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PEDIATRIC PRIORITIES: LEGISLATIVE AND REGULATORY INITIATIVES TO EXPAND RESEARCH ON THE USE OF MEDICINES IN PEDIATRIC PATIENTS

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I. INTRODUCTION

The evolution of prescription drug regulation in the United States has been inextricably tied to pediatric health issues. In the fall of 1901, thirteen children died of tetanus in St. Louis after being treated with a diphtheria antitoxin made from the blood of an infected milk wagon horse.¹ Less than a year later, Congress enacted the Biologics Control Act of 1902,² which remains the cornerstone of the federal regulation of biologics.³ In 1937, scores of children died after taking Elixir of Sulfanilamide, a new “wonder drug” for the treatment of infections that contained the solvent diethylene glycol (better known today as antifreeze).⁴ Congress subsequently enacted the landmark Food, Drug, and Cosmetic Act of 1938⁵ (FDCA) to provide the Food and Drug Administration (FDA) with new authority to require that drugs be demonstrated to be safe before they may be introduced into interstate commerce.⁶ In the late 1950s and early 1960s, some 10,000 children worldwide were born with birth defects to women who had taken the sedative thalidomide during their pregnancy.⁷ Spurred in large part by the

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1. Ramunas A. Kondratas, *Biologics Control Act of 1902, in THE EARLY YEARS OF FEDERAL FOOD AND DRUG CONTROL* 8, 14-15 (Glenn Sonnedecker ed., 1982).

2. Pub. L. No. 244, 32 Stat. 728 (1902).

3. PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW* 661 (2d ed. 1991).

4. Charles Wesley Dunn, *Report of the Secretary of Agriculture on Deaths Due to Elixir Sulfanilamide--Massengill*, in *FEDERAL FOOD, DRUG, AND COSMETIC ACT: A STATEMENT OF ITS LEGISLATIVE RECORD* 1316-27 (G.E. Stechert & Co. ed., 1938).

5. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C.S. §§ 301 et seq. (LEXIS 1997 & Supp. 2002)).

6. M.L. Yakowitz, *The Evolution of the Drug Laws of the United States, 1906-1964*, 19 *FOOD DRUG COSMETIC L. J.* 296, 297-98 (1964); David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 *LAW & CONTEMP. PROBS.* 2, 20 (1939).

7. MORTON MINTZ, *THE THERAPEUTIC NIGHTMARE* 248-64 (1965); RICHARD HARRIS, *THE REAL VOICE* 184-90 (1964). Although thalidomide was never approved in the United States, some women were still able to obtain it. HARVEY TEFF AND COLIN MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 4-7 (1979). Many of the affected babies were born in Europe, where thalidomide was available commercially. *Id.*

tragedy, Congress enacted the Drug Amendments of 1962⁸ to require that all new drugs be proven not only safe but also effective before coming onto the market.⁹

Pediatric health crises have thus prompted fundamental changes to the laws that govern the review and approval of human drugs in the United States. While these events have led to overarching reforms in the drug approval process, however, children themselves have often been left behind. Years ago, Dr. Harry Shirkey labeled children "therapeutic orphans" because the medicines being used to treat children had not been adequately studied and labeled for use in pediatric patients.¹⁰ Dr. Shirkey's pronouncement has been echoed often over the years. One survey based on data from 1991 to 1994 indicated that 71 per cent of all new molecular entities lacked labeling information on pediatric use.¹¹ The Congress similarly concluded in 1997: "When it comes to pharmaceuticals, our Nation's children are 'therapeutic orphans.'"¹²

Without information on pediatric use for a particular drug, physicians can be left in the difficult position of having either to prescribe a drug without knowing its precise effects in children, or to use a potentially inferior alternate treatment for which pediatric information is available.¹³ Both the safety and efficacy of therapy can suffer as a result. The need for securing the study and labeling of more medicines for pediatric use is thus clear. Unfortunately, however, so are the obstacles.

There are comparatively small numbers of pediatric patients with any particular disease in most cases.¹⁴ As a result, there are fewer patients available to recruit for clinical trials, and a smaller commercial market in which the medication can be used.¹⁵ Where patient numbers are adequate, it can still be difficult to find patients (and parents) who are willing to participate in research.¹⁶ Additionally, conducting research in children can raise heightened legal and ethical considerations surrounding matters such as informed consent, and the risk of liability can be greater.¹⁷ Where these concerns can be overcome, there may be technical difficulties in conducting research with children. For example, it may be

8. Pub. L. No. 87-781, 76 Stat. 780 (1962).

9. *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 191 n.45 (1971); Teff & Munro, *supra* note 7, at 121-24.

10. Harry Shirkey, *Editorial Comment: Therapeutic Orphans*, 72 PEDIATRICS 119, 119 (1968).

11. See John T. Wilson, *An Update on the Therapeutic Orphan*, 104 PEDIATRICS 585, 586 (at Table 2) (1999).

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

13. See generally Committee on Drugs, American Academy of Pediatrics, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286 (1995).

14. Ralph E. Kauffman, *Therapeutic Challenges: Prenatal and Paediatric Safety Considerations*, 5 DRUG SAFETY 65, 69 (1990).

15. *Id.*

16. Benedetto Vitiello, MD & Peter S. Jensen, MD, *Medication Development and Testing in Children and Adolescents*, 54 ARCH. GEN. PSYCHIATRY 871, 873 (1997).

17. See, e.g., *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807 (Md. App. 2001).

difficult to develop a drug formulation for use with younger age groups (e.g., a liquid for infants).¹⁸ Or it may be more difficult to measure the outcomes of certain kinds of treatments in the pediatric population, including, for example, treatments like anti-depressants that may require self-evaluation by patients to determine effectiveness.¹⁹

The net effect of all these factors is that the incentives to conduct pediatric research can be small and the disincentives significant, particularly when pharmaceutical research companies are considering how to allocate their scarce research dollars among competing projects. As Congress concluded in 1997:

[T]here 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.²⁰

It is therefore, perhaps, not that surprising that the challenge of meeting Dr. Shirkey's call for more pediatric research has persisted for so long. Real progress requires an approach that addresses the seemingly intractable root causes that underlie the problem in the first instance.

