. These products include the Dalkon Shield and Copper–7 IUDs, oral contraceptives causing kidney failure, and silicone-gel breast implants."). *See generally Vaccine Injury Compensation, 1984: Hearings on H.R. 556 Before the Subcomm. on Health and the Env't of the*

Academy of Science conducted a two-year study that concluded that United States pharmaceutical companies had "fled the field" of contraceptive research and development.[79] The study asserted that the exodus was directly related to the enormous tort liability that drug manufacturers faced in the field.[80] It noted that in the 1970s, eight firms were participating in the field of contraceptive drug development, but by the 1980s, the only company still actively participating was Ortho Pharmaceutical Corp.[81] The link between the contraceptive and vaccine cases was all too obvious to the pharmaceutical industry.[82] The industry would be resoundingly punished in the courtroom for injuring women's reproductive capabilities, their fetuses, or their children. Thus, the pharmaceutical industry generally sought to avoid pediatric liability by neither labeling nor marketing drugs for children.

C. General Difficulties in Testing Children

In addition to the negative connotations of testing on children and the potential exposure to enormous liabilities, pediatric research has structural impediments that make it difficult to undertake.[83] First, the issue of consent is highly complicated in the case of pediatric subjects.[84] The contemporary standard for voluntary, informed consent provides that potential adult research subjects must be made aware of the risks and side effects involved as well as alternative treatments available, but the standard leaves much freedom in the hands of researchers to create and subjects to participate in any degree of risk in a given study.[85]

House Comm. on Energy and Commerce, 98th Cong. 295 (1984) (statement of Dr. D.L. Shaw, Jr., Wyeth Laboratories) (stating that the company had stopped marketing the DTP vaccine "because of extreme liability exposure, cost of litigation and the difficulty of continuing to obtain adequate insurance").

[79] Pogatchnik, *supra* note 59, at 24.

[80] *Id*.

[81] *Id.*

[82] *Product Liability Reform Act: Hearings on S. 1400 Before the Subcomm. on the Consumer of the Sen. Comm. on Commerce, Science, and Transp.*, 101st Cong. 466 (1990) (statement of Richard Kingham, Partner, Covington & Burling) (testifying that "liability concerns in general, and particularly about punitive damages, have caused manufacturers to withdraw beneficial drugs from the market and reduce research and development activities that could yield important new drugs" and that concerns are greatest in litigation prone areas, such as vaccines and contraceptives).

[83] *See, e.g.*, *Evaluating the Effectiveness of the Food and Drug Administration Modernization Act*: *Hearings Before the Subcomm. on Health of the House Comm. on Energy and Commerce,* 107th Cong. 97 (2001) [hereinafter *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*] (statement of Timothy R. Franson, Vice President, Clinical Research and Regulatory Affairs, Lilly Research Laboratories, Eli Lilly and Company on behalf of the Pharmaceutical Research and Manufacturers of America) (describing the scientific, ethical, technical, and regulatory difficulties of pediatric testing).

[84] *See* Notice of Publication of the Executive Summary of the Report "Ethical and Policy Issues in Research Involving Research Participants," by the National Bioethics Advisory Commission, 66 Fed. Reg. 45,998, 46,000 (Aug. 31, 2001).

[85] General Requirements for Informed Consent, 21 C.F.R. § 50.20 (2002); Elements of

The 2001 regulations regarding clinical tests implemented a new set of rules to govern the ethics of testing and procurement of consent from children and their parents.[86] For any study including children, the IRB is charged with the task of ensuring that the child's assent and the parent's permission were informed.[87] This means that the IRB must consider the "ages, maturity, and psychological state of the children involved."[88] The IRB must also consider the degree of risk involved in a study in relation to the degree that study might directly benefit the child subject.[89] As risk increases, the IRB must ensure that the probability of direct benefit to the child subject increases.[90] The IRB may also consider other factors including the overall benefit of the study to the understanding of the given disease.[91]

Designing pediatric studies and obtaining the consent of children and their parents is, therefore, a highly complicated process that must account for degrees of risk and individual maturity levels of potential subjects. The terms of a valid consent are not necessarily clear.[92] Moreover, there are many points in design and consent that could lead to malpractice and tort liability for the sponsoring pharmaceutical company.[93] Not only would this litigation be fact-intensive and costly, it could also generate damaging press coverage for that company.

Many other challenges also make pediatric testing unappealing to researchers. It is difficult to find consenting subjects. The pool of children with a given disease is smaller than the corresponding adult population, and the general unwillingness of parents to subject their children to tests

---

Informed Consent, 21 C.F.R. § 50.25 (2002).

[86] *See generally* Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589, 20,590 (Apr. 24, 2001) (to be codified at 21 C.F.R. pts. 50 and 56).

[87] Requirements for Permission by Parents or Guardians and for Assent by Children, 21 C.F.R. § 50.55 (2002).

[88] *Id.* § 50.55(a).

[89] Clinical Investigations Not Involving Greater Than Minimal Risk, 21 C.F.R. § 50.51 (2002); Clinical Investigations Involving Greater Than Minimal Risk but Presenting the Prospect of Direct Benefit to Individual Subjects, 21 C.F.R. § 50.52 (2002).

[90] 21 C.F.R. §§ 50.51–.52.

[91] Clinical Investigations Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subjects' Disorder or Condition, 21 C.F.R. § 50.53 (2002).

[92] *See* Ryan, *supra* note 30, at 854–55. *See, e.g.*, *supra* text accompanying notes 36–38 (explaining the case of Saul Krugman). Krugman was vilified for his testing of mentally disabled children in a state facility, even though he had received consent. *See* Ryan, *supra* note 30 at 854; Robert M. Nelson, *Children as Research Subjects*, *in* BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 47, 49–50 (Jeffrey P. Kahn et al. eds., 1998). He had offered the parents of his patients the hope of better care for their children. Ryan, *supra* note 30, at 854–55. Critics of the research characterized this inducement as coercive to parents desperate to help their children receive better care. Others question the legitimacy of even lesser inducements such as gift certificates to Toys 'R Us in exchange for consent. *See, e.g.*, Rachel Zimmerman, *Child Play: Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids*, WALL ST. J., Feb. 5, 2001, at A1.

[93] *See generally* Glantz, *supra* note 22, at 118–30.

limits children's availability.[94] Also, it is difficult to obtain patient compliance or collect data from young subjects.[95] Young children cannot always communicate their reactions or feelings well, and have limited patience, mood swings, and fatigue that can interfere with testing.[96]

Furthermore, pharmacologic and pharmakinetic differences between children and adults necessitate that researchers develop special studies for child subjects.[97] Children's organs and metabolisms change rapidly throughout infancy and childhood, requiring adjustments for the rate of elimination of a drug from a child's system.[98]

Thus, working with pediatric patients is both legally and technically more challenging than working with adults.[99] By opting not to perform pediatric studies, the companies could avoid the complex world of pediatric research, liability for drugs marketed for children, and complicated consent and scientific issues that could have led to high costs and legal liability.[100] These factors explain why children were excluded from mainstream pharmaceutical research and illustrate why children needed special regulatory and legislative attention.

D. Children as Therapeutic Orphans and Pediatrician Outrage

The fact that drug companies declined to market or label their drugs for the pediatric population did not prevent children from using those drugs on a regular basis. Coined "therapeutic orphans" because of the scarcity of pediatric drugs on the market, children have been forced to

---

[94] *See* S. REP. NO. 105-43, at 51 (1997).

[95] *Id.*

[96] Gerald P. Koocher & Patricia Keith-Spiegel, *Scientific Issues in Psychosocial and Educational Research with Children*, *in* CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW 47, 49 (Michael A. Grodin & Leonard H. Glantz eds., 1994).

[97] *See Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearings Before the House Comm. on Gov't Reform and Oversight*, 104th Cong. 106–14 (1996) [hereinafter *Hearings on Off-Label Drug Use*] (statement of Ralph Kauffman, M.D., on behalf of the American Academy of Pediatrics).

[98] *See id.*; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,899, 43,901 (Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, and 601b).

[99] *See generally* Elizabeth J. Jameson & Elizabeth Wehr, *Drafting National Health Care Reform Legislation to Protect the Health Interests of Children*, 5 STAN. L. & POL'Y REV. 152, 152–55 (1993).

[100] *See Better Pharmaceuticals for Children: Assessment and Opportunities: Hearings Before the Sen. Comm. on Health, Educ., Labor and Pensions*, 107th Cong. 43–44 (2001) [hereinafter *Hearings on Better Pharmaceuticals for Children*] (statement of Janet Heinrich, Director, Health Care-Public Health Issues) ("[S]everal factors appear to have contributed to the lack of pediatric studies. Drug companies indicated that they had little incentive to perform pediatric studies on drugs they intended to market primarily to adults and that these drugs would provide little additional revenue from use in children. Companies also said they were concerned about liability and malpractice issues and the difficulty of attracting enough pediatric patients for studies because of the small number of children with a particular disease.").

look to adult medicines for treatment.[101] In a practice called "off-label" prescribing,[102] pediatricians treat children's illnesses with medicines labeled for adults with the same affliction.[103] Such prescriptions are legal and are a part of mainstream medical practice.[104] Indeed, the AMA estimates that forty to sixty percent of all prescriptions are off-label.[105]

Neither the FDCA nor the FDA regulates off-label prescriptions, although the FDA does monitor and may take action where a drug is prescribed on a widespread basis for an off-label indication.[106] The AMA, however, adopted guidelines to which physicians must conform in off-label practice.[107] The AMA uses the same standard that the FDA uses for drug approvals, permitting physicians to prescribe off-label when such a prescription is based on substantial medical evidence.[108] Substantial medical evidence is defined as "two or more adequate and well-controlled studies performed by experts qualified by scientific training and expertise."[109] The obvious problem, however, is that it takes a great deal of time for substantial medical evidence to accrue. For example, it might take years before sufficient dosing information for children becomes available in references such as journal articles and pediatric handbooks.[110]

Unlike other areas of medicine in which some drugs might be prescribed off-label, pediatricians faced situations in which the majority of the drugs that they were prescribing to children were off-label, leaving children at continual risk of experiencing adverse reactions.[111] Some

---

[101] *See* S. REP. NO. 105-43, at 51–52 (1997); Ryan, *supra* note 30, at 855–57.

[102] "Off-label" means a prescription for ages or diseases other than those indicated on a drug's label. *See* Nicole Endejann, *Is the FDA's Nose Growing?: The FDA Does Not "Exaggerate Its Overall Place in the Universe" When Regulating Speech Incident to "Off-Label" Prescription Drug Labeling and Advertising*, 35 AKRON L. REV. 491, 502–05 (2002); Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 186–92 (1999).

[103] *See* Althea Gregory, *Denying Protection to Those Most in Need: The FDA's Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI & TECH. 121, 130–31 (1997).

[104] *See* Veronica Henry, *Off-Label Prescribing: Legal Implications*, 20 J. LEGAL MED. 365, 365 (1999).

[105] *Id.*

[106] *See* Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rule Making, 37 Fed. Reg. 16,503 (Aug. 15, 1972); FOOD AND DRUG LAW: CASES AND MATERIALS 619 (PETER Barton Hutt & Richard A. Merrill eds., 2d ed., 1991) [hereinafter FOOD AND DRUG LAW].

[107] Gregory, *supra* note 103, at 128.

[108] *See* Henry, *supra* note 104, at 370.

[109] *Id.*

[110] Nordenberg, *supra* note 16, at 28. *See also Reauthorization of the Prescription Drug User Fee Act and FDA Reform: Hearings Before the Subcomm. on Health and Environment, of the House Comm. on Commerce*, 105th Cong. 118–24 (1997) [hereinafter *Hearings on FDA Reform*] (statement of Sanford N. Cohen, M.D., on behalf of the American Academy of Pediatrics).

[111] *See Hearings on FDA Reform*, *supra* note 110 (statement of Sanford N. Cohen,

common childhood afflictions were, and still are in many cases, treated with pharmaceuticals without pediatric labeling.[112] These areas included depression, epilepsy, severe pain, gastrointestinal problems, allergies, and high blood pressure.[113] As the FDA explained in a 1992 proposed rule, the lack of labeling resulted in a situation in which pediatricians were forced to estimate proper dosages

> arbitrarily based on the child's age, body weight, or body surface area without regard for the interaction of those factors or age-related physiological and biochemical factors. As a result, children may be exposed to an increased risk of adverse reactions, or decreased effectiveness of prescription drugs, or may be denied access to valuable therapeutic agents.[114]

Pediatricians were worried they would improperly medicate their patients,[115] concerned about their own medical malpractice liability,[116] and angry that the FDA continued to fail to assist them in treating children.[117] As one physician complained, "We are operating in a vacuum . . . I might be able to treat [children's] cancer more aggressively, but I don't know how to safely do that."[118]

Historical examples buttressed pediatrician claims that poor labeling endangered children.[119] One of the most recent examples occurred in 1999, where seven newborns were forced into surgery after being treated with erythromycin, a commonly prescribed antibiotic, because there was no pediatric label warning against use in newborns.[120] Indeed, infamous

---

M.D., on behalf of the American Academy of Pediatrics); S. REP. NO. 107-79, at 3 (2001) ("Some drugs may have different adverse side effects or toxicities in children than in adults, so estimating dosages for children from dosages found to be safe and effective in adults may not be appropriate. The lack of pediatric studies and labeling information may lead to unintended medical errors and place children at risk of being under-dosed or over-dosed with medication.").

[112] Nordenberg, *supra* note 16, at 24.

[113] *Id.*

[114] Specific Requirements on Content and Format of Labeling, 57 Fed. Reg. 47,423, 47,424 (Oct. 16, 1992) (codified at 201 C.F.R. pt. 201).

[115] *See* Nordenberg, *supra* note 16 at 24 (quoting Rosemary Roberts, M.D., chair of the pediatric subcommittee of the FDA's Center for Drug Evaluation and Research, as stating that "[s]ome physicians won't even try a drug in a child if they don't have enough information.").

[116] *See* Henry, *supra* note 104, at 380; James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 80 (1998).

[117] *See Hearings on Off-Label Drug Use*, *supra* note 97 (statement of Ralph Kauffman, M.D., on behalf of the American Academy of Pediatrics).

[118] Sheryl Gay Stolberg, *Children Test New Medicines Despite Doubts*, N.Y. TIMES, Feb. 11, 2001 at Sec. 1. p.1.

[119] *See Better Pharmaceuticals for Children: Assessment and Opportunities: Hearings Before the Sen. Comm. on Health, Educ., Labor and Pensions*, 107th Cong. 305 (2001) (statement of Senator Barbara Mikulski (D-Md.)).

[120] *Id. See also* 147 Cong. Rec. E2368 (daily ed. Dec. 20, 2001) (statement of Rep.

adverse reactions go back many years. For example, in the 1960s, the antibiotic chloramphenicol was given to newborns, but their livers were too immature to break it down, leading to "gray syndrome."[121] Twenty-three babies died as a result.[122] Children have also experienced teeth staining, seizures and cardiac arrest, and hazardous interactions between drugs while using drugs not labeled for pediatric use.[123]

Using these examples as ammunition along with their own assertions that they felt ill-equipped to medicate childhood diseases, pediatricians pressed their case for better labeling. They argued that children could not be treated as "little adults"; they were different from adults, with their own set of metabolic and chemical designs.[124] Children, they argued, needed to be protected by special regulations that encouraged pediatric testing.[125]

Through the early 1990s, however, the federal government was complicit in the pharmaceutical companies' decision to avoid pediatric research. As the following Part discusses, the FDA's early attempts to protect children from unsafe medicines focused on restricting pharmaceutical marketing and labeling and not on the frequency or accuracy of pediatric research. By the 1990s, much to the dismay of the FDA, the result was a dismal record of pediatric testing that endangered children instead of protecting them.

II. The FDA's Evolving Role as the Protector of Children's Medicine and Research

The FDA did not initially require testing of new or marketed drugs on children. Through the 1990s, the FDA focused on ensuring that manufacturers did not label drugs for use on children unless they had first conducted pediatric tests to establish the drugs' safety and effectiveness in

---

Sheila Jackson-Lee (D-Tex.)) (noting that the lack of labeling for children was contributing to potentially fatal physician errors in the treatment of children).

[121] Miller-Keane Medical Dictionary (2000). Gray syndrome, or gray baby syndrome, is a "potentially fatal condition seen in neonates." *Id.* An affected neonate becomes ashen, listless, weak, and prone to hypotension. *Id.*

[122] Nordenburg, *supra* note 16. *See also* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900, 43,901 (Aug 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[123] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness, 62 Fed. Reg. at 43,901.

[124] William Rodriquez et al., *Adverse Drug Events in Children: The U.S. Food and Drug Administration Perspective*, Current Therapeutic Res., Oct. 2001, at 714–15. *See also Hearings on FDA Reform*, *supra* note 110 (statement of Sanford N. Cohen, M.D., on behalf of the American Academy of Pediatrics).

[125] *See* Rodriquez et al., *supra* note 124, at 714–15; *Hearings on FDA Reform*, *supra* note 110 (statement of Sanford N. Cohen, M.D., on behalf of the American Academy of Pediatrics).

children.[126] While this policy served to protect children from false claims about drugs, it did little to ensure that there were sufficient numbers of drugs on the market that had been proven effective for children.[127] At the time that the FDA began to address the dearth of medicines tested for and marketed to children, only twenty percent of drugs were labeled for use in children[128] and six out of the ten leading drugs prescribed to children had never been tested in pediatric studies.[129]

A. A Brief History of the FDA and Its Initial Steps To Protect Children from Unsafe and Ineffective Drugs

The FDA's sluggishness in regulating pediatric testing and promoting a strong pediatric agenda is ironic given the considerable role that children played in both the birth and later empowerment of the FDA.[130] The tragic side effects of drugs on children propelled much of the legislation that led to the creation of the FDA in its modern incarnation. The first national statute dedicated to food and drug regulation was enacted after several children were killed from a diphtheria antitoxin that was infected with tetanus.[131] Subsequently, Congress enacted the Pure Food and Drug Act of 1906 ("PFDA"), which was the first legislation to prohibit misbranding and adulteration of drugs.[132] The PFDA created the Bureau of Chemistry to address the growing epidemic of unsanitary food production facilities and ineffective medicinal remedies marketed without regulation.[133] The Bureau was charged with removing ineffective drugs from the market if it could prove a given drug did not work and that the seller actually knew this to be the case.[134] With no authority to require pre-market testing of drugs, however, the Bureau was left without the power to prevent hazardous drugs from reaching the market.[135]

---

[126] *See* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Revision of the "Pediatric Use" Subsection on Labeling, 59 Fed. Reg. 64,239, 64,240 (Dec. 13, 1994) (codified at 21 C.F.R. pt. 201).

[127] *See generally* Nordenberg, *supra* note 16.

[128] S. REP. NO. 107-79, at 1 (2001).

[129] 62 Fed. Reg. 43,899, 43,900 (Aug. 15, 1997) ("These ten drugs were . . . prescribed over 5 million times in 1 year for pediatric patients in age groups for which the label carried a disclaimer or lacked adequate use information.").

[130] *See Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83 (statement of Richard Gorman, M.D., on behalf of the American Academy of Pediatrics).

[131] *See* FOOD AND DRUG LAW, *supra* note 106, at 8.

[132] Pure Food and Drug Act of 1906, ch. 3915, 34 Stat. 768 (repealed 1938). *See* FOOD AND DRUG LAW, *supra* note 106, at 4.

[133] Pure Food and Drug Act of 1906, ch. 3915, 34 Stat. 768 (repealed 1938). *See* Jeffrey E. Shuren, *The Modern Regulatory Administrative State: A Response to Changing Circumstances*, 38 HARV. J. ON LEGIS. 291, 299–300 (2001).

[134] *See* Shuren, *supra* note 133, at 300; Mary T. Griffen, *AIDS Drugs and the Pharmaceutical Industry: A Need for Reform*, 17 AM. J.L. & MED. 363, 375–76 (1991).

[135] *See* Shuren, *supra* note 133, at 300.

A tragic result of this ill-conceived regulatory structure occurred in the 1937 "Elixir of Sulfanilamide" disaster.[136] In order to make the key element of sulfanilamide soluble, the manufacturer included diethylene glycol in the drug's formula.[137] Diethylene glycol, a solvent commonly used in antifreeze, had never been tested in humans.[138] In 1938, within two months of its being on the market, the formula caused fatal renal failure in over one hundred people, mostly children.[139]

This disaster motivated Congress to take further action with respect to the safety of marketed drugs.[140] In 1938, Congress repealed the Pure Food and Drug Act and enacted the Federal Food, Drug, and Cosmetic Act ("FDCA"), which created the FDA.[141] The FDCA gave the FDA authority to monitor and control new drugs. The FDA was authorized to require a manufacturer to demonstrate the safety and effectiveness of its drugs before that manufacturer could market them.[142] Still, the provision was limited to those drugs that were not yet marketed, offering the FDA no power to control already marketed drugs.[143]

It took another public health disaster involving children, however, before any significant changes were made to the FDCA. Senator Estes Kefauver (D-Tenn.) held hearings in the late 1950s and early 1960s to spark interest in strengthening the FDA, but his efforts did not receive great attention until the Thalidomide disaster in Europe.[144] In the late 1950s and early 1960s, women in Europe began to use Thalidomide to treat morning sickness.[145] Under the authority granted to the FDA by the FDCA, the examiner reviewing the Thalidomide application, refused to approve it because of the manufacturer's failure to provide certain evidence about the product's safety.[146] European women were not so fortunate, however, and Thalidomide caused severe deformities in thousands of babies.[147]

With the knowledge that the FDA had saved thousands of children and their families from a lifetime of suffering, Senator Kefauver's hearings took on a new life, and, in 1962, resulted in major amendments to the FDCA.[148] The Kefauver-Harris Amendments, as the new legislation

---

[136] *Id.*
[137] *Id.*
[138] *Id.*
[139] *Id. See also* Rodriquez et al., *supra* note 124, at 712.
[140] Karst, *supra* note 18, at 746 n.33.
[141] Federal Food, Drug, and Cosmetic Act of 1938, ch. 675, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301–395 (2000)).
[142] 21 U.S.C. §§ 301–395 (2002). *See also* FOOD AND DRUG LAW, *supra* note 106, at 13.
[143] *See* Shuren, supra note 133, at 301–02.
[144] FOOD AND DRUG LAW, *supra* note 106, at 452.
[145] *See* Gregory, *supra* note 103, at 125 (1997); Shuren, *supra* note 118, at 301.
[146] Shuren, *supra* note 133, at 102.
[147] *See* Gregory, *supra* note 103, at 125.
[148] FOOD AND DRUG LAW, *supra* note 106, at 452.

came to be known,[149] confirmed the FDA's authority to determine which drugs could be marketed and empowered the FDA to pull unsafe or ineffective drugs from the market.[150] Thus, the effects of drugs on children prompted some of the most important public health movements in congressional history.[151]

Despite the fact that children served as the impetus for strengthening the FDA's authority over drugs, they hardly benefited from the new enabling legislation.[152] In fact, many critics later came to blame these regulations for the isolation of children from the mainstream of clinical research.[153] A pharmaceutical company could conduct clinical tests for a drug in adults and market that drug without ever considering that drug's effects on children.

In addition, as discussed in Part I, the FDA's earliest protections of children were regulations regarding the ethics of public clinical studies.[154] These regulations did not extend to private studies, nor did they require testing of drugs that were likely to be used in children.[155] Therefore, a manufacturer could claim a drug worked for children's illnesses despite the lack of a clinical foundation for this assertion.

In 1979, the FDA made its first effort to limit these claims by pharmaceutical companies. The FDA promulgated a final rule that provided that if a pharmaceutical company marketed a drug to children, it would need to include pediatric information on its label.[156] Such information

---

[149] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C. (2000)).

[150] *See* 21 U.S.C. § 321 (2000).

[151] *See* Shuren, *supra* note 133, at 302.

[152] *See* Henry, supra note 104, at 379 ("Infants and children have been referred to as therapeutic orphans. The irony of this situation is that both the 1938 and 1962 Amendments to the Food, Drug and Cosmetic statutes grew out of therapeutic catastrophes in children.").

[153] *See, e.g.*, *FDA Modernization Act: Implementation of the Law: Hearings Before the Senate Comm. on Health, Educ., Labor and Pensions*, 107th Cong. 54–57 (2001) [hereinafter *Hearings on Implementation of the FDA Modernization Act*] (statement of Myron Genel, M.D., on behalf of the American Academy of Pediatrics) (crediting the amendments as taking away the incentive for pharmaceutical companies to research the safety and effectiveness of their drugs in children); *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83 (statement of Christopher-Paul Milne, Assistant Director, Tufts Center for the Study of Drug Development).

[154] Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814 (Mar. 8, 1983) (codified at 45 C.F.R. pt. 46 subpt. D). *See also* Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects, 46 Fed. Reg. 8366, 8367–68 (Jan. 26, 1981) (codified at 45 C.F.R. pt. 46).

[155] *See* Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814 (Mar. 8, 1983) (codified at 45 C.F.R. pt. 46 subpt. D); Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects, 46 Fed. Reg. 8366, 8367–68 (Jan. 26, 1981) (codified at 45 C.F.R. pt. 46).

[156] Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434 (June 26, 1979) (codified at 21 C.F.R. pts. 201 and 202).

would necessitate pediatric testing.[157] Any drug that had not been tested for safety and effectiveness in children would need to indicate as much on its label.[158]

The FDA thought that this provision would prompt pediatric testing by drug manufacturers.[159] Instead, the opposite result ensued. Manufacturers simply chose to forego pediatric testing and use labels which stated that safety and effectiveness had not been established in children.[160] As admitted in a subsequent FDA proposed rule, the 1979 rule failed to improve pediatric research or health.[161] Despite being an attempt to protect children, the FDA regulation actually combined with historical pressures to reinforce the lack of pediatric testing.

B. The FDA Takes Steps To Promote Pediatric Labeling

In the 1990s, David Kessler, then FDA Commissioner, began to respond to pediatricians' concerns that children were therapeutic orphans in need of direct assistance from the FDA.[162] In 1992, the FDA proposed a rule that sought to revise and augment its 1979 predecessor concerning pediatric labeling.[163] The FDA was concerned that pharmaceutical companies were choosing labels without pediatric safety and effectiveness levels because they believed that in order to label a drug for children they would have to actually perform clinical testing in children.[164] The proposed rule sought to eliminate this misunderstanding by stating that a manufacturer did not necessarily have to complete pediatric clinical tests to qualify for a pediatric label.[165] In 1994, the final rule ("1994 rule") was published in the hopes that it would increase pediatric labeling and offer pediatricians "more reliable information."[166]

Under the 1994 rule, pharmaceutical companies could use "adequate and well-controlled" adult studies in addition to pharmacokinetic, safety,

---

[157] *Id.*

[158] *Id.*

[159] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Proposed Revision of "Pediatric Use" Subsection in the Labeling, 57 Fed. Reg. 47,423, 47,423–24 (Oct. 16, 1992) (codified at 21 C.F.R. pt. 201) (stating that "the 1979 regulations were intended to encourage drug labeling that would regularly provide adequate information about use of prescription drugs in children"). *See also* S. REP. NO. 107-79, at 3 (2001).

[160] Rodriquez et al., *supra* note 124, at 713. *See also* Gregory, *supra* note 103, at 129.

[161] Specific Requirements on Content and Format of Labeling, 57 Fed. Reg. at 47,423–24.

[162] *See Hearings on FDA Reform*, *supra* note 110 (statement of Sanford N. Cohen, M.D., on behalf of the American Academy of Pediatrics).

[163] Specific Requirements on Content and Format of Labeling, 57 Fed. Reg. at 47,423.

[164] *Id.* at 47,424.

[165] *Id.*

[166] Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. 64,240 (Dec. 13, 1994) (codified at 21 C.F.R. pt. 201).

and pharmacodynamic data to satisfy the pediatric labeling requirements.[167] While the 1994 rule did not make any new testing mandatory, it did require companies to review their existing data to determine if they could lead to pediatric information.[168] The 1994 rule maintained the requirement that any manufacturer who did not submit valid information regarding pediatric safety and effectiveness include a disclaimer on its labels stating that the drug had not been tested for safety and effectiveness in children.[169] The FDA hoped that this easing of pediatric labeling standards would provide an incentive for pharmaceutical companies to assemble data and avoid the disclaimer label.[170]

In addition, in the 1994 rule, the FDA noted that although it was not requiring pediatric testing for new drugs, it could have chosen to do so.[171] Along these lines, the general comments of the 1994 rule explain that the FDA may require new drug application holders to submit studies to determine whether the drug can be safely and effectively used in populations likely to receive it.[172] By explicitly letting manufacturers know that it was not taking advantage of its full authority under this new rule, the FDA went further than ever in stating its authority to require pediatric testing.[173] The FDA anticipated that this assertion of authority would inspire—and perhaps warn—drug sponsors to change their approach to pediatric labeling.[174]

To the dismay of the FDA and pediatricians, the 1994 rule did little to encourage pharmaceutical companies to label for pediatric populations.[175] As pharmaceutical companies faced few repercussions for refus-

---

[167] *Id.* at 64,241.

[168] *See id.*; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,901 (Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[169] Specific Requirements on Content and Format of Labeling, 59 Fed. Reg. at 64,241.

[170] Specific Requirements on Content and Format of Labeling, 57 Fed. Reg. at 47,426.

[171] Specific Requirements on Content and Format of Labeling, 59 Fed. Reg. at 64,242.

[172] *Id.* at 64,243.

[173] *Id.* at 64,242–43.

[174] *See id.* at 64,242.

[175] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,632 (Dec. 2, 1998) (to be codified at 21 C.F.R. pts. 201, 312, 314, and 601).

> Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information. Over half of the total supplements submitted simply requested the addition of the statement 'Safety and effectiveness in pediatric patients have not been established.' Others requested minor wording changes or submitted unorganized, unanalyzed collections of possibly relevant data. Approximately 15 percent (approximately 65) of the supplements provided adequate pediatric information for all relevant pediatric age groups, and another 8 percent (approximately 35) provided adequate pediatric information for some but not all relevant age groups.

ing to submit pediatric data, the FDA's rules again served only to further solidify the industry's ability to use a disclaimer and avoid pediatric research.[176] As a result, neither patent nor generic manufacturers made significant strides toward changing labels to reflect pediatric data.

It was not for the FDA's lack of effort that manufacturers failed to respond to the 1994 rule's call. The FDA's Center for Drug Evaluation and Research ("CDER") identified the ten drugs most commonly prescribed to children and requested that the manufacturers of such drugs adhere to the 1994 rule by reviewing their literature.[177] Few of the manufacturers complied.[178] While the FDA had received seven promises to conduct post-approval testing, by 1996, only one manufacturer had reported any results.[179] The FDA faced similarly poor results with new drugs, despite the fact that the 1994 rule expected the manufacturers of such drugs to consider pediatric labeling. In 1996, only thirty-seven percent of the new molecular entities likely to be used in children had pediatric labels pending approval.[180] The FDA's voluntary rule was considered a failure, and the FDA decided that it would need to take a more radical approach if it was going to improve the state of pediatric medicine.[181] Consequently, in 1997, the FDA proposed a new rule, under which the FDA would require the pediatric testing of new and marketed drugs.[182] There were three main parts to the 1997 proposal, all of which made it, in some form, into the 1998 final rule. First, the rule would apply to both new and marketed drugs, including biological products that were widely used in pediatric patients or indicated or prescribed for very significant or life threatening illnesses.[183] Second, the FDA would be able to require information for all pediatric sub-populations, from neonates to teenagers, according to the actual use of the drug.[184]

Finally, the rule would allow both partial and full waiver of pediatric testing in certain products as well as deferment of such tests if appropriate in light of the need to release the drug to adult populations.[185] A

Id.

[176] *See* Karst, *supra* note 18, at 748; *Hearings on FDA Reform*, *supra* note 110 (statement of Sanford N. Cohen, M.D., on behalf of the American Academy of Pediatrics); Gregory, *supra* note 103, at 129.

[177] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,902 (Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[178] *Id.*

[179] *Id.*

[180] *Id.*

[181] *Id. See also* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling; Extension of Compliance, 61 Fed. Reg. 68,623, 68,623 (Dec. 30, 1996) (codified at 21 C.F.R. pt. 201).

[182] *See generally* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness, 62 Fed. Reg. at 43,900, 43,902.

[183] *Id.* at 43,913.

[184] *Id.*

[185] *Id.* at 43,903–05.

company could receive a full waiver where studies on children were impossible or highly impractical, or where there was evidence that a drug would be ineffective or unsafe for children.[186] The FDA would grant a partial waiver when at least three conditions were satisfied: (1) the drug was not for a serious or life-threatening disease; (2) the drug was not likely to be used by a substantial number of patients in the age group in question; and (3) the applicant was able to demonstrate that reasonable attempts to make a pediatric formulation had failed.[187]

This proposed rule was far more aggressive than its passive predecessors in procuring pediatric testing. Rather than forcing the FDA to cajole manufacturers into tests, manufacturers now had to proactively demonstrate why they should not have to conduct pediatric testing. This groundbreaking proposal would elevate children from their status as therapeutic orphans and exploited clinical subjects. The pharmaceutical industry protested the proposed rule, claiming that it was neither legal nor necessary.[188]

Before the FDA finalized its rule, however, Congress enacted the FDAMA, bringing about a sweeping reform of the FDCA.[189] This legislation changed the landscape of pediatric testing.

III. The Creation of "Pediatric Exclusivity" and Its Impact on Pediatric Testing

The FDAMA overhauled the FDCA.[190] One of the most radical additions was Section 111, the Better Pharmaceuticals for Children Act, which was codified as the pediatric exclusivity provision.[191] The pediatric exclusivity provision sought to promote pediatric labeling by offering pharmaceutical companies a six-month extension in their patent or exclusivity period on a particular drug in exchange for conducting a pediatric study of that drug.[192] The provision was limited in scope as it was voluntary and affected only those companies that had drugs on patent or in an exclusivity term.[193] While most viewed the provision as a success for pediatric health, even the provision's most ardent supporters recognized its

---

[186] *Id.*

[187] *Id.* at 43,914.