Well, help has finally arrived due in large part to innovative new federal initiatives that have been pursued in the past five years. These initiatives have brought unprecedented progress precisely because they address the systemic obstacles that have previously inhibited pediatric research. At the center of the federal government's current pediatric initiative are new incentives for drug sponsors to conduct pediatric studies. These incentives were established by the Better Pharmaceuticals for Children Act, which was enacted as part of the FDA Modernization Act of 1997 (FDAMA).²¹ The incentives have been complemented by pediatric study requirements that FDA has imposed through regulation under the so-called Pediatric Rule.²² FDA's authority to mandate studies in this way is

18. See BERT SPILKER, GUIDE TO CLINICAL TRIALS 132 (1991) (discussing potential problems associated with dosage forms such as solutions and suspensions typically used for children).

19. Vitiello & Jensen, *supra* note 16, at 873 (discussing the difficulties that can arise in detecting drug effects in children).

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

21. Pub. L. No. 105-115, 111 Stat. 2296 (1997), available at <http://www.fda.gov/opa/comp/7modact.html> (last visited Dec. 19, 2002).

22. 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).

controversial, and was in fact invalidated in a recent federal court decision holding that FDA exceeded its statutory authority in promulgating the Pediatric Rule.²³ Even before this ruling, however, the agency had allowed the incentives to work first in practice, and only used the Pediatric Rule as a default to ensure that needed studies are completed.²⁴

The pediatric incentives from FDAMA and the requirements from the Pediatric Rule had worked together like the proverbial carrot and stick to ensure that drugs are studied and labeled for pediatric use. These laws were and are further complemented, in turn, by the final piece of the current federal pediatric initiative, the Best Pharmaceuticals for Children Act (BPCA).²⁵ The BPCA was enacted at the beginning of 2002 and addresses gaps in the pediatric incentive provisions of FDAMA by establishing new public programs through the National Institutes of Health (NIH) to fund studies on off-patent and certain other drugs. The BPCA also reauthorized the incentives that had been created in FDAMA, and modified certain other aspects of the incentive provisions.

This article discusses these three legislative and regulatory enactments in detail to understand the differing provisions in each, as well as how they have worked together to promote pediatric research and labeling. Section one provides some historical context by summarizing prior FDA pediatric initiatives tracing back to the 1970s. Section two explains how the incentives from FDAMA work, and why (after surviving an early legal challenge by generic drug manufacturers) the incentives have been so successful. Section three reviews the study requirements of the Pediatric Rule, how they related to the FDAMA incentives, the recent court decision holding the Rule invalid, and legislative proposals to revive the Rule. Finally, section four covers the BPCA, including the new NIH study programs established by the legislation and the modifications that were made to the FDAMA incentive provisions.

In reviewing FDAMA, the Pediatric Rule, and the BPCA, it is striking how much attention the federal government has paid in the past five years to encouraging pediatric research and pediatric drug labeling. While children may have been left behind during earlier reforms of the country's drug approval laws, it is clearly now a top public health priority for both the executive and legislative branches to find specific solutions to pediatric health needs.

23. See *Ass'n of Am. Physicians and Surgeons, Inc., et al., v. U.S. FDA, et al.*, No. CIVA.00-02898, 2002 WL 31323411, *6 (D.D.C. Oct. 17, 2002).

24. See, e.g., 63 Fed. Reg. at 66,654 ("[B]efore imposing any requirements under [the Pediatric Rule], FDA intends to allow manufacturers eligible for FDAMA incentives an adequate opportunity to voluntarily conduct studies of marketed drugs in response to those [FDAMA] incentives. If, following such an opportunity, there remain marketed drugs for which studies are needed and the compelling circumstances described in the rule are met, the agency will consider exercising its authority to require studies.").

25. Pub. L. No. 107-109, 115 Stat. 1408 (2002).

All indications are that these efforts are producing demonstrable results. Although it may be premature to provide a final report card on the initiatives, at least two basic lessons have emerged. First, it seems clear that government intervention was needed. The obstacles to pediatric research that are otherwise present have simply been too difficult to overcome without legal and regulatory action. Second, the most effective government intervention has proven to be the adoption of meaningful incentives that encourage voluntary industry action. This is not to say that there has been no role for regulatory mandates or publicly-funded programs. But the experience thus far demonstrates that the incentives created by FDAMA, and reauthorized in the BPCA, most directly address the underlying causes for the lack of pediatric research.

As FDA itself concluded, the incentives have “done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.”²⁶ At least on this issue, then, government-generated incentives have proven most effective, while the more traditional approaches of establishing regulatory mandates and providing public funding operate to address gaps and provide a safety net where the voluntary incentives have not worked.

II. PRIOR PEDIATRIC INITIATIVES

FDA has appreciated the need to study medicines for pediatric use for some time. It may be necessary to develop and validate new formulations that younger patients can take. Where the formulations exist, without appropriate clinical testing there may not be a sound scientific basis for knowing whether a medicine is safe and effective for children, or for knowing what dosing should be used for different pediatric populations.²⁷ Where adult data exist, the data may or may not be extrapolated to children. Children are not “miniature adults,”²⁸ and differences in metabolism and physiology can influence how drugs work in different age patients.

Younger patients may require lower dosing because their reduced ability to clear drugs from the body creates a risk of toxicity.²⁹ Alternatively, some drugs can be cleared more rapidly by the immature systems in younger patients, and

26. U.S. FDA, Dep't of Health and Hum. Servs., *The Pediatric Exclusivity Provision: January 2001 Report to Congress* at ii (2001) *available at* <http://www.fda.gov/cder/pediatric/reportcong01.pdf> (last visited Oct. 8, 2002) (soliciting comments for report) [hereinafter *FDA Report to Congress*]; *see also* Report to Congress on Pediatric Exclusivity; Requests for Comments, 65 Fed. Reg. 26,217 (May 5, 2000).