[188] *See, e.g.*, *Hearings on Implementation of the FDA Modernization Act*, *supra* note 153 (statement of Alan F. Holmer, President, Pharmaceutical Research and Manufacturers of America) (urging the FDA to "delay finalizing the August 11, 1997 proposed regulation until Congress, the pharmaceutical industry, and the agency are able to measure the effectiveness of Section 111.").

[189] *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2309 (codified as amended in scattered sections of 21 U.S.C.).

[190] *Id.*

[191] 21 U.S.C. § 355a.

[192] *Id.*

[193] *Id.*

limitations and sought reforms.[194] This Part reviews the components of the provision, how it affected the 1997 proposed rule, and what its supporters and critics believed to be its strengths and weaknesses.

A. The FDAMA's Pediatric Exclusivity Provision and the FDA's 1998 Final Rule

1. The Food and Drug Administration Modernization Act's Pediatric Exclusivity Provision

The FDAMA's pediatric exclusivity provision is quite limited in length, but had an enormous impact on pediatric health. Although it did not require pediatric testing, an important incentive it did provide was that a manufacturer could extend its patent or exclusivity term for a new or already marketed drug by six months by conducting pediatric tests.[195] While the provision aimed to increase pediatric labeling, it did not require a label change for the six-month extension to commence.[196] The tests only needed to be completed.[197] The six-month extension was a financial boom for manufacturers. For example, pharmaceutical company Schering-Plough, faced with no competition from generic drugs, earned an additional $975 million in sales during the six-month patent extension on its drug Claritin.[198]

The provision outlined the procedure by which a drug company could procure the extension.[199] The FDA[200] was to issue a written request for a pediatric study to any manufacturer of a new or already marketed drug either on-patent or on its exclusivity term under the Drug Competition and Patent Term Restoration Act of 1984 ("Waxman-Hatch Act").[201]

---

[194] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (statement of Janet Heinrich, Director, Health Care-Public Health Issues).

[195] *Id.* These sections outline how the six-month extension attaches to the patent term or the exclusivity terms under 35 U.S.C. § 156 (2000). Section 355a(a) applies to new drugs, and section 355a(c) applies to already marketed drugs.

[196] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 25.

[197] *Id.*

[198] *User Fees, Pediatric Exclusivity Keys in FDAMA Reauthorization*, FOOD & DRUG LETTER, June 22, 2001 [hereinafter *User Fees*], *available at* 2001 WL 8214943.

[199] *See* 21 U.S.C. § 355a.

[200] The Act does not refer to the FDA, but rather to the Secretary of Health and Human Services ("HHS"). For purposes of describing the Act, the FDA and the Secretary of HHS are used interchangeably because, in practice, the FDA carries out the pediatric exclusivity provision. *See* Delegations from the Secretary of Health and Human Services to the Commissioner of Foods and Drugs, 21 C.F.R. § 5.10 (2002).

[201] 21 U.S.C. §§ 355a(a), (c); Drug Price Competition and Patent Term Restoration Act of 1984 ("Waxman-Hatch Act"), Pub. L. No. 98-417, 98 Stat. 1585 (codified at 35 U.S.C. § 355). The Waxman-Hatch Act established periods of exclusivity in addition to the patent term. *Id.* § 335j. It offers two main "exclusivity" terms: (1) up to five years of market exclusivity for a pioneer drug (on-patent drug) when its manufacturer completes research about that drug's usefulness for new indications and (2) 180 days generic exclusivity to the first generic to have its abbreviated new drug application approved by the FDA. 35 U.S.C.

If the manufacturer agreed to the request and completes its pediatric studies for the drug within the requested timeframe, the six-month extension automatically began.[202] If the manufacturer wanted to perform the study but did not like the terms of the written request, it could negotiate with the FDA for different terms and come to a "written agreement."[203] In practice, manufacturers were held to higher standards in completing terms of written agreements as opposed to written requests, and it was actually more difficult for the manufacturer to meet its burden under the written agreement protocols.[204] In addition to making these agreements, the provision instructed the FDA to "develop [a] list of drugs for which additional pediatric information may be beneficial."[205] A drug did not need to be included on the list to be eligible for the exclusivity term subject to pediatric studies.[206]

Significantly, Congress included a section in the provision entitled "Relationship to Regulations."[207] In this section, Congress stated that if any rule promulgated by the Secretary of HHS required a manufacturer to complete a pediatric study and the required study met the "completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity."[208] The Senate report explained that even though the Senate chose to make the legislative provision voluntary, it had supported the FDA's policy toward pediatric testing thus far.[209] The Report remarked that the FDA's regulations "are clearly steps in the right direction, and the committee commends the FDA's initiatives in this area."[210] The language suggested support for further regulation along the lines of the 1997 proposed rule.

---

§ 156.

[202] 21 U.S.C. § 355a(a), (c). Under FDA guidelines, a manufacturer can submit a proposal for a request to the FDA. *See Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (prepared statement of Janet Woodcock, M.D., Director for Center for Drug Evaluation and Research, Food and Drug Administration)**.** The FDA uses this proposal as a basis for its request. *Id*.

[203] 21 U.S.C. § 355a(d)(1).

[204] *See Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (prepared statement of Janet Woodcock, M.D., Director for Center for Drug Evaluation and Research, Food and Drug Administration)**.**

[205] 21 U.S.C. § 355a(b). The FDA created a draft list by the middle of March 1998. *See* National Pharmaceutical Alliance v. Henney, 47 F. Supp. 2d 37, 39 (D.D.C. 1999). The FDA received input for the list from: the American Academy of Pediatrics, Pharmaceutical Research and Manufacturers of America, National Pharmaceutical Alliance, Generic Pharmaceutical Industry Association, National Institutes of Health, Pediatric Pharmacology Research Units Network, National Association of Pharmaceutical Manufacturers, and U.S. Pharmacopoeia. *Id.*

[206] *See Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (prepared statement of Janet Woodcock, M.D., Director for Center for Drug Evaluation and Research, Food and Drug Administration)**.**

[207] 21 U.S.C. § 355a(i).

[208] *Id.*

[209] S. REP. NO. 105-43, at 52 (1997).

[210] *Id.*

Thus, the "Relationship to Regulations" section ensured that the FDA could continue to make regulations that were broader than the congressional provision.[211] The only distinction would be that any manufacturer that satisfied the broader regulation and, thereby, satisfied the requirements of the Act, would benefit from a six-month patent or exclusivity extension, just like a manufacturer that voluntarily complied with the provision.[212] Congress avoided the controversial step of requiring pediatric studies while, at the same time, approving the authority of HHS to create regulations that promoted the policy of pediatric labeling.[213]

Despite these steps, Congress remained uncertain about whether a voluntary structure would be successful. The Senate referred to the voluntary provision as "a modest step toward a better resolution of [the] problem" of limited pediatric research and labeling.[214] Thus, Congress created some precautions to ensure that the legislation would be evaluated and reviewed. It instituted a provision requiring the Secretary of HHS to study and report on the "effectiveness of the program," the "adequacy of the incentive," the "economic impact of the program on taxpayers and consumers," and to make "suggestions for modification" by January 1, 2001.[215] Congress also included a January 1, 2002 sunset clause for the pediatric exclusivity provision.[216]

Upon implementation, the FDA broadly interpreted the incentive structure in the provision, maintaining that the six-month extension at-

---

[211] 21 U.S.C. § 355a(i).

[212] S. REP. NO. 105-43, at 52.

[213] Pharmaceutical companies have a vested interest in avoiding pediatric studies. As long as off-label pediatric prescriptions are permissible, the manufacturers can avoid liability for an adverse reaction in a child if that drug was not indicated for use in children. *See* Specific Requirements on Content and Format of Labeling, 59 Fed. Reg. 64,242 (codified at 21 C.F.R. pt. 201) (stating that drug manufacturers, for example, were nervous that the 1994 rule would expose them to liability if they were forced to include pediatric labeling even though the data was not, in their view, sufficient); Rachel Zimmerman, *Drug Makers Find a Windfall Testing Adult Drugs on Kids*, WALL ST. J. INTERACTIVE ED., Feb. 5, 2001, at 1, 3 (arguing that publicity could hurt drug sales in all age groups).

Furthermore, pharmaceutical companies would need to overcome numerous financial, ethical, and scientific boundaries in order to conduct successful studies on an ongoing basis. *See supra* Part I. As the Senate report for the FDAMA noted:

> there is little incentive for drug sponsors to perform studies for medications which they intend to market primarily for adults and whose use in children is expected to generate little additional revenue. Pediatric studies pose ethical and moral issues relating to using new unapproved drugs in young patients. Second, there are substantial product liability and medical malpractice issues. Third, pediatric patients are more difficult to attract into studies. Fourth, for some drugs, pediatric use represents more difficult issues of drug administration and patient compliance than adult use.

S. REP. NO. 105-43, at 51 (1997).

[214] *See* S. REP. NO. 105-43, at 51 (1997).

[215] 21 U.S.C. § 355a(k).

[216] *Id.* § 355a(j).

tached to the active moiety studied,[217] rather than just the drug.[218] Thus, a manufacturer could conduct a pediatric study in a drug with an active moiety and then receive a patent extension for all the drugs that used that active moiety.[219] The FDA believed that this interpretation was in tune with the purpose and language of the statute and was necessary to give effect to the incentive structure of the statute.[220] By applying the six-month extension to all the drugs that used a particular active moiety, the FDA attempted to further induce manufacturers to conduct studies because they would now be able to tap into an adult market in addition to the pediatric market, augmenting sales.[221]

Accordingly, by April of 2001, the FDA "issued [a total of] 188 written requests covering 155 drugs already on the market and 33 new drugs not yet approved."[222] These requests reached a broad range of drugs, ranging from those for cardiovascular disease and cancer to dermatological and dental treatments.[223] Despite the number of requests, however, only twenty-eight drugs were granted exclusivity periods.[224] While most of these twenty-eight did result in a labeling change of some degree, only 37.5% of those pediatric labels resulted in a significant change in safety or dosing.[225] By the reauthorization discussions in 2001, only twenty-five

---

[217] An active moiety is the "molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108 (2002).

[218] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 7.

[219] *Id.*

[220] *Id.*

[221] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drug Products and Biological Products in Pediatric Populations, 63 Fed. Reg. 66,632, 66,633 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601). Generic drug companies, led by the General Pharmaceutical Industry Association ("GPIA"), were dismayed by this interpretation, which could potentially cost generic manufacturers billions of dollars. *Generic Makers Fight for Level Playing Field*, CHAIN DRUG REV., Aug. 30, 1999, at RX 80. The six-month extension was already a setback for them because they now had to wait an extra six months before their drugs could hit the market. The application of the extension to all drugs containing a given moiety only further cut into the generic manufacturers' share of the pharmaceutical market. *See id.*; *Debate Over Exclusivity for Pediatric Provision Testing Heats Up; Generic Pharmaceutical Industry Association*, CHAIN DRUG REV., Apr. 26, 1999, at RX 38; 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 17. Generic manufacturers argued that the "moiety interpretation" of the provision "frustrates incentives for pediatric research by conferring lucrative benefits on 'innovator' drug manufacturers that are completely out of proportion to the useful pediatric data generated in return." National Pharmaceutical Alliance v. Henney, 47 F. Supp. 2d. 37, 39 (D.D.C. 1999) (internal citation omitted). GPIA sought a preliminary injunction against implementation of the FDA policy in the District Court of the District of Columbia. *Id.* at 38. The District Court denied the preliminary injunction, finding that the FDA was "entitled to the deference normally accorded to regulatory agencies." *Id.* at 38–40.

[222] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 4 (statement of Janet Heinrich, Director, Health Care-Public Health Issues). By September 30, 2002, the FDA had issued a total of 253 written requests. Pediatric Exclusivity Studies as of September 30, 2002, *available at* http://www.fda.gov/cder/pediatric/wrstats.htm.

[223] *Id.*

[224] *Id.* at 45.

[225] Rodriquez et al., *supra* note 124, at 718. At the time the article was written, twenty-seven drugs had been granted pediatric exclusivity and, in the authors' estimation, only six

percent of drugs had been studied in children—a five percent increase from the 1994 statistic.[226] Thus, while the pediatric incentive of the FDAMA sparked activity, it did not accomplish a sweeping change in the number of drugs with pediatric labeling.[227]

2. The 1998 Final Rule

As the FDA and the pharmaceutical industry negotiated the terms of a voluntary testing process, the FDA contemporaneously pursued rules that would make such testing mandatory. In the 1998 final rule, a modestly adapted version of the 1997 proposed rule, the FDA recognized the enactment of the FDAMA's pediatric exclusivity provision as an intervening event, but it did not believe that the provision should alter its present course of regulation.[228] The FDA believed that the FDAMA "specifically recognize[d the] FDA's intention to require pediatric studies by regulation" and extended the six months to any manufacturer who satisfied provisions of the FDAMA in satisfying FDA regulations.[229] Without such regulations, the FDA explained, the FDAMA would not provide a comprehensive policy with respect to pediatric labeling.[230] For example, the FDA noted that the FDAMA's incentives were insufficient to promote studies in smaller markets and in younger pediatric groups that are more difficult to test.[231] Additionally, the provision provided no incentive for manufacturers to study more than one age group for a given drug because any further studies would not result in a subsequent extension of the manufacturer's patent or exclusivity term.[232] Concerned about these gaps in the provision's incentive structure and trying to better balance pediat-

---

of those drugs resulted in significant improvement in pediatric labeling. *Id.* The authors found that the following drugs had greatly improved labels: Midozolam, Etodolac, Fluxamine, Gabapentin, Loratadine, and Propofol. *Id.*

[226] S. REP. NO. 107-79, at 1–2 (2001).

[227] The FDA itself may have been at fault for some of the delay. *See* Karst, *supra* note 18, at 767 (noting that some pharmaceutical companies believed the FDA purposefully withheld patent extensions). At least one court found that the FDA was reading its requirements too strictly. *See* Merck v. FDA, 148 F. Supp. 2d 27 (D.D.C. 2001). In *Merck*, the court granted Merck, the pharmaceutical company that sued the FDA, an injunction pending a trial on the merits to determine whether the FDA had fairly interpreted the language of the statute. *Id.* at 30. Subsequently, the FDA conceded that it had used an incorrect legal standard. Merck v. FDA, Civ. Action No. 01-01343(JR). The Merck lawsuit captures the sentiment of many in the industry that the FDA was doing a poor job of implementing the exclusivity program—that it was abusing its authority over drug companies and thwarting the potential incentive.

[228] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,633 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[229] *Id.*

[230] *Id.*

[231] *Id.*

[232] *Id.*

ric labeling needs, children's vulnerability as test subjects, and the desirability of quick drug approval, the FDA promulgated the 1998 final rule.

The 1998 final rule empowered the FDA to require pediatric testing of already marketed drugs and instituted a presumption favoring pediatric testing and labeling for new drugs. The first part of the 1998 final rule addressed already marketed drugs. Under the rule, the FDA could require testing for products used by a substantial number of pediatric patients[233] or products that provided a meaningful therapeutic benefit[234] over an existing treatment for pediatric patients.[235] A pharmaceutical company could request a full or partial waiver under certain circumstances where the company could show good cause for not performing the tests.[236] A full waiver would be granted where the necessary studies would be "impossible or highly impractical" or where there was "evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups."[237] The manufacturer could seek a partial waiver for a speci-fic sub-population for similar reasons.[238] Unlike the voluntary 1994 final rule and the FDAMA, the 1998 final rule authorized the FDA to punish manufacturers for noncompliance by deeming an existing drug misbranded or a new drug an unlicensed biologic.[239]

The 1998 final rule also established strict protocols for new drug applications with respect to pediatric testing.[240] Under the rule, each application for a new drug[241] needed to contain data that were "adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric sub-populations."[242] The 1998 final

---

[233] The 1998 final rule defined a substantial number of pediatric patients with the disease or condition for which the drug or biological product is indicated as 50,000. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness, 63 Fed. Reg. at 66,636.

[234] The 1998 final rule explained that a "meaningful therapeutic benefit" is created if the drug provides a significant improvement over existing adequately labeled remedies or if the drug is indicated for diseases for which there are currently few products labeled for pediatric use and more therapeutic options needed. *Id.* at 66,635.

[235] 21 C.F.R. § 201.23(a), (b) (2002).

[236] *Id.* § 201.23(c)(1)–(2).

[237] *Id.* § 201.23(c)(1). If a waiver were granted because of safety or ineffectiveness concerns, the waiver would be conditioned on the manufacturer's labeling the drug to reflect that it was unsafe or ineffective. *Id*. § 201.23(c)(3).

[238] *See id.* § 201.23(c)(2). In addition to the two waiver conditions available for the full waiver, a partial waiver would be granted where the product: "(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and (B) Is not likely to be used in a substantial number of patients in that age group, and (C) The absence of adequate labeling could not pose significant risks to pediatric patients." *Id*.