27. Kauffman, *supra* note 14, at 68; John T. Wilson et al., *Paediatric Labelling Requirements: Implications for Pharmacokinetic Studies*, 26 CLIN. PHARMACOKINET. 308, 310 (1994).

28. William R. Crom, *Pharmacokinetics in the Child*, 102 ENVTL. HEALTH PERSP. 111, 111 (1994).

29. Kauffman, *supra* note 14, at 68.

higher dosing may be needed to ensure that enough drug is absorbed to be effective.³⁰ It may therefore often be necessary to conduct clinical trials to ensure that an adequate scientific basis exists for use of a drug in pediatric patients. Additionally, it is important to capture the available data in FDA-approved drug labeling. This official labeling does not necessarily contain the latest available scientific and clinical information on use of a drug, and physicians remain free to prescribe a drug outside of the FDA labeling.³¹ Nevertheless, the labeling provides pediatricians and other physicians at least one widely available and authoritative source for guidance.³²

For these reasons, FDA has made various attempts over the years to prompt drug manufacturers to conduct pediatric studies and submit proposed pediatric labeling. The most significant agency actions in this regard prior to those of the past five years occurred in 1979 and in 1994. These administrative measures, combined with other related agency actions, provide the historical backdrop leading up to the enactment of the FDAMA pediatric provisions in 1997 and final promulgation of the Pediatric Rule in 1998.

A. FDA's 1979 Prescription Labeling Rewrite

FDA has struggled perennially with how to improve the format and content of the agency-approved labeling for human prescription drugs (also known as the package insert or full prescribing information), so that the labeling will be useful and informative for prescribers.³³ The labeling contains detailed information approved by FDA on a drug's properties and official conditions for use, including sections on clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, dosage and administration, etc.³⁴ One major attempt to enhance prescription drug labeling came in the 1970s. FDA proposed the new rules in 1975³⁵ and promulgated final regulations in 1979.³⁶ In addition to making general improvements to prescription drug labeling, these new regulations sought specifically to address the need for greater information on the use of drugs in pediatric patients.

30. *Id.*

31. David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 15 HARV. J. ON LEGIS. 693, 723 (1978).

32. Wilson, *supra* note 11, at 585.

33. See, e.g., Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81,082 (Dec. 22, 2000) (setting forth FDA's most recent proposed rewrite of the requirements for prescription drug labeling).

34. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs, 21 C.F.R. § 201.57 (2002).

35. Labeling for Prescription Drugs Used in Man, Proposed Format for Prescription Drug Advertisements, 40 Fed. Reg. 15,392 (Apr. 7, 1975).

36. Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434 (June 26, 1979).

Under the rule, all prescription drugs were required to include a pediatric use subsection within the precautions section of the labeling.³⁷ The rule required that if the drug is approved for a pediatric indication, that indication must be described under the indications and usage section of the labeling, with dosing information provided under the dosage and administration section.³⁸ If there is no approved pediatric use, the labeling must state that “[s]afety and effectiveness in children have not been established” or that “[s]afety and effectiveness in children below the age of [] have not been established.”³⁹ Such statements have appeared in drug labeling ever since.

The limitations of the 1979 rule are obvious. The labeling requirements “inform physicians if data are unavailable concerning the safe and effective use of a drug in pediatric patients.”⁴⁰ However, the requirements did nothing to develop additional information on whether or how to use a drug in children. As FDA explained, the rule “neither requires nor is intended to require that studies be performed to develop data for inclusion in prescription drug labeling.”⁴¹

III. FDA’S 1994 PEDIATRIC LABELING RULE

In 1994, FDA went a step further. Due to growing agency concerns about the lack of pediatric information in existing prescription drug labeling, FDA proposed in 1992,⁴² and then finalized in 1994,⁴³ a requirement that all sponsors of drug and biologics products examine available data on pediatric use and submit a supplemental application for a pediatric indication if supported by the existing data.⁴⁴ At the same time, FDA clarified that its standards for approving new pediatric uses are flexible, and can permit expanded pediatric labeling based on available adult data and supporting pediatric information.

FDA explained that it can be difficult to conduct controlled clinical trials with pediatric patients because of “the many problems associated with the testing of drugs in the pediatric population (e.g., obtaining informed consent for tests not directly of benefit to the child, use of placebo controls in a vulnerable

37. 44 Fed. Reg. at 37,465 (codified as 21 C.F.R. § 201.57(f)(9) (2002)). This basic requirement remains in place today, as amended.

38. 21 C.F.R. § 201.57(f)(9) (2002).

39. *Id.*

40. 44 Fed. Reg. at 37,453.

41. *Id.*

42. 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 (Oct. 16, 1992).

43. 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).

44. *Id.* at 64,248 (“Sponsors must, therefore, reexamine existing data to determine whether the “Pediatric use” subsection of the labeling can be modified . . . , and, if appropriate, submit a supplemental application . . .”).

population).”⁴⁵ FDA emphasized that the law provides flexibility, though, where other evidence is available of a drug’s effectiveness in a population:

A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug’s effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.⁴⁶

The 1994 regulation thus sought to encourage pediatric labeling both by making clear the different criteria that may be used to obtain pediatric approval, and by directing drug and biologic sponsors to determine whether available data could support pediatric use.⁴⁷

The 1994 rule is significant in several regards. First, it constitutes an explicit acknowledgement by FDA of the difficulties of conducting classic placebo-controlled trials in pediatric patients, and the resulting need in at least some cases to extrapolate from adult data with limited supporting pediatric data. Second, the rule broke new ground by imposing an affirmative requirement on drug sponsors to submit supplemental applications if supported by available data. In imposing this requirement, the rule was limited in scope. FDA made clear that a sponsor need not seek pediatric labeling if the sponsor determined that the data were inadequate to establish that the benefits of pediatric use outweighed the risks.⁴⁸

Although the agency maintained its legal authority to compel new pediatric studies,⁴⁹ the agency emphasized that the 1994 rule “does not add a new requirement that sponsors carry out new pediatric studies, nor does it require that sponsors submit labeling with claims that are inadequately supported.”⁵⁰ In cases where the sponsor determined that the existing data did not support pediatric use, labeling could simply state, as before, that “safety and effectiveness in pediatric patients below the age of [] have not been established.”⁵¹

45. *Id.* at 64,240.