[239] *Id*. § 201.23(d). See Misbranded Drugs and Devices, 21 U.S.C. § 352 for the definition of "misbranded drug."

[240] Pediatric Use Information, 21 C.F.R. § 314.55(a) (2002).

[241] The rule included in the definition of "new drug": a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. *Id*. § 314.55(a).

[242] *Id.*

rule, therefore, was distinct from both the 1994 proposed rule and the FDAMA pediatric exclusivity provision in that the FDA could require tests before the drug hit the market in *all* age groups, including those extremely young age groups, such as neonates, that manufacturers had particularly avoided.[243] The rule provided a waiver structure similar to that for already marketed drugs,[244] and it also contained a deferral clause, under which manufacturers could seek to defer pediatric studies until after the drug had been approved for adults.[245] The main reason for the deferral provision was that the FDA did not want to prevent adults from accessing beneficial drugs while pharmaceutical companies focused on pediatric studies.[246] The 1998 final rule, therefore, attempted to balance the medical needs of children and adults.

Many considered the 1998 final rule to be a great victory. As the Executive Director of the Pediatric AIDS Foundation, an organization active in the campaign for pediatric clinical testing, explained, "[w]e see the rule as a real victory . . . . For too long, children have been seen as an afterthought, with so many drugs not available to them. A child is not just half an adult to be given half the adult dose."[247] Others maintained, however, that the FDA did not have the authority to require that private companies test their drugs in children,[248] especially when the drugs at issue were not intended for children.[249] This claim rested on the assertion that the FDA could not predict what customary or usual uses of the involved drug would come to pass.[250]

To support the historic and legal argument that the FDA could not require testing without congressional authorization, industry advocates pointed to a 1992 statement made by former FDA Commissioner David Kessler that the FDA did not have the authority to require a manufacturer to complete pediatric tests if the manufacturer did not indicate that the drug would be used by children.[251] They also argued that the FDA was bound by its previous voluntary approach to pediatric testing. Some of these opponents of the rule filed suit against the FDA, claiming that it had overstepped the bounds of the FDAMA.[252]

---

[243] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,633–34 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[244] 21 C.F.R. § 314.55(c); 21 C.F.R. § 201.23.

[245] 21 C.F.R. § 314.55(b).

[246] *Id.*

[247] Nordenberg, *supra* note 16, at 28.

[248] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness, 63 Fed. Reg. at 66,657.

[249] *Id.*

[250] *Id.*

[251] Karst, *supra* note 18, at 762.

[252] *See, e.g.*, Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, No. CV. 00-02898, 2002 WL 31323411, at *1 (D.D.C. Oct. 17, 2002).

The FDA vigorously defended the 1998 final rule. In the "Legal Authority" section of the rule, the FDA justified its departure from Kessler's statement, arguing in part that "statements made in speeches, even by Commissioners, are informal expressions of opinion and do not constitute a formal agency position . . . [and] are not binding on the agency."[253] The FDA also pointed to its explanations in the 1992 and 1997 proposed rules and the 1994 final rule to demonstrate that the 1998 final rule did not suggest a drastic change in the FDA's interpretation of the FDAMA.[254]

Before 2002, it seemed as though the FDA had strong arguments in favor of its position based on the generous language of the FDAMA's Senate Report.[255] The reauthorization of the pediatric exclusivity provision in 2002, however, greatly transformed the law of pediatric clinical research and added another dimension to the litigation regarding the 1998 final rule.[256] The numerous and comprehensive changes to the pediatric exclusivity provision were the result of heated debate among critics and supporters of the provision as to how and whether the provision should be reauthorized.

B. The Successes of FDAMA's Pediatric Exclusivity Provision

In general, pediatricians, politicians, and children's health advocates have applauded the results of the pediatric exclusivity provision.[257] As Dr. Myron Genel of the American Pediatric Association told the Senate Committee on Health, Education, Labor, and Pensions in 1999, "rarely is it possible to witness such dramatic advances in such a short time."[258] Dr. Robert Ward, speaking on behalf of the American Academy of Pediatricians, noted that the numbers proved the success of the FDAMA's pediatric exclusivity provision: the FDA granted twenty-eight products exclusivity and eighteen of those contained new dosage, safety, or adverse event-reporting information.[259] In contrast to the seven years before the

---

[253] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness, 63 Fed. Reg. at 66,657.

[254] *Id.*

[255] S. REP. NO. 105-43, at 52 (1997). *See also supra* text accompanying notes 209–210.

[256] *See* Ass'n of Am. Physicians, 2002 WL 31323411, at *4, *12 (noting that the 2002 legislation "reauthorized and expanded" the pediatric testing incentive set forth in the FDAMA and finding that with the legislation, Congress, "demonstrate[d] its intention to occupy the field").

[257] *See* S. REP. NO. 107-79, at 4 (2001) ("The pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative decision to date."). *See generally Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 6 (statement of Janet Heinrich, Director, Health Care-Public Health Issues).

[258] *Hearings on Implementation of the FDA Modernization Act*, *supra* note 153 (statement of Myron Genel, M.D., on behalf of the American Academy of Pediatrics).

[259] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 55 (statement of Robert Ward, M.D., on behalf of the American Academy of Pediatrics).

enactment of the FDAMA in which only eleven studies were completed,[260] these numbers were impressive. Indeed, the FDA itself reported that the "pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."[261] Even pharmaceutical groups commended the legislation for inspiring them to undertake the complicated task of pediatric clinical research, admitting that prior federal regulations had done little to accomplish this end.[262]

Although some critics claimed that the incentive program was too costly, many pediatricians condemned the notion of putting any price tag on children's health.[263] Dr. Ward testified that while pharmaceutical groups may have benefited from the program, "the greatest windfall has been in the area of pediatric research and information now available for pediatricians . . . . Dollars and cents arguments can not adequately provide the evidence of the effectiveness or importance of this program."[264] In fact, some patient advocacy groups felt that the extension was not a sufficient incentive and wanted Congress to allow even longer exclusivity terms in some cases.[265] The importance of the provision is even clearer in light of claims by pharmaceutical groups that, but for the six-month incentive, they might not have conducted the work entailed in assembling a study to meet the guidelines for pediatric labeling.[266]

New pediatric labels were not the only signs of robust pediatric research activities.[267] Since the enactment of the FDAMA, the infrastructure for pediatric testing has grown dramatically. For example, the National Institute for Children's Health and Development ("NICHD"), which often works in conjunction with pharmaceutical companies, enlarged its pediatric testing capacity from seven to thirteen units to meet the demand for more pediatric studies.[268] This increase in the number of studies has resulted in more researchers being prepared to conduct pedi-

---

[260] *See id.*

[261] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at ii.

[262] *See, e.g.*, *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 96 (statement of Timothy R. Franson, Vice President, Clinical Research & Regulatory Affairs, Lilly Research Laboratories, Eli Lilly and Company on behalf of the Pharmaceutical Research and Manufacturers of America).

[263] *See id.* at 79 (statement of Richard Gorman, M.D., on behalf of the American Academy of Pediatrics).

[264] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 58 (statement of Robert Ward, M.D., on behalf of the American Academy of Pediatrics).

[265] *See* 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 24. For example, oncology groups argued that the exclusivity provision had not done enough to promote research in cancer drug therapies. *Id.*

[266] *See* Zimmerman, *supra* note 92, at 4–5. For example, Eli Lilly's spokesperson noted that the incentive was key to its decision to proceed with three pediatric studies for which it had already developed protocols but had not yet initiated. *Id.* at 4.

[267] *See* Stolberg, *supra* note 118, at 1.

[268] *See Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 43–45 (statement of Janet Heinrich, Director, Health Care-Public Health Issues).

atric studies and has generally furthered the science of pediatric research.[269] Moreover, in its report to Congress, the FDA estimated the savings that increased pediatric research would offer. The FDA conducted a study of five serious illnesses in which the hospitalization rates were much higher for children than adults.[270] It attributed a substantial portion of this higher hospitalization rate for children to the lack of informed drug treatment.[271] The FDA concluded that if this disparity could be reduced by just twenty-five percent, the populace would save $228 million annually.[272] Thus, the FDA argued that the cost of any effort to conduct pediatric studies must be viewed in light of the health care savings that such studies would produce.[273] An overwhelming consensus emerged among supporters of pediatric testing that Congress should not risk modifying and potentially ruining the exclusivity program.[274]

Moreover, many felt the voluntary program was the proper approach to pediatric testing.[275] The incentive gave companies more liberty to choose an approach best suited to them.[276] It also helped the drug industry to overcome the financial barriers in testing drugs that would be marketed to smaller markets.[277] Dr. Stephen Spielberg, Vice-President of the Jansen Research Foundation and a spokesperson for the Pharmaceutical Research and Manufacturers of America, explained that the incentives created an environment that promoted pediatric studies by the government's showing increased favor for companies that conducted them.[278] He reasoned that even if the biggest money-making drugs, or "blockbuster drugs," are tested before drugs for smaller markets, the overall effect of

---

[269] *See Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 113 (statement of Christopher-Paul Milne, Assistant Director, Tufts Center for the Study of Drug Development) (explaining that the provision sparked an increase in research facilities and researchers).

[270] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 14. *See also* S. REP. NO. 107-79, at 11 (2001).

[271] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 14.

[272] *Id.*

[273] *Id.* (reporting that the Tufts Center for the Study of Drug Development estimates that the pediatric exclusivity provision saves up to $7 billion per year "by making treatments more effective for pediatric patients").

[274] *See generally User Fees, supra* note 198.

[275] Marilyn Elias, *Plan to End Pediatric Drug Trials Draws Fire; Lawsuit Says FDA Exceeds Its Powers By Ordering Tests*, USA TODAY, Apr. 3, 2002, at D9 (quoting a member of the Competitive Enterprise Institute as saying that the FDA "has no business telling private companies to add pediatric tests and label claims.").

[276] S. REP. NO. 105-43, at 51 (1997). *See also* Marc Kaufman, *Judge Rejects Drug Testing on Children; Ruling Finds FDA Overstepped Authority in Forcing Pediatric Studies*, WASH. POST, Oct. 19, 2002, at A9.

[277] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (statement of Stephen P. Speilberg, M.D., Ph.D., Vice-President, Pediatric Drug Development, Janssen Research Foundation, on behalf of the Pharmaceutical Research and Manufacturers of America) ("The difficulties of the studies and the small market for these drugs were acting as major impediments for pediatric drug development, and the basis of the legislation was that an incentive to do pediatric studies would overcome those obstacles.").

[278] *Id.*

increased studies would be to create a stronger pediatric research environment.[279]

C. Criticisms of the Pediatric Exclusivity Provision and Suggestions for Reform

The pediatric exclusivity provision had numerous problems that even its most ardent supporters recognized.[280] In the introductory section of the 1998 final rule, the FDA noted, for example, that the provision did not promote study in more than one age group per drug and that it failed to give incentives to manufacturers of drugs that reached small markets or that were already off-patent.[281] As January 1, 2002, the sunset date, approached, criticism of the pediatric exclusivity provision became more intense and better defined.[282]

Concerns about the provision fell into four main categories: (1) its failure to address off-patent and off-exclusivity drugs, (2) the pharmaceutical companies' "windfall" from extended patent terms, (3) its failure to ensure testing in smaller markets such as neonates, and (4) its limited capacity to ensure pediatric labeling and dissemination of information.[283]

1. The Provision's Failure To Address Off-Patent and Off-Exclusivity Drugs

The lack of incentive for off-patent and off-exclusivity drugs[284] was a major area of concern, since pharmaceutical companies lacked incentives

---

[279] *Id.* ("Establishing and maintaining excellence in pediatric drug development is crucial to the success of the pediatric research incentive program, and to its goal of early, timely pediatric studies in the life cycle of medicines. This is driven to a great extent by the higher performing drugs within a company's portfolio. It is crucial for future drug development and innovation in pediatrics.").

[280] *See, e.g.*, *Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83 (letter dated June 11, 2001 from Abbey S. Meyers, President, National Organization for Rare Disorders, Inc.) ("The real issue is that some drug companies receiving pediatric exclusivity are reaping rewards far greater than their investment in pediatric clinical trials. The financial rewards can sometimes be so great that they focus their research on only the most lucrative drugs, rather than the drugs children need most. *Nevertheless, my testimony clearly supports reauthorization of the pediatric exclusivity.*") (emphasis added).

[281] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[282] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children, supra* note 100, at 55–60 (2001); *Hearings Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 165–66.

[283] *See Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, supra note 83 (statement of Travis Plunkett, Legislative Director, Consumer Federation of America on behalf of the Patient and Consumer Coalition) (providing an outline of most of the main ideas considered); 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 18.

[284] Hereinafter, the term "off-patent drugs" will include drugs that are no longer on a patent term and those drugs that no longer have an exclusivity period under the Hatch-Waxman Act or the Orphan Drug Act. *See* Regulations Requiring Manufacturers to Assess

to research these drugs.[285] There was nothing in the provision that independently promoted the research of off-patent drugs.[286] This lack of incentive had huge implications for children's medicine as six of the ten drugs most widely prescribed to children were older antibiotics[287] that would not be included in the incentive structure.[288] Members of Congress began calling for reform, citing these drugs and others such as Ritalin—a drug that had not been tested for children but is commonly prescribed to children with Attention Deficit Disorder—as proof that the pediatric exclusivity provision needed to be reformed.[289]

Some members of Congress advocated the codification of the 1998 rule, which would address this problem. A significant reform proposal that received broad, though tentative, support, codification of the 1998 final rule would confirm the FDA's power to require pediatric testing without financial incentives.[290] Many supporters of the rule, however, feared that the pharmaceutical industry would kill a bill that codified the rule.[291]

Some consumer groups, on the other hand, suggested a combined requirement and incentive approach.[292] For example, Public Citizen Con-

---

the Safety and Effectiveness, 63 Fed. Reg. at 66,633.

[285] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 15–20 (statement of Sen. Mike DeWine (R-Ohio)); H.R. REP. 107-277, at 14 (2001) (noting that the exclusivity provision was inadequate because drugs without patent protection or exclusivity were not eligible for its incentive).

[286] The pediatric exclusivity provision did not use any language that referred to or encompassed drugs without patent or exclusivity terms. *See* Better Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2001) (codified at 21 U.S.C. § 355a); Zimmerman, *supra* note 92.

[287] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 13. These ten drugs were prescribed 5 million times in 1994 and included albuterol inhalation solution for nebulizaiton, phenergan, ampicillin injections, auralgan otic solution, lotrisone cream, Prozac, Intal, Zoloft, Ritalin, Alupent. Nordenberg, *supra* note 16.

[288] *See Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 98 (statement of Timothy R. Franson, Vice President, Clinical Research and Regulatory Affairs, Lilly Research Laboratories, Eli Lilly and Company on behalf of the Pharmaceutical Research and Manufacturers of America).

[289] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 19 (2001) (statement of Sen. DeWine).

[290] *See id.* at 21, 24 (noting that the FDA, pediatrician groups and consumer groups supported the rule's codification); Public Citizen Congress Watch, *Pediatric Exclusivity: Changes Needed to Assure Safety Effectiveness of Medications for Children and More Affordable Drugs for Seniors* [hereinafter *Pediatric Exclusivity*], *available at* http://www.citizen.org/congress/reform/drug_patents/pediatric/articles.cfm?ID=5001 (last visited Oct. 2, 2002); *Exclusivity Periods: Pediatric Exclusivity Provision Battle Begins; Generic Consumer Groups Question FDAMA*, PHARMACEUTICAL L. & PUB. POL'Y, Aug. 2, 2001 [hereinafter *Exclusivity Periods*].

[291] *See, e.g.*, Press Release, American Academy of Pediatricians, Law Providing Safer Medications for Children Must Continue (May 4, 2001). For example, Dr. Philip Walson, a member of the AAP Committee on Drugs, stated: "We cannot lose sight of the law's goal to improve the safety and effectiveness of medications taken by children. If we tinker too much within the existing law or fail to renew the law altogether, the health of children will be compromised." *Id*.

[292] *Pediatric Exclusivity*, *supra* note 290.

gress Watch requested that Congress allow the FDA to require exclusivity for new drugs and already marketed, on-patent drugs without the reward of an extra exclusivity term.[293] For on-patent drugs used for off-label purposes, Public Citizen Congress Watch recommended giving the FDA authority to require pediatric studies in exchange for a patent extension, with a limitation on that extension for blockbuster drugs.[294]

A transfer mechanism was another, less radical, alternative offered to reach off-patent and off-exclusivity drugs.[295] A pharmaceutical company could perform a pediatric clinical study on an off-patent drug, thereby earning a six-month credit, which it could attach to one of its on-patent drugs.[296] These options, while not ultimately adopted, demonstrate the creative ways that policymakers attempted to reform the exclusivity provision.