46. *Id.* at 64,241.

47. *Id.* The 1994 rule also required that more comprehensive information be included on pediatric use in the different sections of the labeling, including, for example, in the sections on indications and usage, dosage and administration, clinical pharmacology, clinical studies, contraindications, and warnings. *Id.*

48. *Id.* at 64,243.

49. *Id.* (“[V]arious provisions of the Federal Food, Drug, and Cosmetic Act (the Act), the Public Health Service Act (the PHS Act), and existing regulations authorize FDA to require [pediatric] studies under certain circumstances.”).

50. *Id.* at 64,242.

51. *Id.* at 64,241.

IV. RELATED AGENCY ACTIONS

FDA followed publication of the 1994 pediatric rule with various less formal agency attempts to expand the development of pediatric labeling. For example, the groups within FDA responsible for the review and approval of new drugs and biologics (the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research) adopted a "Pediatric Plan" intended to raise pediatric issues with sponsors during the drug research and development process and encourage pediatric studies.⁵² In addition, FDA reviewers began completing a "pediatric page" for each new drug or biologics application, which stated whether the product was labeled for pediatric use, and whether additional pediatric studies were needed and planned.⁵³ Both of these agency initiatives were aimed solely at prompting voluntary actions on the part of sponsors to undertake additional pediatric research.

A. Results from FDA Actions

The effectiveness of the 1994 rule and the FDA's related pediatric initiatives was mixed, and somewhat disputed. In public comments submitted to FDA in November 1997, the Pharmaceutical Research and Manufacturers of America (PhRMA) (a trade association representing research-based pharmaceutical and biotechnology companies) reported that 75 companies were then developing 146 new drugs that had been or would be studied in children.⁵⁴ According to the PhRMA comments, 19 of the 20 new drugs that were approved in the prior year, and that had potential for pediatric use, also had been or would be studied in children.⁵⁵ In addition, PhRMA cited reports that drug sponsors had responded to the 1994 pediatric rule by submitting some 200 supplemental applications to FDA.⁵⁶

FDA took a different view. In August 1997, the agency acknowledged that its initiatives had "produced some gains in pediatric labeling."⁵⁷ However, the agency ultimately concluded that its prior actions "have not yet substantially increased the number of drugs and biological products for which there is adequate pediatric use information."⁵⁸ FDA thus prepared to take further action. Congress also decided to enter the mix, thereby ushering in the current phase of federal initiatives to broaden pediatric drug labeling.

52. See 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).

53. See *id.* at 43,901-02; see also Wilson et al., *supra* note 27, at 314.

54. Comments of the PhRMA Submitted to the Dockets Management Branch of the FDA on Docket No. 97N-0165, at 2 (Nov. 13, 1997) (on file with the Journal of Health Care Law & Policy).

55. *Id.*

56. *Id.* at 3.

57. 62 Fed. Reg. at 43,902.

58. *Id.*

B. The Current Pediatric Initiative Part 1: The Carrot of Pediatric Exclusivity

As a matter of chronology, the next milestone in our unfolding pediatric story was FDA's determination in 1997 to propose a regulation that would compel manufacturers of certain drugs to conduct pediatric studies, the so-called Pediatric Rule.⁵⁹ Before the Pediatric Rule was finalized, however, Congress intervened and adopted a quite different approach as part of the FDA Modernization Act of 1997.

V. THE FDA MODERNIZATION ACT OF 1997 (FDAMA)

The FDA Modernization Act of 1997 (FDAMA)⁶⁰ was a broad reform statute with provisions addressing a wide range of issues under FDA's regulatory umbrella. Section 111 of FDAMA established a new detailed statutory program to enhance the incentives for the sponsor of a new drug application (NDA) to conduct pediatric studies and collect pediatric use information at FDA's request on new and already approved drugs.

These pediatric incentive provisions are codified at section 505A of the Federal Food, Drug, and Cosmetic Act (FDCA).⁶¹ Companies that satisfy the requirements of section 505A earn six months of additional marketing "exclusivity" for a drug. The six months of exclusivity effectively extend existing patent and other exclusivity protections by lengthening by six months the period during which FDA cannot approve a generic copy of an innovator drug based on an abbreviated NDA that relies on the safety and effectiveness data in the innovator's full NDA.⁶²

Under the new statute, the procedures for obtaining pediatric exclusivity for a drug that is already approved are as follows:

A. Pediatric List

FDA was required to develop, prioritize, and publish annually a list of "approved drugs for which additional pediatric information may produce health

59. *Id.*

60. Pub. L. No. 105-115, 111 Stat. 2296 (1997).

61. See 21 U.S.C.S. § 355a (LEXIS 1997 & Supp. 2002) (FDCA § 505A). As noted below, the provisions have been amended somewhat, and renumbered, by the Best Pharmaceuticals for Children Act (BPCA). For reference, citations are provided to both the original and renumbered provisions of the FDCA, and an explanation of significant amendments to the provisions is noted.

62. See *id.* at §§ 355a(b) & (c) (FDCA § 505A(b) & (c)), formerly 21 U.S.C. §§ 355a(a) & (c) (FDCA §§ 505A(a) & (c)). Orphan drug exclusivity is also extended by six months, which prevents approval of both generic and branded versions of drugs that enjoy orphan drug exclusivity under 21 U.S.C. § 360cc(a) (FDCA § 527(a)). The generic copies of innovator drugs may be approved based on the safety and effectiveness data submitted for the innovator drug. See *id.* §§ 355(b)(2) & (j) (FDCA §§ 505(b)(2) and (j)). However, generic approvals are subject to the patent and other exclusivity rights that apply to the innovator drug that the generic is copying. *Id.*; see also *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998) (explaining the generic drug approval process).

benefits in the pediatric population.”⁶³ Marketed drugs had to be on this list to receive a written request for pediatric studies.

B. Written Request

Next, FDA makes a “written request” for pediatric studies to the holder of an approved NDA for a drug included on the pediatric list.⁶⁴ The written request must include a timeframe for completing the studies.⁶⁵ “Pediatric studies” are defined under the law as “at least one clinical investigation (that, at the Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups in which a drug is anticipated to be used.”⁶⁶ Qualifying studies can therefore range from smaller pharmacokinetic studies to broader studies evaluating safety or effectiveness.

C. NDA Holder Agrees to the Request

The pediatric exclusivity provisions are intended to be voluntary. Accordingly, drug sponsors remain free to respond to a written request or not to respond.⁶⁷

D. Agreement on Study Design (Protocols)

Studies may be conducted in response to a written request pursuant to an agreement with FDA on study protocols or, in the absence of such an agreement, “in accordance with commonly accepted scientific principles and protocols.”⁶⁸

E. Completion of Requested Studies

Once studies are completed, study reports must be submitted in accordance with either the agreement reached with FDA on study protocols or commonly accepted scientific principles and protocols.⁶⁹

63. See U.S.C. § 355a(b) (FDCA § 505A(b)) (repealed).

64. See 21 U.S.C.S. § 355a(c) (FDCA § 505A(c)).

65. *Id.*

66. See *id.* § 355a(a) (FDCA § 505A(a)), formerly 21 U.S.C. § 355a(g) (FDCA § 505A(g)). “Pharmacokinetic studies” are studies that assess “the activity or fate of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.” DORLAND’S ILLUSTRATED MEDICAL DICTIONARY 1272 (28th ed. 1994). This definition was revised slightly by the BCPA to make clear that “pediatric studies” could include neonate studies. See 21 U.S.C.S. §§ 355a(a) (FDCA § 505A(a)); 115 Stat. at § 4 and see *infra* note text accompanying note 211.

67. See 21 U.S.C.S. § 355a(c) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(c)).

68. See *id.* § 355a(d) (FDCA § 505A(d)).

69. See *id.* § 355a(c) (FDCA § 505A(c)).

F. FDA Acceptance of Studies

Within 60 days of receipt of study, reports conducted pursuant to a written agreement on protocols (or within 90 days of receipt of reports conducted without an agreement on protocols), FDA must determine whether the reports “fairly respond” to FDA’s written request and otherwise comply with FDA’s requirements for earning extended exclusivity.⁷⁰ FDA must publish a notice of any exclusivity award made under these provisions.⁷¹

As discussed further below, these provisions remain in place today, except that the pediatric list requirement for marketed drugs has been eliminated.⁷² New drugs that have not yet been approved for marketing by FDA follow the same basic procedures, except that written requests for pediatric studies are issued during FDA’s review of the NDA for the drug, and there was never a requirement that drug not be identified on the pediatric list before receiving a request.⁷³

These new pediatric exclusivity provisions of FDAMA greatly enhance the incentives for drug sponsors to conduct pediatric studies. Even where the patient population for the pediatric indication is small, the potential for earning pediatric exclusivity fundamentally alters the cost-benefit calculus. The key to the new incentives is that they leverage the potential of the adult drug market to ensure that pediatric studies are conducted. Under the statute, the additional exclusivity period, once earned, applies to the drug as a whole and not just to whatever pediatric indication or formulation might result from the requested study or studies. That is, if a company conducts pediatric studies at FDA’s request on Drug X, and earns pediatric exclusivity, Drug X will enjoy six additional months of sales free from generic competition.

Merely providing exclusivity for the pediatric indication or formulation would not be a substantial incentive for manufacturers. The market for the pediatric indication or formulation might simply be too small to justify conducting the studies. In addition, follow-on producers could circumvent exclusivity that only covered new pediatric indications by nominally selling their product for other indications while knowing that physicians could prescribe the product, and

70. See *id.* § 355a(d) (FDCA § 505A(d)). The “fairly responds” standard was confirmed in *Merck & Co. Inc. v. FDA*, 148 F.Supp.2d 27 (D.D.C. 2001). In that case, FDA denied pediatric exclusivity for Merck’s drug Mevacor (lovastatin). *Id.* at 30. The court vacated the FDA’s determination, holding, in relevant part, that “a denial of pediatric exclusivity for failure to meet a single term of a written request would not be in accordance with [21 U.S.C. § 355a(d)(3)], which plainly does not require compliance with every single provision of a written request, but requires only that a pediatric study ‘fairly respond’ to a written request.” *Id.*

71. See 21 U.S.C.S. § 355a(f) (FDCA § 505A(f)).

72. See *infra* text accompanying notes 207-210.

73. 21 U.S.C.S. § 355a(b) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(b)), formerly 21 U.S.C. §§ 355a(a) (FDCA §§ 505A(a)).

pharmacists dispense it, for the pediatric indication.⁷⁴ The FDAMA pediatric exclusivity provisions are based on the premise that meaningful incentives can only be provided if completing a pediatric study or studies as required for a particular drug causes exclusivity to be extended for the drug as a whole.