2. The Pharmaceutical Companies' "Windfall" from Extended Patent Terms

A second major concern was that the provision was paying drug manufacturers too much to perform studies they should have done in the first place—pharmaceutical companies received a windfall.[297] Estimates as to the cost of conducting a pediatric test vary. The NICHD estimates that safety and effectiveness studies in children can cost from $1 million to $7 million.[298] Pharmaceutical Research and Manufacturers of America, a pharmaceutical lobbying group, estimates the cost at anywhere from $5 to $35 million.[299] A Tufts-based group, whose numbers are often cited, places the cost at an average of $3.87 million.[300]

The payout for a six-month extension, on the other hand, often far exceeds these numbers. For example, the *Wall Street Journal* calculated the additional revenue for six drugs granted exclusivity, estimating their gains to be as follows: Claritin $975 million, Prozac $831 million, Glucophage $648 million, Pepcid $290 million, Vasotec $318 million, and Buspar $284 million.[301] In the case of Prilosec, its pediatric clinical study cost between $2 and $4 million, but it earned $1.4 billion during its six-

---

[293] *Id.*

[294] *Id.*

[295] *See* 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 22.

[296] *See User Fees*, *supra* note 198.

[297] *See generally* Rachel Smolkin, *Pros, Cons of Pediatric Drug-Testing are Debated as Congress Debates Extending a Law that Promotes Testing Drugs for Use with Children, the Benefits and Drawbacks are Volleyed*, PITTSBURGH POST-GAZETTE, Aug. 5, 2001 at A3.

[298] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 3–4 (statement of Janet Heinrich, Director, Health Care-Public Health Issues).

[299] *Id.* at 4.

[300] *Id.*

[301] Zimmerman, *supra* note 92, at 2. These numbers represent the additional revenue earned on the extended exclusivity term of six months as compared to the revenue from the same amount of time in competition with generic drugs. *Id.*

month extension.[302] This 36,000% return on an investment in medical research[303] should be contrasted with the entire 2002 budget for the NICHD of $1.1 billion.[304] The FDA performed a cost study of the pediatric exclusivity provision and found that the six-month patent and exclusivity extension would cost American consumers $13.9 billion over the next twenty years.[305] The present value of that amount using Office of Management and Budget standards is about $7.2 billion over the next twenty years.[306] Many children's advocates, politicians, and consumer advocates argued that this was simply too great a windfall for the pharmaceutical industry, already the wealthiest in the nation.[307]

Critics further argued that these costs disproportionately burdened the generic industry and its primary consumers, the elderly.[308] The total cost of the program on an annual basis was $695 million, which amounted to half a percent of the nation's pharmaceutical bill.[309] The FDA predicts that the government will pay for twenty-one percent of this extra burden, while the private sector will pay for seventy-nine percent.[310] According to generic drug manufacturers, the increased costs will affect the elderly more than any other group.[311] As Public Citizen Congress Watch points out, to a senior taking three of the most popular drugs, the increase will seem more costly than half a percent of his budget.[312] As for

---

[302] PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12, at 4.

[303] *Id.*

[304] *User Fees*, *supra* note 198.

[305] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 14.

[306] *Id.*

[307] *See Markup of H.R. 2985, H.R. 2887, and H.R. 2983: Hearings Before the House Energy and Commerce Comm.*, 107th Cong. (Oct. 11, 2001) (statement of Rep. John D. Dingell, (D-Mich.)) (stating that "[I]t is now my view that we made a mistake in enacting the pediatric exclusivity law. First, it establishes a voluntary 'incentive' for activity that should instead simply be required. Second, assuming that we choose to provide an incentive, the exclusivity program is more expensive, less equitable, and less efficient than any number of alternatives . . . . The central feature of this bill, exclusivity, is about further increasing the profits of an already bloated industry . . . . What have the parents, patients, and pediatricians received for this government-provided largess? Nothing."); *User Fees*, *supra* note 198 (arguing that **"**these windfalls come out of Americans' pockets because of this legislation as surely as they would if we had increased taxes and paid billions for pediatric trials directly . . . each time we extend patents of exclusivity, however laudable the purpose, we spend the public's money"); Zimmerman, *supra* note 92, at 2.

[308] *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 71–75 (2001) (statement of Carole Ben-Maimon, President and CEO, Proprietary Research and Development, Barr Laboratories) (expressing concern that the program disproportionately burdened the elderly). *See also Pediatric Indication Will Become Subject to User Fees*, WASH. DRUG LETTER, Dec. 24, 2001 [hereinafter *Pediatric Indication*], *available at* 2001 WL8205608. Representative Waxman argued that the "windfall has contributed to soaring out-of-pocket cost for seniors." *House Panel Clears Pediatric Study Bill*, GENERIC LINE, Oct. 19, 2001, *available at* WL 15571315.

[309] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 16–17.

[310] *Id.* at 17.

[311] *Id.* at 25.

[312] PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12, at 10. *See also Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 165–66 (let-

the generic companies, they will lose $10.7 billion in new sales over twenty years, and they could potentially lose up to $48 million a year in unrealized profits.[313] Furthermore, the biggest critics of the program charged that the provision paid pharmaceutical companies to release pediatric information that they already had or that they should have acquired on their own accord.[314]

To address these concerns, legislators and consumer advocates proffered various proposals as alternatives to the six-month incentive structure. One idea that received broad support and endorsements from Senators Ted Kennedy (D-Mass.) and Hillary Rodham Clinton (D-N.Y.) was the "tiered approach."[315] Under this approach, the term of the extension would be limited by how much money the drug grossed.[316] A simpler version of the reduced-incentive approach would target the blockbuster drugs alone, reducing the provision's extension to drugs that would earn over $800 million in sales during the extension.[317] Senator Christopher Dodd (D-Conn.) argued, however, that this approach would result in litigation, as manufacturers and the FDA would argue over how much a drug would actually earn in a given time period.[318] Another approach, touted by the generic industry and Donna Shalala, the former Secretary of HHS, was to award a tax-credit to manufacturers who conducted pediatric studies.[319] Some thought that only a government guarantee of a 100% return on investment would provide enough incentive.[320] This approach, however, was criticized both for providing too little incentive to conduct tests and for being impractical because the money for such reimbursements would have to come out of taxpayer dollars.[321] Finally, some members of the generic drug industry advocated attaching exclusivity only to the drug studied rather than the active moiety studied, but few beyond the generic industry supported this approach.[322]

---

ter dated June 11, 2001 from Abbey S. Meyers, President, National Organization for Rare Disorders, Inc.) (expressing concern that for the elderly and uninsured, half a percent is a significant amount).

[313] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 17.

[314] *See* Zimmerman, *supra* note 92, at 4–5; *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 4–5 (statement of Rep. Frank Pallone, (D-N.J.)) (expressing concern for the amount paid to drug companies for putting forth information that they already have and for paying them to do research on children that they should have done anyway).

[315] *See User Fees*, *supra* note 198; *Pediatric Exclusivity*, *supra* note 290.

[316] *See User Fees*, *supra* note 198.

[317] *See* S. REP. NO. 107-79, at 7 (stating that Senator Clinton proposed and then withdrew such an amendment).

[318] *User Fees*, *supra* note 198.

[319] *See Exclusivity Periods*, *supra note* 290; *Pharmaceuticals*: *Pediatric Exclusivity Provision Battle Begins, as Generic Consumer Groups Questions Law*, BNA's HEALTH CARE DAILY REP., July 27, 2001.

[320] *See* H.R. REP. NO. 107-277, at 56 (2001) (referring to the Waxman-Brown Substitute).

[321] *User Fees*, *supra* note 198.

[322] Stolberg, *supra* note 118, at 1.

3. The Provision's Failure To Ensure Testing in Smaller Markets Such as Neonates

Critics also focused on the lack of attention that the pediatric exclusivity provision gave to smaller market drugs, which tended to include drugs for neonates.[323] Neonates were rarely studied as a result of the provision's limited opportunity for a second exclusivity term.[324] In order to establish a safe study for neonates, information usually must be gathered from older pediatric age groups first.[325] Once a pharmaceutical company performed a study in any pediatric age group and it received its six-month extension, however, it had little incentive to study other age groups since the provision provided no extra incentives.[326]

Many critics of the provision also felt that the incentive structure prompted drug companies to study only blockbuster drugs that would garner the greatest profits in six months, as opposed to lesser selling drugs.[327] Proponents disputed this analysis, arguing that only two of the seventeen drugs that were labeled for children under the exclusivity provision had sales of greater than $1 billion.[328] Public Citizen Congress Watch, however, claims that blockbuster drugs comprise an increasing number of pediatric exclusivity extensions, estimating that fifteen of nineteen of the drugs with over $1 billion in sales in 2000 were likely to seek and receive extensions.[329]

To address this problem, Public Citizen Congress Watch advocated codification of the 1998 final rule, which would allow the FDA to require testing in smaller markets. On the opposite side of the spectrum, some reformers sought to introduce mechanisms to promote testing of drugs in neonates through secondary periods of exclusivity.[330] For example, Sena-

---

[323] *See Hearings on Better Pharmaceuticals for Children*, *supra* note 100 (prepared statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration); *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 55 (statement of Robert Ward, M.D., on behalf of the American Academy of Pediatrics) (noting that the degree of caution necessary to neonatal study should not render such studies outside the scope of the incentives of pediatric exclusivity). *See, e.g.*, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601) (noting that the incentives of the FDAMA were insufficient to promote neonatal studies).

[324] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 13, 21. *See also New Incentive Proposed for Studies in Youngest Children*, WASH. DRUG LETTER, Sept. 10, 2001 [hereinafter *New Incentive*], *available at* 2001 WL 8205396.

[325] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 13. *See also New Incentive*.

[326] *See* 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at iii.

[327] PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12, at 2.

[328] *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 68–69 (statement of Gregory L. Kearns, M.D., Professor and Chief, Division of Clinical Pharmacology and Medical Toxicology, Children's Mercy Hospital and Clinics).

[329] PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12, at 10.

[330] *See* 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 20; *New Incentive*, *supra* note 325.

tor Kit Bond (R-Mo.) proposed an additional three month period of exclusivity for those drugs that were tested in neonatal populations.[331]

4. The Provision's Limited Capacity To Ensure Pediatric Labeling and Dissemination of Information

The pediatric exclusivity provision did not require that labels actually be changed.[332] The provision stated that the six-month extension on a drug's patent or exclusivity period begins when the pharmaceutical company satisfies the research requirements of the written request or agreement.[333] **T**he pharmaceutical company did not have to change its labels for the extension to activate.[334] In fact, if the required testing produced no new labeling information, the FDA had the freedom to grant an extension without requiring a change to the pediatric label.[335] The provision left pharmaceutical companies with little incentive to assent to labeling changes in a timely matter.[336] The General Accounting Office ("GAO") found that, on average, it took nine months for the FDA and drug manufacturers to agree on labeling changes.[337] Moreover, the FDA reported great difficulty in convincing drug manufacturers to list "unfavorable pediatric research results" on their drug labels.[338]

This situation disturbed many, as it appeared that drug companies were merely taking advantage of a loophole in the legislation to avoid releasing important information about the hazards of their drugs to parents and their physicians. Representative Bart Stupak (D-Mich.), an active advocate for strengthening the provision,[339] was outraged by what he believed to be the pharmaceutical companies' foot-dragging.[340] Indeed,

---

[331] *New Incentive*, *supra* note 325.

[332] 21 U.S.C. § 355a(a)–(b) (2000).

[333] *Id.*

[334] *Id.*

[335] *Id.*

[336] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 7–8 (statement of Janet Heinrich, Director, Health Care-Public Health Issues).

[337] *Id.* at 7. This finding was based on the eighteen drugs granted pediatric exclusivity at the time the GAO conducted its survey. *Id.*

[338] *Id.*

[339] Representative Stupak's son committed suicide while on the prescription drug Accutane. *See* Jennifer Frey, *With Little Warning a Teen's Parents Were Not Aware that Their Son's Acne Medication Could Lead to Thoughts of Suicide, and They Never Suspected He Would Follow Through*, FLA. SUN-SENTINEL, Feb. 4, 2001, at E1. The drug, manufactured by Hoffman la Roche, did not contain a label warning that the drug might produce depression in teens, even though, by the time of Stupak's son's death, there appeared to be a correlation. *Id.* Accutane is prescribed for acne and is known to have a range of side-effects. *See generally* Tara Parker-Pope, *Alternative to Accutane: Parents Search for New, Less-Toxic Acne Treatments*, WALL ST. J., Apr. 30, 2002, at D1.

[340] 147 CONG. REC. E23,890–901 (daily ed. Dec. 20, 2001) (statement of Rep. Stupak) ("What I find horrifying [about the pediatric exclusivity provision] is the grant of exclusivity takes place after the drug company does its study but before anyone knows what is included in the results of the study. Nothing is said to the general public—which includes

two of the companies that grossed the most in their six-month patent extensions were Astra Zenaca for Prilosec ($1.4 billion) and Eli Lilly for Prozac ($900 million).[341] Neither drug changed its labeling as a result of the pediatric studies.[342]

Thus, Stupak, along with others in the House and Senate, the AAP, the FDA, and consumer groups, called on Congress to tie labeling changes to the grant of exclusivity.[343] They sought to condition the six-month extension on the manufacturer's compliance with the FDA's labeling recommendations.[344] Still, others feared that such a conditional approach would lead to less research since drug companies that predicted that their clinical tests would result in no labeling changes or detrimental changes would decide not to conduct the research.[345]

5. Other Concerns

Other critics noted smaller problems with the pediatric exclusivity provision. For example, the FDA and industry members generally regarded the list of additional drugs needing pediatric testing required by the provision as a waste of the FDA's time, since it produced so few studies.[346] Additionally, the FDA protested that it was underfunded and understaffed.[347] Also, some drug companies were attempting to exploit loopholes in the provision to obtain a three-year exclusivity extension based upon a combination of the pediatric exclusivity provision and the Waxman-Hatch exclusivity provision.[348] Both supporters and opponents

---

parents and pediatricians—or prescribing physicians about the safety, effectiveness, or dosage requirements.")

[341] H.R. REP. NO. 107-277, at 56 (2001).

[342] *Id.*

[343] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 25.

[344] *See, e.g.*, *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 43–48 (statement of Janet Heinrich, Director, Health Care-Public Health Issues); Letter from Consumers Union Opposing House Pediatric Exclusivity Bill to Unspecified Representatives in Congress (Oct. 21, 2001), *available at* http://www.citizen.org/congress/ reform/drug_patents/pediatric/articles.cfm?ID=6242; H.R. REP. NO. 107-277, at 57 (2001).

[345] *See Hearings Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 3–4 (statement of Rep. Charlie Norwood (R-Ga.)) (expressing concern that making extensions conditional on labeling would counteract the incentive because pharmaceutical companies would want to avoid labeling drugs with negative information); *id*. at 8–11 (statement of Rep. Sherrod Brown (D-Ohio)).

[346] The provision required the FDA to develop such a list, 21 U.S.C. § 355a(b), but a drug did not need to be on the list to be awarded exclusivity, nor did the FDA's selection of a drug for the list mean that the drug's manufacturer was required to complete testing on pediatric populations. 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 19.

[347] 2001 STATUS REPORT TO CONGRESS, *supra* note 6, at 22.

[348] *See* Jill Wechsler, *Policy Makers Seek to Limit Payments for Medicines*, PHARMACEUTICAL EXEC., Feb. 1, 2002, *available at* 2002 WL 13373489. These companies argued that a new pediatric label could also qualify as a new indication under the terms of the Waxman-Hatch Act, entitling a company that satisfied the requirements of the provision to the six-month extension as well as to the three-year exclusivity term under the Waxman-Hatch Act. *Id*. Bristol-Myers Squibb even delayed the reauthorization of the legislation

of this position wanted this issue clarified in the reauthorized legislation.[349] The pediatric exclusivity provision's strongest advocates and critics sought ways to improve the provision, hoping to strengthen it without harming its political viability.[350]

As the January 1, 2002, deadline for reauthorization drew near, the BPCA began to crystallize, responding to many of the aforementioned concerns. Significantly, it addresses most of the major concerns without modifying the six-month incentive structure. As the following Partwill show, Congress adopted other financial and regulatory measures to meet some of the concerns about the FDAMA's exclusivity provision.

IV. The Reauthorization of the Pediatric Exclusivity Provision, an Overhaul within the Incentive Structure

The BPCA is a greatly matured successor to the original pediatric exclusivity provision of the FDAMA.[351] The new legislation, which passed resoundingly in both houses of Congress,[352] will undoubtedly transform the field of pediatric studies, as it both addresses the testing of off-patent drugs and on-patent drugs that pharmaceutical companies decline to test, and it expedites labeling changes. Nonetheless, it still retains many of the policy and ethical tensions of the original legislation. As this Partwill demonstrate, while Congress has sought to protect as many groups of children as possible through the BPCA, its insistence on an incentive-based system and its reluctance to require manufacturers to conduct pediatric studies will continue to cost consumers billions of dollars and enormous amounts of administrative time and energy. While the BPCA is not due to sunset until October 1, 2007,[353] policymakers should

---

with its attempts to convince Congress of this interpretation. *Id.* After losing the general battle to have Congress include such an interpretation in the new legislation, it sought to obtain a special three-year extension for its diabetes drug Glucophage, continuing to bog down the entire bill's passage. *See infra* text accompanying notes 424–429. In the end, the legislation made no special provisions for Bristol-Myers Squibb. *Bush Signs Pediatric Incentive Bill Extending Exclusivity Provision until 2007*, BNA Health Care Daily Rep., Jan. 9, 2002.

[349] *See* Wechsler, *supra* note 348.

[350] *See, e.g.*, *Hearings on the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 166 (letter dated June 11, 2001 from Abbey S. Meyers, President, Nat'l Org. for Rare Disorders, Inc.).

[351] Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified in scattered sections of 21 U.S.C. and 42 U.S.C.).

[352] The House passed House Bill 2887, its version of the bill, by a vote of 338 yeas, 86 nays, and 8 not voting. 147 Cong. Rec. H8216 (daily ed. Nov. 15, 2001). The Senate passed its version of the bill, Senate Bill 1789, by voice vote on December 12, 2001. 147 Cong. Rec. S13,070, 13,071 (daily ed. Dec. 12, 2001). The House approved the Senate's version by voice vote on December 18, 2001. 147 Cong. Rec. H10,200, H20,212 (daily ed. Dec. 18, 2001).

[353] 21 U.S.C. § 355a(n) (2002).

begin to think about non-incentive based policies that could be enacted to improve pediatric testing and health.

A. The Amendments and Reforms To the Pediatric Exclusivity Provision

1. Off-Patent Drug Research Funding

Perhaps the most significant reform of the BPCA is the "Program for Pediatric Studies of Drugs Lacking Exclusivity" ("Program for Pediatric Studies"), which establishes a program by which off-patent drugs can be tested.[354] The Program for Pediatric Studies requires the National Institutes of Health ("NIH") and the FDA to develop an annual list of drugs that are off-patent and off-exclusivity terms "for which additional studies are needed to assess the safety and effectiveness of the drug in pediatric populations."[355] The list may also include certain on-patent drugs, which are not voluntarily studied by pharmaceutical manufacturers or studied through the Foundation for Pediatric Research.[356] The FDA is then to take action to ensure that those drugs are actually studied through the Program for Pediatric Studies.[357] The BPCA met the FDA's requests to eliminate one section that required the FDA to develop a list of drugs that would benefit from pediatric testing.[358] Under the BPCA, when the FDA[359] decides that a drug requires research, it will issue written requests to all the drug's application holders.[360] These sponsors must respond to the FDA's request within thirty days. If they decline to perform the test or do not respond, then the FDA may publish requests for proposals from third parties to study the drug.[361] The FDA will accept proposals from organizations such as universities, teaching hospitals, laboratories, contract research organizations, and pediatric pharmacology research units.[362]

The BPCA also addresses the information dissemination problems of the pediatric exclusivity provision. The BPCA mandates that all reports completed pursuant to the Act are part of the public domain and will be

---

[354] 42 U.S.C. § 284m (2002). *See generally* S. REP. NO. 107-79, at 7 (2001).

[355] H.R. REP. NO. 107-277, at 34 (2001); 42 U.S.C. § 284m(a).

[356] 42 U.S.C. § 284m(a)(1)(A)(iv); H.R. REP. NO. 107-277, at 34 (2001). The Foundation for Pediatric Research, which the BPCA establishes, is discussed below. *See infra* Part IV.A.2.

[357] 42 U.S.C. § 284m(b)–(c).

[358] S. REP. NO. 107-79, at 6 (2001). The section eliminated was U.S.C. § 355a(b).

[359] The BPCA refers to the "Secretary," but for purposes of this Act, the two are interchangeable and will be used so here. *See* Delegations from the Secretary of Health and Human Services to the Commissioner of Foods and Drugs, 21 C.F.R. § 5.10 (2002).

[360] 42 U.S.C. § 284m(c).

[361] *Id.* § 284m(c)(2). Once a drug application holder has declined to conduct a test or misses the thirty day deadline, it is not eligible to respond to a written request for a contract from the FDA. *Id.* § 284m(c)(3).

[362] *Id.* § 284m(b).

published in the Federal Register.[363] Indeed, any pediatric report conducted pursuant to the Act must be published in the Federal Register within 180 days after its submission to the FDA.[364]

Additionally, the Program for Pediatric Studies establishes a structure for the FDA to negotiate labeling changes with drug application holders.[365] The BPCA created a clear timeline for labeling negotiations and affirmed the FDA's authority to compel label changes.[366] The FDA and all application holders have 180 days to negotiate the labeling changes.[367] At the point of agreement or at the end of the 180 days, the FDA will publish the requested labeling change, along with a copy of the clinical report, in the Federal Register.[368] In cases where no agreement is reached, the BPCA requires the FDA Commissioner to refer his recommendation to the newly formed Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.[369] The Subcommittee has ninety days to review the Commissioner's recommendation and return its own recommendation to the Commissioner concerning the appropriate labeling changes.[370] The Commissioner must then consider, but need not accept, the Committee's recommendation.[371] Within thirty days, the FDA Commissioner will forward final requests to the application holder,[372] who will then have thirty days to comply.[373]

If the manufacturer still refuses to accept the labeling change, under the BPCA the FDA has the authority to deem the drug misbranded.[374] The BPCA further states that the FDA has full authority to bring an enforcement action against the offending drug manufacturer.[375] The Program for Pediatric Studies, therefore, is a considerable departure from the

---

[363] *Id.* § 284m(c)(6)(B). *See also* S. REP. NO. 107-79, at 3 (2001).
[364] 21 U.S.C. § 355a(j); 42 U.S.C. § 284m(c)(7)(C).
[365] 42 U.S.C. § 284m 409I(c)(7).
[366] S. REP. NO. 107-79, at 3 (2001).
[367] 42 U.S.C. § 284m(c)(8).
[368] *Id.* § 284m(c)(7)(C).
[369] *Id.* § 284m(c)(8)(A).
[370] *Id.* § 284m(c)(8)(B).
[371] *Id.* § 284m(c)(9).
[372] *Id.*
[373] *Id.* § 284m(c)(10).
[374] *Id.*
[375] *Id.* § 284m(c)(11). The Senate Report explains that the

> government would make its case that a company's drug is misbranded before the court by showing that FDA made an initial request for relabeling that the company refuse [sic], that FDA referred the issue of [sic] the Pediatric Advisory Subcommittee, which reviewed the matter and made a recommendation about a labeling change to FDA, that FDA made a second request for a labeling change, which the company refused, and that FDA's second requested labeling change was appropriate because without the change the drug would lack adequate direction for use in children.

S. REP. NO. 107-79, at 9 (2001).

FDAMA's approach, which failed to address either off-patent drug testing or the efficiency and effectiveness with which the FDA can negotiate label changes. Still, the cost of this newfound attention does not fall on manufacturers unless they volunteer. Instead, its cost falls on the public, which supports pediatric testing through tax dollars under the Program for Pediatric Studies.[376] To fund the program, the BPCA appropriated $200 million for the fiscal year 2002, and as much as deemed necessary for the following five years.[377]

2. New Requirements for Drug Manufacturers with Patents or Exclusivity Terms

For on-patent drugs, the BPCA modifies 21 U.S.C. § 355a, entitled Pediatric Studies of Drugs, to address areas of timing and labeling in a manner similar to the Program for Pediatric Studies' treatment of off-patent drugs.[378] The BPCA compels manufacturers to make a decision regarding the FDA's written request within 180 days.[379] Manufacturers who agree to conduct pediatric studies pursuant to a written request then receive the same six-month extension as they would under the original provision.[380] The BPCA, however, eliminates a fee waiver for pediatric supplements that the FDAMA had allowed.[381] Now, as with all other supplemental applications, manufacturers will pay a mandatory user fee; the Congressional Budget Office estimates that the fee will generate $6 million in 2002 and $33 million over the 2002 to 2006 period.[382] The funds garnered by the user fees are earmarked to help maintain efficient approval of labels.[383] The BPCA also ensures that pediatric supplements proposing labeling changes will be considered priority supplements[384] under the standards established for all priority drugs.[385]

As with off-patent drugs, manufacturers of on-patent and on-exclusivity drugs now face a time limit for the labeling negotiation process. The FDA and the application holder have 180 days to agree on a pediatric label.[386] If no agreement is reached, the Commissioner of the FDA refers his or her labeling request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, which must return a

---

[376] 42 U.S.C. § 284m(d).
[377] *Id. See also* S. REP. NO. 107-79, at 12 (2001).
[378] 21 U.S.C. § 355a(d)(4)(A).
[379] *Id*.
[380] *Id*. § 355a.
[381] *Id.* § 379h(a)(1).
[382] *See Pediatric Indication*, *supra* note 308.
[383] S. REP. NO. 107-79, at 2 (2001).
[384] *See* 21 U.S.C. § 321(kk) (defining a "priority supplement" as "a drug application referred to in section 101(4)" of the FDAMA); H.R. REP. NO. 107-277, at 36 (2001); S. REP. NO. 107-79, at 12 (2001).
[385] 21 U.S.C. § 355a(b)(1)(F).
[386] *Id*. § 355a(d)(4)(A).

recommendation to the Commissioner within ninety days.[387] The Commissioner then has thirty days to consider the Committee's recommendation and make a labeling request to the drug sponsor.[388] Again, as with off-patent drugs, the drug sponsor has thirty days in which to agree to the labeling request.[389] If the manufacturer continues to decline the labeling request, the FDA may deem the drug misbranded and take action against the manufacturer.[390]

If, on the other hand, a manufacturer declines to perform a pediatric study or has already completed a study of one age group and has no incentive to complete another study, the BPCA sets up a fallback system for testing on that drug.[391] Once a study has been declined, the FDA may refer the drug to the Foundation for the National Institutes of Health ("Foundation for Pediatric Research").[392] The Foundation for Pediatric Research is a private, non-governmental foundation[393] designed to allay concerns that if public funding is not available there would be no independent funding for pediatric studies.[394] The Foundation is commissioned to collect funds (gifts, grants, and donations) and award grants for pharmacologic pediatric research on already-marketed drugs still on patent or exclusivity terms.[395] The Foundation contracts with an outside group under the guidelines described in the program for pediatric studies.[396] The BPCA also directs that the contract and labeling negotiations function like those of the publicly funded studies in the Program for Pediatric Studies.[397] If the Foundation has insufficient funds to conduct the study, the drug can then be included on the list of drugs for the Program for Pediatric Studies.[398] Hence, although different provisions apply to off-patent and on-patent drugs, the format by which the FDA negotiates with the various manufacturers is consistent throughout the BPCA.

3. Structural Administrative Changes

The BPCA increases the capacity of the FDA, enabling it to handle its new role as the initiator and arbitrator of pediatric studies—something that the original bill had failed to do. The BPCA establishes the Office of

---

[387] *Id.* § 355a(d)(3).
[388] *Id.* § 355a(i)(2)(C).
[389] *Id.* § 355a(i)(2)(D).
[390] *Id.*
[391] 42 U.S.C. § 290b.
[392] *Id.*
[393] The Foundation is designed to serve the National Institutes of Health. *Id.* § 290b(a)–(b). Pediatric studies are one of its charges, but not its only responsibility. *See id.* § 290b(c).
[394] *See id.* § 290b(a)–(b); H.R. REP. NO. 107-277, at 39 (2001).
[395] 42 U.S.C. § 290b(c)(1).
[396] *See id.*
[397] H.R. REP. NO. 107-277, at 35 (2001).
[398] 42 U.S.C. § 290b.

Pediatric Therapeutics to oversee and coordinate pediatric activities and programs.[399] The Office will include at least one ethics specialist in pediatric clinical research and at least one person with expertise in agency coordination.[400] The BPCA also establishes a Pediatric Pharmacology Advisory Committee to advise the Secretary of HHS on pediatric pharmacology research priorities and ethical issues.[401] This Committee will help connect the BPCA's provisions to the ethical regulations established to ensure that children are not put at undue risk or used exploitatively for the benefit of research.[402] Finally, the BPCA attempts to address the concerns raised by oncologists that research in their field was particularly absent under the pediatric exclusivity provision.[403] The Act creates a Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, which evaluates and prioritizes cancer drugs for children.[404] It also requires the FDA and NIH to complete a report by January 31, 2003 studying whether pediatric patients have received adequate access to new cancer therapies.[405]

While the BPCA specifies the structure of these offices and their interactions quite precisely, it takes no steps to address criticisms from the pharmaceutical industry that the FDA exercises its authority capriciously. It establishes no guidelines to protect drug companies from the strict requirements and lengthy delays that the FDA has imposed on pharmaceutical companies over the past several years.[406] The timeline and review guidelines that the BPCA establishes are concerned with labeling negotiations, not negotiations regarding the satisfaction of the written request. The Act appears to allocate full discretion to the FDA to determine whether it will request comprehensive tests from drug companies or whether it will request tests of specific age groups.[407] Companies will still need to appeal the FDA's decisions in court, as drug manufacturer Merck did in the case of Lovastatin.[408]

4. Ethics and Equality Issues

The BPCA addresses pediatric ethical issues by directing HHS to contract with the Institute of Medicine to review the guidelines for pedi-

---

[399] 21 U.S.C. § 393a(a).
[400] *Id.* § 393a(c).
[401] 42 U.S.C. § 284m.
[402] *See* Additional Safeguards for Children in Clinical Investigations, 21 C.F.R. §§ 50.50–.56 (2002).
[403] 21 U.S.C. § 355.
[404] *Id.*
[405] *Id.*
[406] *See infra* note 227 and accompanying text.
[407] *See, e.g.*, 42 U.S.C. § 284m(c)(11); 21 U.S.C. § 355a(a).
[408] Merck v. FDA, 148 F. Supp. 2d 27, 29 (D.D.C. 2001).

atric research.[409] The BPCA notes that these reviews should look at issues such as consent, expectations of participants, risks, maturity levels in relation to legal status, payments made to children or their parents in return for participation, compliance with regulations, and the role of internal review boards in pediatric studies.[410]

The BPCA also addresses the right of minority children to be equally protected by the pediatric exclusivity program.[411] The BPCA requires that written protocols take into account the representation of children of ethnic and racial minorities.[412] It also requires the General Accounting Office to review whether minorities are included in pediatric research and whether adequate studies are performed on drugs used to treat diseases that disproportionately affect minorities.[413] This study must be completed by the Comptroller General of the United States by January 10, 2003.[414]

The BPCA also explicitly acknowledges that neonates are considered a pediatric population,[415] making clear that the FDA can request neonatal studies from manufacturers or contract for such studies with outside organizations.[416] Thus, the FDA could request studies in an older age group, to be followed by studies in neonates.[417] This step will help to ensure that neonates receive more equitable attention, but it is unlikely that this acknowledgment will encourage manufacturers to conduct testing on neonates of their own accord because of the risks and costs associated with testing neonates. Instead, such tests will likely be funded by public contracts.[418]

5. Generics

Another main problem with the earlier pediatric exclusivity provision was that its language did not clearly comport with the Waxman-Hatch generic exclusivity provisions.[419] First, the BPCA clarifies that any

---

[409] 42 U.S.C. § 289.

[410] *Id. See also* Internal Review Board Duties, 21 C.F.R. § 50.50 (2002); Clinical Investigations Not Involving Greater than Minimal Risk, 21 C.F.R. § 50.51 (2002).

[411] 21 U.S.C. § 355a.

[412] *Id.* § 355a(d)(2).

[413] *Id.* § 355a.

[414] *Id.*

[415] *Id.* § 355a(a). *See also* S. REP. NO. 107-79, at 3 (2001) (stating that neonates are newborns to one month old).

[416] S. REP. NO. 107-79, at 10 (2001).

[417] *Id.*

[418] This conclusion is based on the difficulty the FDA has had thus far in procuring tests on neonates through voluntary incentives. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,633–34 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[419] 21 U.S.C. § 355(j)(5)(B)(iv); S. REP. NO. 107-79, at 6 (2001) ("When Congress passed the Pediatric Exclusivity Provision in 1997, it had not meant to change the incen-

generic manufacturer that successfully challenged an invalid patent under the exclusivity provision will be awarded 180 days of exclusivity.[420] If the manufacturer also conducts a pediatric study of that drug, it will then receive a six-month extension to run after the initial Waxman-Hatch extension.[421] Some had thought that the pediatric exclusivity provision required the terms to run together, but Congress clarified that a generic manufacturer was to benefit from both in turn.[422]

The BPCA also addresses the three-year exclusivity extensions offered to pharmaceutical companies that labeled for a new indication.[423] As explained earlier, some pharmaceutical companies argued that a new pediatric label warranted not only a six-month extension but a three-year exclusivity period under the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman").[424] Under the BPCA, a pharmaceutical manufacturer will earn a three-year extension for indication changes that meet the requirements of the Act in addition to the six-month pediatric exclusivity period.[425] During the three-year exclusivity period, however, generic manufacturers can market the drug for those indications or aspects of the labeling that are not protected.[426] They simply cannot indicate that they have been tested for use in children.[427] If the drug is dangerous to children in any way, however, the generic manufacturer would need to label it as such.[428] This system creates a strange incentive structure for a drug manufacturer. It has more incentive to complete non-pediatric studies to achieve a supplemental exclusivity term where there will be no generic competition whatsoever. If it achieves such a term with a pediatric medicine, generic drugs will be able to compete with the non-exclusivity drug for pediatric uses through off-label practices. Nonetheless, Congress did not want to award on-patent drugs an extra three years of market exclusivity for pediatric tests, thus it chose this interpretation of the two exclusivity terms.[429]

6. Planning for the Future

Like its predecessor, the BPCA looks toward the future by including a sunset clause of five years, meaning the BPCA will expire on October

---

tives for challenging patents under the Waxman-Hatch Act by reducing periods of [abbreviated new drug application (generic)] exclusivity.").