Moreover, nothing in the law requires that the study or studies be successful in demonstrating safety and effectiveness in a pediatric population to trigger the additional six months of exclusivity. As long as the study or studies are properly carried out and submitted to the FDA, the drug qualifies for exclusivity, even if the results do not support approval of a pediatric formulation or new labeling. Of course, both positive and negative data add value. For example, even if study results are negative, they may suggest labeling that would caution against pediatric use. The important point, however, is that the benefit of the additional six months of exclusivity is earned once the pediatric study or studies are undertaken and reported. This creates a more robust incentive, because it eliminates the risk that would arise were the exclusivity contingent on a particular study outcome.

The value of the incentive for a particular drug ultimately depends on the drug's sales. Six months of additional exclusivity have greater financial impact for a blockbuster drug than a niche drug. Nonetheless, Congress' hope was that the incentive as a whole would raise the stature of pediatric research within the industry. As the congressional sponsors of the law explained:

The pediatric provisions of the FDAMA provide incentives for the pharmaceutical industry to spend the resources necessary to develop the infrastructure to conduct good clinical trials in children. If implemented properly this incentive will create a 'Golden Age for Pediatric Medicine.'⁷⁵

Congressional hopes notwithstanding, the realization of this lofty goal of a "Golden Age for Pediatric Medicine" would depend in large part on FDA's implementation of the new provisions. The statute, although detailed, provided substantial flexibility to the agency. FDA still had to determine what drugs and diseases should be studied, and how the necessary studies should be carried out. Moreover, the clock was ticking. Congress required that FDA report to Congress by January 1, 2001 on the effectiveness and performance of the FDAMA pediatric incentive provisions.⁷⁶ Barring reauthorization, the FDAMA pediatric study provisions would have sunset on January 1, 2002.⁷⁷

74. See *id.* § 355(j)(2)(A)(viii) (FDCA § 505(j)(2)(A)(viii)) (generic applicants may seek approval for certain uses while omitting others); see also 21 C.F.R. § 314.94(a)(12)(iii)(2002).

75. Letter from Congressman Mike Bilirakis, Congressman Jim Greenwood, Senator Mike DeWine, and Senator Christopher Dodd to Donna Shalala, Secretary of Health and Human Services 2 (Apr. 6, 1998) (on file with the Journal of Health Care Law & Policy).

76. 21 U.S.C. § 355a(k) (FDCA § 505A(k)) (1997) [superseded by a new report requirement at 21 U.S.C.S. § 355a(m) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(m))].

77. See *id.* § 355a(j) (FDCA § 505A(j)) (1997) [superseded by a new sunset date at 21 U.S.C.S. § 355a(n) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(n))].

VI. FDA IMPLEMENTATION

FDA's implementation of the new provisions has largely come in the form of agency guidance documents, and not through regulations. Guidance documents state current agency interpretation of statutory requirements and reflect agency policy, but FDA does not view them as legally binding.⁷⁸

FDA's first implementation action came on March 16, 1998, when FDA published for comment a "Draft List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" (the Draft Pediatric List).⁷⁹ In order to develop the Draft Pediatric List, FDA solicited input from the American Academy of Pediatrics, PhRMA, generic industry trade associations, the National Institutes of Health, the Pediatric Pharmacology Research Units Network, and the United States Pharmacopeia.⁸⁰ The Draft Pediatric List identified drugs by therapeutic class (*e.g.*, cardio-renal, oncology, anti-infective, etc.) and indicated the pediatric age groups for which additional information is needed [neonate (birth to 1 month), infant (1 month to 2 years), child (2 to 12 years), adolescent (12 to 16 years)].⁸¹

On May 20, 1998, after reviewing comments on the Draft Pediatric List, FDA published a final "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" (the Pediatric List).⁸² The Pediatric List expanded the Draft Pediatric List to include *all* drugs approved in adults for a disease or condition that occurs in pediatric patients.⁸³ This effectively rendered the statutory requirement that a marketed drug appear on the list before receiving a written request a formality, because all approved drugs with pediatric uses were deemed to be "on the list."

The Draft Pediatric List, in turn, became the basis of a priority list of drugs for which FDA determined that additional pediatric information is needed.⁸⁴ That priority list is organized by therapeutic class and notes particular age groups for which additional information is needed.⁸⁵ FDA put drugs on the priority list that

78. 21 C.F.R. § 10.115 (2002).

79. See Draft List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population; Availability, 63 Fed. Reg. 12,815 (Mar. 16, 1998) (announcing availability of the Draft Pediatric List).

80. See FDA Docket No. 98N-0056, Draft List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population 1 (Mar. 9, 1998) (current version available at <http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>) (last visited Sept. 14, 2002).

81. *Id.* at 4-20.

82. See FDA Docket No. 98N-0056, List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population 1 (May 20, 1998) (current version available at <http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>) (last visited Dec. 19, 2002); Availability, 63 Fed. Reg. 27,733 (May 20, 1998) (announcing availability of the Pediatric List) [hereinafter Pediatric List].

83. Pediatric List at 1.

84. *Id.* at 4-25.

85. See *id.*

are approved in adults for an indication that occurs in children, and that FDA also determined meet one or more of the following criteria:

The drug, if approved for pediatric use, would be a “significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of a disease in the relevant pediatric population;”

The drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year;

The drug is in a class or for an indication for which additional therapeutic or diagnostic options for the pediatric population are needed.⁸⁶

After finalizing the Pediatric List, on July 7, 1998, FDA issued a guidance document entitled “Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act” (the Section 505A Guidance).⁸⁷ This guidance document was revised in September 1999, and sets forth FDA’s primary interpretation of the FDAMA pediatric incentive provisions, as well as its procedures for administering the new statutory scheme.⁸⁸ The Section 505A Guidance makes clear that FDA views its statutory mandate as seeking all studies that could potentially result in beneficial pediatric information. FDA stated that it would issue written requests seeking “all necessary pediatric information for an active moiety.”⁸⁹ FDA’s intent to seek broad-ranging pediatric studies is also reflected in the series of sample written requests that FDA has issued for different therapeutic categories.⁹⁰

In keeping with the agency’s intent to require that companies perform extensive pediatric trials in order to qualify for pediatric exclusivity, the agency has construed the pediatric exclusivity benefit in an expansive manner. Under the Section 505A Guidance, if a sponsor conducts pediatric trials and earns pediatric exclusivity, the exclusivity will apply to all of the sponsor’s drug products that

86. *Id.* at 2.

87. See Guidance for Industry on Qualifying for Pediatric Exclusivity; Availability; Request for Submissions, 63 Fed. Reg. 36,707 (July 7, 1998) (announcing availability of the Section 505A Guidance).

88. See Guidance for Industry on Qualifying for Pediatric Exclusivity; Availability; Request for Submissions, 64 Fed. Reg. 54,903 (Oct. 8, 1999) (announcing availability of revised Section 505A Guidance); FDA Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (Sept. 1999), *available at* <http://www.fda.gov/cder/guidance2891fnl.pdf> (last visited Dec. 19, 2002) [hereinafter Section 505A Guidance]. Additional procedures are set forth in a document published by FDA’s Center for Drug Evaluation and Research on October 6, 1998 to guide FDA staff. See Manual of Policies and Procedures (“MAPP”) § 6020.6 (Oct. 6, 1998) (“Process for Handling Pediatric Exclusivity”), *available at* <http://www.fda.gov/cder/mapp.htm> (last visited Dec. 16, 2002).

89. Section 505A Guidance at 5.

90. CTR. FOR DRUG EVALUATION RES., PEDIATRIC MED., U.S. FDA, FDA MODERNIZATION ACT, SAMPLE WRITTEN REQUESTS, *available at* <http://www.fda.gov/cder/pediatric> (last visited Sept. 14, 2002).

contain the active moiety studied.⁹¹ That means that if a sponsor conducts a study on a particular drug formulation, the exclusivity earned could apply to other formulations, provided that they contain the active moiety that was part of the study.

Two other aspects of the Section 505A Guidance are worth special mention. First, FDA stated that a sponsor can use studies conducted by third parties and previously existing data to respond to a written request and earn pediatric exclusivity.⁹² Existing data may not be used if “the data are already known to provide no useful information,” or if the data have already been submitted to FDA as part of an application for a new drug approval.⁹³ This policy ensures that there is an incentive for drug sponsors not only to conduct new studies, but also to collect and analyze existing data from all available sources to determine whether the data could support expanded pediatric use of a drug.

Second, FDA stated that pediatric studies once completed must be reported to FDA in the form of an NDA or an NDA supplement (e.g., a supplement for new labeling).⁹⁴ FDA confirmed that the statute does not require that an NDA or supplement be *approved* in order to earn pediatric exclusivity, since the exclusivity is based solely on the completion and submission of the studies.⁹⁵ Nonetheless, by requiring that sponsors submit study reports in the form of an NDA or supplement, FDA further ensured that the studies would ultimately yield FDA-approved pediatric information, either in the form of new pediatric formulations or new pediatric labeling.

FDA’s various implementation measures filled the gaps that were not addressed in the legislation itself. Consistent with Congress’ stated intent, FDA’s policies reflect a broad interpretation of the statutory provisions and are designed to produce the maximum amount of pediatric information. However, not all interested parties appreciated the FDA’s approach, including, most notably, generic drug manufacturers. Generic drug makers stood to lose the most from these provisions because their products faced delayed approvals due to grants of pediatric exclusivity, and they responded by challenging FDA’s actions in court.

91. Section 505A Guidance at 13. FDA defines “active moiety” as the “molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative . . . of the molecule, responsible for the physiological or pharmacological action of the drug substance.” 21 C.F.R. § 314.108(a) (2002). For a given active moiety, there may be several different particular product formulations (e.g., different dosage forms or dosage strengths). *Id.*

92. Section 505A Guidance at 4.

93. *Id.* (“Therefore, FDA will not generally accept studies conducted prior to issuance of a Written Request unless the studies would potentially support a change in the labeling to incorporate pediatric information.”).

94. *Id.* at 11.

95. *Id.*

A. National Pharmaceutical Alliance v. Henney

On February 19, 1999, just as FDA's implementation of the statute was beginning to take effect, two generic drug trade associations—the National Pharmaceutical Alliance (NPA) and the Generic Pharmaceutical Industry Association (GPIA)—jointly filed suit against FDA in the United States District Court for the District of Columbia to challenge FDA's implementation of the pediatric incentive provisions of FDAMA.⁹⁶ NPA and GPIA charged that FDA implemented Section 111 of FDAMA in a manner that violates the procedural requirements of the Administrative Procedures Act (APA)⁹⁷ and the substantive provisions of FDAMA itself.

Among other things, NPA and GPIA alleged that FDA's publication of the Pediatric List failed to comply with FDAMA's requirements regarding 1) consultation with pediatric experts, 2) assessment of whether a drug might produce health benefits, and 3) prioritization of the list.⁹⁸ They also took aim at the Section 505A Guidance, arguing that it was a "substantive rule" that could only be issued with notice and comment rulemaking, and that it conflicted with FDAMA's standards regarding the scope of an extended exclusivity award and the types of studies that can qualify for exclusivity.⁹⁹ Based on these allegations, NPA and GPIA requested that the Court declare the Pediatric List, Section 505A Guidance, existing written requests, and existing pediatric exclusivity awards invalid, and require FDA to rescind each for conflict with FDAMA. They also asked that FDA be required to suspend all future actions related to Section 111 of FDAMA until FDA promulgated final regulations pursuant to notice and comment rulemaking and reissued a proper pediatric list.