[420] 21 U.S.C. § 355a(k).

[421] S. REP. NO. 107-79, at 5 (2001).

[422] H.R. REP. NO. 107-277, at 36–37 (2001).

[423] 21 U.S.C. § 355a(l).

[424] *Id.* at § 355(c).

[425] 21 U.S.C. § 355a(l)(1). A drug company may be awarded three years of exclusivity if it discerns new clinical uses for a drug already approved. 21 U.S.C. § 355(j)(5).

[426] H.R. REP. NO. 107-277, at 37 (2001).

[427] *Id.*

[428] 21 U.S.C. § 355a(l)(2)(a)–(b). *See also* H.R. REP. NO. 107-277, at 37 (2001).

[429] S. REP. NO. 107-79, at 8 (2001); H.R. REP. NO. 107–277, at 37 (2001).

1, 2007.[430] Also, the BPCA requires the United States Comptroller General, in consultation with HHS, to complete a comprehensive report on the effectiveness and costs of the program by October 1, 2006.[431] The report must consider several factors, including the effectiveness of the BPCA; the number and importance of the drugs tested as a result of the BPCA; the relationship between the grant of exclusivity and labeling; the cost to taxpayers in the form of higher expenditures by Medicaid and other government programs; the benefits to government, private insurers, and consumers that result from better health care for children; and the costs of privately and publicly funded studies.[432]

An additional reporting device was also instituted in order to catch adverse events more quickly:[433] each pediatric label will include a toll-free telephone number.[434] The BPCA requires the FDA to promulgate a rule ensuring that the toll-free number reaches the broadest consumer audience while minimizing the costs of the rule to pharmaceutical companies.[435] For example, it might require that the phone number be written on an auxiliary label on the drug vial itself.[436] Furthermore, for a one-year period after pediatric exclusivity is granted, drug sponsors must report all adverse events to the Office of Pediatric Therapeutics.[437]

The BPCA addressed many of the concerns that were raised in the years before the reauthorization of the pediatric exclusivity provision, but it did so within the framework of the incentive structure. Manufacturers may still make their own decisions as to whether or not they want to conduct a study and receive a six-month extension on their patent or exclusivity term of a drug. The BPCA, however, attempts to control for this voluntariness by instituting the Pediatric Studies Program and the Foundation for Pediatric Research to support research in drugs that the pharmaceutical companies do not investigate on their own. While further improving pediatric testing, the Act puts very little pressure—beyond the pressures of time and necessitated labeling changes—on manufacturers to change the way they approach researching and marketing new drugs. Manufacturers bear few costs beyond the user fees, while the public is now asked to support not only the six-month extensions but also the public funding of some pediatric research.

---

[430] 21 U.S.C. § 355a(n).
[431] *Id.* § 355a(m).
[432] *Id.* §§ 355a(m)(1)-(4).
[433] *Id.* § 355b(a).
[434] *Id.*
[435] *Id.* §§ 355b(a)(1)-(2).
[436] H.R. REP. NO. 107-277, at 27 (2001) (recommending that "auxiliary labels" be placed on the bottles or vials themselves).
[437] 21 U.S.C. § 355b(b)(1).

B. Reaction To the BPCA

At the end of the day, the incentive structure won out over proposals to codify the 1998 final rule or to condition exclusivity on new labeling. Some supported renewal of the voluntary incentive structure mainly because, to date, it had been the most effective legislation passed to ensure pediatric testing.[438] Pediatricians expressed hesitation at tampering with a legislative product that actually produced results.[439] Indeed, the idea that the cost of the incentive program should close the program down seemed contrary to the spirit of protecting children's health.[440]

Other groups, however, were committed to the voluntary structure for philosophical and economic reasons.[441] For example, the American Association of Physicians, the Competitive Enterprise Institute, and Consumer Alert believed that the government should not regulate off-label prescriptions, as the 1998 final rule would.[442] They worried that this would lead to other areas of government regulation of physician practices.[443] Additionally, these groups maintained that if pharmaceutical companies were forced to conduct studies in children, the result might be a costlier approval process overall.[444] The incentive process allows phar-

---

[438] *See* 147 CONG. REC. H10,200–01 (daily ed. Dec. 18, 2001) (statement of Rep. Michael Bilirakis (R-Fla.)) ("If it's not broken—don't fix it. By all accounts . . . this program is a resounding success. According to the FDA, 'the pediatric exclusivity provision has been highly effective in generating pediatric studies on many drugs and in providing useful new information in product labeling.' The American Academy of Pediatrics states that they 'can not overstate how important this legislation has been in advancing children's therapeutics.'") *Id.* at H10,202. *See also* 147 CONG. REC. E2073 (daily ed. Nov. 14, 2001) (statement of Rep. Albert Wynn (D-Md.)) (expressing his view that Congress included a sunset provision in the original enactment out of concern that the program would not work, but arguing that since it had been successful it should be renewed.).

[439] *See, e.g.*, Jim Geraghty & Megan Scully, *Child Drug Incentives Challenged Watchdogs Wary of Pharmaceutical Industry "Windfall,"* RECORD (Bergen County, N.J.), (Aug. 8, 2001) (quoting Dr. Steve Berman, then-president of the American Academy of Pediatrics, to say "What this law has given us over the last four years is a windfall of new, quality information about medications children use every day . . . . We can't go back to the days when children's needs are ignored, and that's what could happen if we tinker with this bill at this stage . . . . [W]e should not be willing to sacrifice the tremendous progress we've made."). *Id.*

[440] *Hearings on Better Pharmaceuticals for Children*, *supra* note 100, at 55 (statement of Robert Ward, M.D., on behalf of the American Academy of Pediatrics).

[441] Robert Pear, *Judge Rules on Pharmaceutical Tests*, N.Y. TIMES, Oct. 19, 2002, at A9.

[442] *See* Kaufman, *supra* note 276, at A9; Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, No. CV. 00-02898, 2002 WL 31323411, at *1 (D.D.C. Oct. 17, 2002). The plaintiffs in this case "argue[d] that the FDA has no authority to require manufacturers to (1) conduct studies of drug uses for which they do not intend to seek approval or (2) devise formulations of the drug tailored to those uses." *Id.* at *5.

[443] *See, e.g.*, Kaufman, *supra* note 276, at A9. Competitive Enterprise Institute's general counsel explained: "The FDA essentially claimed it could force new uses, or new patient populations—in this case, children—on a label. While the rule was limited to pediatric uses, it opened the door for testing requirements for other off-label special patient populations and for other off-label uses." *Id.*

[444] Pear, *supra* note 441, at A9. The Competitive Enterprise Institute general counsel

maceutical manufacturers to more easily consider undertaking the costs of pediatric research.[445] Ultimately, the arguments of those in favor of the incentive structure overcame those in favor of codification of the 1998 final rule.

Others, however, felt that the BPCA insufficiently addressed the problems latent in the incentive scheme. Several members of the House wrote a strong dissent in the House Report.[446] They argued that pediatric testing should have been required in some cases.[447] The BPCA, they maintained, only further confirmed that children were not a part of the general mandate of the FDCA that required drugs to be safe and effective for intended use.[448] They also criticized the incentive structure for imposing unnecessary costs on consumers, "costing consumers and taxpayers billions of dollars while producing only 19 new labels."[449] The dissenters highlighted the cases of Astra Zeneca's Prilosec and Eli Lilly's Prozac, which earned $1.4 billion and $900 million, respectively, from pediatric extensions without making label changes.[450] They argued that the House should have considered alternative structures such as the Waxman-Brown substitute, which would have been a more "cost-effective alternative" than the incentive structure.[451] This substitute would have directly reimbursed drug manufacturers for the cost of pediatric studies and guaranteed them 100% profits on the costs of the studies.[452]

The House dissenters also took issue with the BPCA's failure to condition the grant of exclusivity on labeling, and they were dissatisfied by the provisions that required publication of labeling requests and test reports in the Federal Register as a temporary measure.[453] Few pediatri-

---

also emphasized the economic risks of a mandatory structure, saying that allowing the FDA to require testing "would have made drugs scarcer and more expensive in the long run, by adding to the risk and the expense of drug development." *Id.*

[445] *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 97 (May 3, 2001) (prepared statement of Timothy Franson, Vice President, Clinical Research and Regulatory Affairs, Lilly Research Laboratories, Eli Lilly and Company on Behalf of the Pharmaceutical Research and Manufacturers of America) ("Thanks to . . . the FDAMA, a company R&D director today can weigh the substantial cost of pediatric drug development against the incentive . . . provided in FDAMA . . . . The incentive has meant that kids are now standing on equal terms with adults in the stiff competition for research dollars at our companies.").

[446] *See* H.R. REP. NO. 107-277, at 56–58 (2001). These members included Representatives John D. Dingell, Sherrod Brown, Henry A. Waxman, Peter Deutsch (D-Fla.), Frank Pallone, Jr., Tom Barrett (D-Wis.), and Bart Stupak. The House members were actually writing about House Bill 2887, their version of the Best Pharmaceuticals for Children Act. The two versions are slightly different, but not for the purposes of the dissenters' arguments, so the BPCA is used for the sake of clarity.

[447] *Id.* at 56.

[448] *Id.*

[449] *Id.*

[450] *Id.*

[451] *Id.*

[452] *Id.*

[453] *Id.* at 57.

cians, parents, or children would look there for advice on dosing or treatment, as most rely solely upon labels.[454] In the end, the dissenters believed that the FDAMA's pediatric exclusivity provision compounded the initial mistake of not requiring pediatric testing. The BPCA, in the dissenters' view,[455] was another flawed piece of legislation that isolated children from the full protections of the FDCA.[456] In general, consumer activists[457] were concerned that the BPCA unjustifiably forced consumers, especially the elderly, to pay more for drugs; that it forced the public to subsidize pharmaceutical research; and that drug makers were gaining hundreds of millions of dollars from studies that cost them only a couple of million dollars—an incentive far out of proportion to the costs of the studies.[458]

C. The Impact of the BPCA on the 1998 Final Rule

The BPCA caused further controversy because of its impact on the 1998 final rule. First, in May 2002, the Bush administration decided to suspend the rule in light of the BPCA's comprehensive structure.[459] The FDA maintained that the BPCA sufficiently addressed safety concerns for pediatric pharmaceutical users, likely making the rule unnecessary.[460] The same Democratic leaders who were disappointed with the BPCA

---

[454] *Id*.

[455] For a discussion of the dissent in the Senate, see S. REP. NO. 107-79, at 6 (2001) (noting that some amendments to BPCA were offered and withdrawn).

[456] *Id.*

[457] These consumer advocacy groups included, among others: Alpha 1 Foundation; Alliance for Retired Americans; American Federation of State, County and Municipal Employees; Center on Disability and Health; Center for Medical Consumers; Consumer Federation of America; Consumers Union; Families USA; Gray Panthers; International Union; National Consumer League; National Organization for Rare Disorders; National Women's Health Network; Public Citizen; Scleroderma Foundation; Service Employees International Union; USAction; and USPIRG. Public Citizen Congress, *Watch List of Groups that Also Oppose Dodd-DeWine in Its Current Form but May Not Subscribe to All the Points of Public Citizen's Analysis of the Bill*, *available at* http://www.citizen.org/congress/reform/drug_patents/pediatric/articles.cfm?ID=5000 (last visited Sept. 20, 2002).

[458] PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12. Indeed, consumer advocates accused pharmaceutical companies of unduly influencing legislators. *Id.* After the reforms it supported were not included in the BPCA, Public Citizen Congress Watch wrote a letter claiming that more comprehensive legislation was impossible because of industry lobbying. *Id.* The organization reported that those members of the Health Subcommittee of the House Energy and Commerce Committee who voted to retain the six-month patent extension had received on average $64,691 in campaign contributions from drug companies since 1990, while those who voted for amendments that would have reduced the extension accepted an average of $25,493 from drug companies during the same period. *Id*. at ii. Moreover, it found that three of the four sponsors of the BPCA—Senator Christopher Dodd, Senator Mike DeWine, and Representative Anna Eshoo (D-Cal.)—were among the top ten recipients of campaign contributions from the drug industry. *Id.*

[459] *See* Ceci Connolly, *FDA to Suspend a Rule on Child Drug Testing; Agency Says Patent Plan Meets Safety Goal*, WASH. POST, Mar. 19, 2002, at A10.

[460] *See* Associated Press, *FDA Changes Course on Child Tests,* L.A. TIMES, Apr. 20, 2002, at A17; Connolly, *supra* note 459, at A10.

expressed immediate outrage at the FDA's decision to forgo the rule.[461] Representatives Waxman, Dingell (D-Mich.), and Brown (D-Ohio) signed a letter dated March 18, 2002 to President Bush that urged him to prevent the FDA from suspending the rule.[462] They argued that it was a necessary component of pediatric clinical testing, asserting that without it pharmaceutical companies would only engage in the most profitable tests and not conduct tests that were the most worthwhile for children's health.[463]

In response to this harsh public criticism, HHS quickly reversed its policy, stating that it would enforce the 1998 final rule.[464] HHS announced that the BPCA and the 1998 final rule could coexist, but also asked for public comment on "what additional steps [the FDA could] take to assure adequate study of drugs in children in light of" the BPCA.[465] Accordingly, the FDA issued an Advanced Notice of Proposed Rulemaking in the Federal Register.[466] The notice acknowledged that the BPCA might not adequately ensure that all drugs, especially human biologics and antibiotics, are tested in pediatric populations.[467] It also acknowledged the BPCA's limitations: that public funding was dependent on yearly congressional outlays and that the legislation had a built-in sunset provision.[468] It then requested comments on how to "integrate the BPCA and the pediatric rule more effectively."[469]

While advocates of the 1998 rule were pleased that the FDA reversed its position, the near-suspension of the rule renewed efforts to codify it. Such a codification would remove discretion from the FDA as to whether pediatric testing could be required.[470] Senator Clinton explained her position on the importance of codification of the 1998 rule: "While I am pleased that the FDA has changed its mind about the pediatric rule, the fact that it can change its mind illustrates how important it is to make this rule the law of the land."[471] Significantly, codification would also moot legal challenges to the legitimacy of the 1998 rule.[472] Accord-

---

[461] *Democrats Protest FDA Plan to Suspend Pediatric Testing Rule*, WASH. DRUG LETTER, Mar. 25, 2002.

[462] *Id.*

[463] *Id.*

[464] Marc Kaufman & Ceci Connolly, *U.S. Backs Pediatric Tests in Reversal on Drug Safety*, WASH. POST, Apr. 20, 2002, at A3.

[465] Press Release, U.S. Dep't of Health and Human Servs., HHS Launches New Pediatric Drug Safety Initiative (Apr. 19, 2002), *available at* http://www.hhs.gov/news/press/2002pres/20020419b.html.

[466] *Id. See also* Obtaining Timely Pediatric Studies of and Adequate Pediatric Labeling for Human Drugs and Biologics, 67 Fed. Reg. 20,070 (Apr. 24, 2002) (to be codified at 21 C.F.R. pts. 201, 312, 314, and 601).

[467] *Id.* at 20,070.

[468] *Id.* at 20,071.

[469] *Id.* at 20,072.

[470] Kaufman & Connolly, *supra* note 464, at A3.

[471] *Id.*

[472] *See* Jennifer Silverman, *FDA to Retain, Update Pediatric Drug Rule as Part of New*

ingly, Senators Dewine and Dodd have proposed a bill to codify the 1998 rule.[473] There is even evidence that pharmaceutical companies would not strongly oppose such a codification as long as the six-month incentives were kept intact.[474]

On the heels of the flip-flop in the executive branch, the fragility of the 1998 rule's foundation was again thrown into question, this time by the United States District Court for the District of Columbia.[475] The court ruled that the 1998 rule exceeded the scope of the FDA's authority under both the FDAMA and the BPCA.[476] The court made this decision based on an examination of the principles of administrative law and the legislative history, noting a concern that acceptance of the 1998 rule might mean that all off-label practices could be regulated by the FDA—a situation contrary to established food and drug law practice, which allows the manufacturer, and not the FDA, to determine how to label its drug.[477] In the end, though, it concluded that the BPCA was incompatible with the 1998 final rule, stating that "Congress adopted an incentive scheme while the FDA adopted a command and control approach . . . . The two schemes differ in almost every possible regard."[478] Thus, for the FDA to enforce the 1998 final rule, Congress would need to codify it.

This result was not inevitable, though.[479] Upon its passage, the impact of the BPCA on the FDA's 1998 final rule was unclear.[480] The 1997 legislative history had endorsed the FDA's approach to the promotion of pediatric labeling,[481] but the BPCA's legislative history did not include a similar statement of approval. The BPCA did not alter the section of the exclusivity provision that endorsed FDA regulations that were broader than the pediatric exclusivity provision.[482] Rather, it allowed this "regulatory clause" to stand with the knowledge that the FDA had been enforcing the 1998 final rule since its enactment. Neither the Senate Report nor the House Report that accompany the BPCA mentions anything about

---

HHS Initiative, FAM. PRAC. NEWS, May 15, 2002, *available at* 2002 WL 18106374. The General Counsel for the Competitive Enterprise Institute, one of the groups suing the FDA along with the Association of American Physicians and Surgeons to prevent enforcement of the 1998 final rule, conceded that if the rule were codified their "claim . . . would be gone." *Id*. *See also Sanity on Pediatric Drug Safety*, N.Y. TIMES, Apr. 23, 2002 at A28.

[473] S. 2394, 107th Cong. (2002). *See also* Silverman, *supra* note 472.

[474] Kaufman & Connolly, *supra* note 464, at A3 (reporting that a spokesperson for PhRMA stated that the group was willing to accept such a requirement "as long as the incentives were in place.").

[475] Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, No. CV. 00-02898, 2002 WL 31323411, at *1 (D.D.C. Oct. 17, 2002).

[476] *Id.*

[477] *Id.* at *11.

[478] *Id.* at *13.

[479] *Id.* at *8 (noting that determining whether the FDA overstepped the bounds of the FDCA's labeling provisions was a close question).

[480] *See id.* at *12–*13.

[481] S. REP. No. 105-43, at 52 (1997).

[482] 21 U.S.C. § 355a(h) (2002).

changing or modifying the "regulatory clause" or the 1998 final rule. Further, many pediatric experts who spoke before Congress also continually referred to the successes of the pediatric exclusivity provision in conjunction with the 1998 final rule,[483] so it would be odd to assume that the BPCA displaced the 1998 final rule without specific direction from Congress.[484]

Children's health advocates expressed immediate disappointment and called on Congress to remedy the situation.[485] Senator Clinton, for one, quickly condemned the Court's decision, calling it a "major step backwards for children's health," and accusing the court of being "ill-informed about how the legislation was intended to work, and how it did work."[486] She and others in the Senate, including Senators DeWine and Dodd, continue, as this Article goes to publication, to lobby for codification of the 1998 final rule.[487] The FDA also announced its dissatisfaction with the court's ruling, saying that it was "very disappointed that the court struck down the pediatric rule, which we have vigorously enforced."[488] At the time of this Article's publication, it was reviewing whether to appeal.[489]

---

[483] *See, e.g.*, *Hearings on Evaluating the Effectiveness of the FDA Modernization Act*, *supra* note 83, at 65–109 (statement of Gregory Kearns, M.D.) (claiming that the "FDAMA conjoined with the 1998 Pediatric Final Rule, provides a most effective 'weapon' to bring pediatric therapeutic injustice to an end.").

[484] Generally, when Congress is silent on an issue, an administrative agency, such as the FDA, is presumed to have discretion to interpret the legislation as it sees fit. *See* Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984) (establishing a deferential standard for reviewing administrative agency interpretations of statutory language if (1) Congress is silent or ambiguous as to the challenged matter and (2) the interpretation is reasonable); Whitman v. American Trucking, 531 U.S. 457 (2001) (reaffirming deferential judicial standard to reasonable agency interpretation of statute). *But see* Ass'n of Am. Physicians, 2002 WL 31323411, at *1 (explaining that congressional inaction on an issue is not a basis for statutory interpretation) (citing Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 170 (4th Cir. 1998)).

[485] Laura Meckler, *U.S. Court Rejects Efforts to Test Drugs On Children: The Decision Means Companies Don't Have to Study Adult Medicines Often Given to Children*, PHIL. INQUIRER, Oct. 20, 2002, at A7. The Director of Public Policy at the Elizabeth Glaser Pediatric AIDS foundation characterized the ruling as "a devastating setback to children's health in this country," promising that "[t]here's going to be a lot of additional enthusiasm and energy behind this [legislation] as a result of the ruling." *Id.*

[486] *Court Tosses Out Rule on Drugs Tests*, CHARLOTTE OBSERVER, Oct. 19, 2002, *available at* 2002 WL 101038056.

[487] *Id.*; Laura Meckler, *Court Tosses Drug Testing Rules for Kids*, MILWAUKEE J. SENTINEL, Oct.19, 2002, at 2A. Senator DeWine noted that the case for codification was now much stronger, as children will be harmed without the legislation. *Id.*

[488] Chris Adams, *FDA Can't Require Drug Makers to Test on Children*, WALL ST. J., Oct. 21, 2002, at B4.

[489] *Id.*

D. The Future of the Pediatric Exclusivity Provision and the BPCA

The BPCA's failure to codify the FDA 1998 final rule is a major deficiency in the legislation, which ultimately may have left the rule open to reversal by the court. Codification of the rule would have been a much stronger step toward ensuring that new and already-marked drugs were tested. This kind of power might not appear necessary when there is public funding available for research, but in the event that congressional expenditures are insufficient to properly test drugs for safety and effectiveness in children, the FDA should be allowed to compel manufacturers to complete such studies. Any such codification could be modeled on the 1998 rule as well as the ethical regulations for pediatric research, which establish a set of rules to determine which drugs should be tested for use in children.[490]

The ethical regulations work to prevent the kinds of exploitative situations that historically developed in pediatric testing. If a study poses more than a minimal risk to children, it must meet conditions such as the potential for direct benefit to the child or approval from the FDA that it will serve the larger ends of children's health.[491] Furthermore, the 1998 rule contains waiver provisions. No study will need to be conducted in children when a drug is unlikely to be used in children when it is highly impracticable to complete the study in children (e.g., a study of a drug for Alzheimer's disease), or when there is evidence that the drug would be dangerous to children.[492] The rule also allays concerns about additional costs and delays in releasing useful drugs to the public by granting deferments of the pediatric testing requirement to drug companies that satisfy safety and effectiveness standards for adults.[493] Thus, a drug should not be delayed from reaching the public any longer than it currently is.

Another concern about codification of the rule is that it would impose substantial costs on consumers. Such concerns are unconvincing in light of the large costs of the six-month extension and the costs of public funding for pediatric research. Certainly, the costs of pediatric studies will increase the price of medicine, as the drug companies will pass the cost increases on to their consumers. Both the industry and the public, however, have bypassed these very costs of drug development for years.[494] Considering the precautions that the 1998 rule and ethical regu-

---

[490] *See* Additional Safeguards for Children in Clinical Investigations, 21 C.F.R. § 50.50–.56 (2002).

[491] *Id.*

[492] *Id.* § 314.55(c).

[493] *Id.* § 314.55(b).

[494] *See supra* Section I.

lations take to avoid unnecessary testing,[495] these costs seem reasonable in the name of better pediatric health.

In addition to its failure to codify the 1998 rule, the BPCA is unnecessarily expensive to consumers. It seems inherently unfair for the public to have to pay twice in this way: either the public pays directly for publicly funded tests or indirectly through the increased exclusivity terms. Indeed, the irony of the BPCA is that on a cost basis, it would be cheaper for consumers if pharmaceutical companies declined to perform any studies as consumers would pay the cost of the study, which on average costs $3.87 million,[496] instead of the extraordinary costs of the six-month patent extensions.

Another problem with the BPCA is in its administratively complex and dispersed design. It fails to place responsibility for pediatric testing on any one institution—public or private. Tests may be performed under the auspices of pharmaceutical companies, the Program for Pediatric Studies, or the Foundation for Pediatric Research. A number of offices have been established to oversee these studies and their resulting labeling, ranging from the Office of Pediatric Therapeutics to the Oncologic Drugs Advisory Committee.[497] Administrative time and financing will be wasted in the coordination of oversight and replication of skills and knowledge, as these offices attempt to oversee the various testing options which the BPCA provides. Instead, Congress should place the responsibility of testing children where it lies: with the pharmaceutical companies that research and market drugs. This requirement would likely save the public through reduced coordination costs, and reduced costs from the delay of requesting studies on a voluntary basis.

The voluntary incentive structure and the complex administrative system that complements it undercut the BPCA's strides toward improving pediatric research. Congress should contemplate other options for ensuring pediatric research besides market incentives. Policymakers should look at the reasons beyond cost that pharmaceutical companies are so reluctant to perform studies. A mere four million dollar study is not the crux of the problem—liability is. Perhaps the new ethics regulations will help to set up guidelines that can serve as defenses in the courtroom.[498] Congress might also consider creating an arm of the FDA that

---

[495] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,654–56, (Dec. 2, 1998) (to be codified at 21 C.F.R. pts. 201, 312, 314, and 601) (noting that because pediatric patients are a vulnerable population, special protections are needed to shield them from undue risk). *See generally* 21 C.F.R. §§ 46, 50.51–.56, 56.101–.102, 56.109, 56.111) (2002).

[496] *See* PUBLIC CITIZEN CONGRESS WATCH, *supra* note 12.

[497] Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, §§ 6, 14, 115 Stat. 1414, 1419 (codified at 21 U.S.C. §§ 284m, 393a). *See also* List of Standing Advisory Committees, 21 C.F.R. § 14.100 (2002).

[498] 21 C.F.R. §§ 50, 56 (2002).

oversees pediatric studies. Such oversight could then serve as a form of an "FDA defense" to a lawsuit.[499] That is, drug companies could have an affirmative defense to a lawsuit for a failed pediatric test or adverse side effect if they followed the FDA's procedures.

Congress could even consider establishing an administrative hearings procedure, much like that of the National Vaccine Program,[500] which compensates children who are victims of vaccines' adverse side-effects. Such a "clinical pediatric compensation program" could be funded by tax dollars as well as separate fees levied upon pharmaceutical companies. This kind of program would not only greatly reduce the risks of litigation to the pharmaceutical companies but would help to assure that children are fairly compensated for participation in pediatric studies on a timely basis.[501] The compensation program could use the administrative apparatus of the vaccine program since the administrative judges in that program are already adept at hearing medical issues concerning children. While this alternative[502] would actually be more administratively complex than the BPCA's structure, it would, at least, avoid the costs of the exclu-

---

[499] *See generally* Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability,* 88 GEO. L.J. 2147 (2000). The problem with this solution, however, is that product liability actions are incredibly expensive to mount. Without the incentive of punitive damages, lawyers will be less willing to take on liability suits on a contingency basis. This explains the importance of a secondary claims system in combination with any form of an FDA defense.

[500] National Childhood Vaccine Injury Act, Pub. L. No. 99-660, § 311, 100 Stat. 3743, 3755–84 (1986) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C. (2000)).

[501] It is worth noting that the vaccine compensation program has become subject to criticism for its failure to compensate children sufficiently for their injuries. *See, e.g.*, Derry Ridgway, *No-Fault Vaccine Insurance: Lessons from the National Vaccine Injury Compensation Program*, 24 J. HEALTH POL. POL'Y & L. 59, 82–83 (1999). Any new program modeled on the vaccine program would need to take the alleged failures of the vaccine program into account and make adjustments accordingly. The current criticisms of the vaccine program are: (1) the process to obtain compensation has become too adversarial and fails to adequately protect and fairly compensate claimants; (2) the industry has lost the incentive to create safer vaccines because it knows that it will not face punitive damages; (3) the special masters who hear claims are not subject to sufficient review; (4) current levels of compensation are insufficient to reflect the costs of caring for an injured child; and (5) costs awarded for attorney's fees fail to reflect the actual cost of hiring a lawyer skilled in children's medicine, which has become increasingly necessary as the process has become more adversarial. *See id.*; Leonard D. Pertnoy, *A Child's View of Recovery Under the National Children's Vaccine Act or "He Who Hesitates is Lost,"* 59 MONT. L. REV. 275, 276–77 (1998); Michael E. Horwin, *Ensuring Safe, Effective Vaccines for Children*, 37 CAL. W. L. REV. 321, 328–29 (2001); Breen, *supra* note 63, at 321–26.

[502] *See* National Swine Flu Immunization Program of 1976, 42 U.S.C. § 247b(k)(1)(A) (repealed 1978) for another example of tort liability protection for manufacturers. In March 1976, there was an outbreak of an influenza named swine flu. Congress attempted to establish a vaccine program, but the manufacturers refused to produce the vaccine without insurance against tort claims, and insurance companies refused to stand behind the vaccine. FOOD AND DRUG LAW, *supra* note 106, at 716. Congress solved the problem by creating the National Swine Flu Immunization Program, which directed all liability suits arising from claims of alleged vaccine injury to be brought against the United States government under procedures almost identical to those of the Federal Tort Claims Act. *Id.* at 717.

sivity incentive, and it would also directly address the liability concerns of the pharmaceutical companies.

Children deserve special treatment, such as larger investments in ethics guidelines, careful oversight, and training of specialists in pediatric research. They are a special-needs group that could benefit from targeted legislation. The history of exploitation and adverse reactions to drugs suggests the importance of creating legislation and regulations devoted to children's needs. Children need to be carefully integrated into mainstream clinical testing in a way that does not put other groups at risk. Nonetheless, Congress has muddled this notion of special treatment with the idea that pharmaceutical companies should not be responsible for pediatric testing. Nothing about children necessitates the placement of pediatric testing outside of the responsibility of the pharmaceutical industry.

Conclusion

Before the 1997 FDAMA pediatric exclusivity provision and the 1998 final rule, pharmaceutical manufacturers had almost free rein to market drugs that they knew would be used in children without performing any pediatric tests. By placing a label on their products stating that the drug had not been tested for safety and effectiveness on children, they could avoid venturing into the complicated area of pediatric testing. To the manufacturers' credit, the world of pediatric studies was highly unregulated, ethically complicated, and scientifically challenging.[503] Still, pharmaceutical companies knew that physicians would go off-label to prescribe to their pediatric patients the drugs that were indicated for adult diseases.[504] It is hard to justify either their decision to avoid testing or the government's decision to ignore this pattern of pediatric research.

With the 1998 final rule, the FDA attempted to include children into general safety and effectiveness standards for drugs. This radical step toward finally integrating pediatric clinical testing into the same regime as that of adults was thrown off course by Congress in 1997 and again in 2002 when Congress offered pharmaceutical companies rewards for such efforts on behalf of children. Thus, Congress set the tone for the pharmaceutical industry and the pediatric health community, suggesting that it was reasonable for pharmaceutical companies to receive inducements to complete basic pediatric tests. This incentive structure framed the entire debate over the BPCA.

---

[503] *See* Children's Health Act of 2000, Pub. L. No. 106-310, 114 Stat. 1101 (codified as amended in scattered sections of 42 U.S.C., 21 U.S.C., 28 U.S.C., 18 U.S.C., and 25 U.S.C.). It was not until this Act that the FDA enacted clear guidelines regarding the ethics of pediatric testing. *See supra* text accompanying note 57.

[504] *See generally* Henry, *supra* note 104, at 379.

The strongest argument in support of this incentive structure is that without it pharmaceutical companies would not be willing to conduct pediatric tests. This argument depends, however, on a voluntary system of pediatric testing. If Congress had codified the FDA's power to require testing in all new and already marketed drugs, the notion of an incentive or reward for testing would appear ludicrous. It is the controlling idea that testing children is a private and sensitive decision for the pharmaceutical company to make, not one to be imposed by the government, that made it possible for the incentive structure to be created and survive.

Congress, the pharmaceutical industry, and children's advocates should dispense with the notion that pediatric testing should be a voluntary decision on the part of a pharmaceutical company. Justifications for a voluntary structure should be met directly by legislation and regulations, and not by an incentive structure. For example, one argument for a voluntary system is that pediatric testing is ethically challenging.[505] Rather than paying companies to undertake "ethical risks," it would be better health policy and more economically efficient to spend time improving ethical guidelines, training pediatric ethicists, and equipping the FDA to actively participate in helping pharmaceutical companies plan studies. Similarly, pharmaceutical companies fear that they will be exposed to litigation both at the testing stage if their tests harm children, and at the marketing stage if their drugs cause adverse affects when used for a labeled indication. Congress could allay industry concerns by creating an arm of the FDA to assist pharmaceutical companies in dealing with the scientific challenges that children pose. It could also create legal protections, such as an FDA defense or an administrative compensation program to minimize the risk of high stakes tort litigation, which is one of the industry's largest concerns.

The current voluntary incentive system costs the public billions of dollars, is inequitable, and is poor health policy. It fails to address the underlying concerns about pediatric health by requiring that studies be performed ethically and safely and that marketed drugs be safe and effective. Thus, while the BPCA is an important step toward improved pediatric health, it is simply a modern extension of past neglect of pediatric clinical testing. Congress should reconsider its legislative effort to encourage pediatric testing. It should codify the 1998 final rule and finance the FDA to address the pharmaceutical companies' concerns regarding pediatric testing.

---

[505] *See* Notice of Publication of the Executive Summary of the Report "Ethical and Policy Issues in Research Involving Research Participants," by the National Bioethics Advisory Commission, 66 Fed. Reg. 45,998, 46,000, (Aug. 31, 2001).