On April 20, 1999, the court rejected these claims across the board in the context of plaintiffs' motion for a preliminary injunction, and the case did not proceed any further.¹⁰⁰ The court held in particular that FDA's moiety-based interpretation of the scope of pediatric exclusivity grants was not at odds with the statute, and was entitled to deference.¹⁰¹ The court further held that FDA was free to implement the statute on the basis of guidance documents, without issuing regulations through formal notice and comment rulemaking.¹⁰² This holding cleared the way for FDA to proceed in accordance with the policies and procedures it had originally set out, and the agency has done precisely that.

96. *Nat'l Pharmaceutical Alliance v. Henney*, 47 F.Supp.2d 37 (D.D.C. 1999).

97. 5 U.S.C. § 553 (2001).

98. *Nat'l Pharmaceutical Alliance*, 47 F.Supp.2d at 39.

99. *Id.*

100. *Id.*

101. *Id.* at 40.

102. *Id.* at 40-41.

B. The Current Pediatric Initiative Part 2: The Stick of the Pediatric Rule

A little over a year after Congress enacted FDAMA, FDA finalized the Pediatric Rule it had proposed earlier.¹⁰³ The rule took effect on April 1, 1999, and required drug sponsors to submit specified pediatric study data by December 2000, unless the sponsor obtained a waiver or deferral.¹⁰⁴ These requirements were new and unprecedented in that they compelled drug sponsors to perform research neither proposed by the sponsor nor related to a use for which the sponsor was seeking approval. The requirements were recently invalidated by a federal district court, and FDA was enjoined from enforcing the rule.¹⁰⁵ At the same time, bills have been introduced in Congress to “codify” the Pediatric Rule, or otherwise grant FDA the authority to require pediatric studies. In light of all of these recent developments, the precise status of the Pediatric Rule was in doubt at the time of the writing of this article.

VII. THE REQUIREMENTS

A. New Products Not Yet Approved

Under the rule, all drug and biologics applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration had to contain data adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and support dosing and administration in all pediatric subpopulations for which the product is safe and effective, unless FDA granted a waiver or a deferral.¹⁰⁶ These requirements only applied to indications that were being sought for adults. Data on safety and effectiveness in pediatric patients were not required for unapproved or unclaimed indications, even for a product widely used in pediatric patients for those indications.¹⁰⁷ In addition, drugs for an indication or indications with orphan designation under the Orphan Drug Act were exempt from the rule.¹⁰⁸

FDA specified what particular pediatric data must be required for a product on a case-by-case basis. Where the course of the disease and the effects of the product are sufficiently similar in adults and pediatric patients, FDA may have permitted the required data on pediatric safety and effectiveness to be supported by

103. 63 Fed. Reg. 66,632 (Dec. 2, 1998).

104. *Id.*

105. *Ass’n of Am. Physicians and Surgeons, Inc., et al. v. U.S. FDA, et al.*, No. CIVA.00-02898, 2002 WL 31323411, *15 (D.D.C. Oct. 17, 2002).

106. 21 C.F.R. §§ 314.55(a), 601.27(a) (2002).

107. 63 Fed. Reg. at 66,634.

108. 21 C.F.R. §§ 314.55(d), 601.27(d) (2002). Orphan drug exclusivity is granted as a special incentive to drugs that treat diseases or conditions with small patient populations. See 21 U.S.C. § 360cc(a) (FDCA § 527(a)).

effectiveness data in adults and additional information such as dosing, pharmacokinetic and safety data in pediatric patients.¹⁰⁹ If data from one age group could be extrapolated to another, studies may not have been needed in each pediatric age group.¹¹⁰

Pediatric studies were required for each age group in which the product would provide a “meaningful therapeutic benefit” or would be used in a “substantial number of pediatric patients” for the indications claimed by the manufacturer.¹¹¹ (The definitions of “meaningful therapeutic benefit” and “substantial number of pediatric patients” are discussed in the waiver section below). FDA defined “relevant age groups” flexibly and did not adhere to fixed categories.¹¹² For products that offer a meaningful therapeutic benefit, manufacturers were required to develop pediatric formulations (if needed) for those age groups in which studies were required, unless they could demonstrate that reasonable attempts to develop a pediatric formulation had failed.¹¹³

B. Already Marketed Products

While the rule created a default presumption that all new applications would include pediatric data, FDA stated that it would only require pediatric studies for already marketed products in “compelling circumstances.”¹¹⁴ When FDA promulgated the Pediatric Rule, it estimated that it would require studies in approximately two marketed drugs per year.¹¹⁵ In fact, it had never exercised this authority.

Nevertheless, under the rule, FDA could require pediatric studies for a product that is already marketed if: (1) the absence of adequate labeling could pose significant risks to patients, and (2) the product is used in a substantial number of pediatric patients, or provides a meaningful therapeutic benefit over existing treatments for pediatric patients.¹¹⁶ As with new products, the applicant may have been required to submit evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents.¹¹⁷ For products that represent a meaningful therapeutic benefit over existing therapies, the applicant also may have been required to develop a pediatric

109. 21 C.F.R. §§ 314.55(a), 601.27(a) (2002).

110. *Id.*

111. *Id.*

112. 63 Fed. Reg. at 66,634.

113. 21 C.F.R. §§ 314.55(a), (c)(3)(iv); §§ 601.27(a), (c)(3)(iv) (2002).

114. 63 Fed. Reg. at 66,634 (“FDA intends to reserve its authority to require studies of marketed drugs and biologics to situations in which the compelling circumstances described in the regulation are present.”).

115. *Id.* at 66,654.

116. 21 C.F.R. § 201.23(a) (2002).

117. *Id.*

formulation, unless reasonable attempts to produce a pediatric formulation have failed.¹¹⁸

These requirements applied to generic manufacturers as well. Where FDA required pediatric studies on a multi-source marketed drug, each manufacturer of that drug, including the generic, would have been required to satisfy the study requirement.¹¹⁹ FDA would have encouraged all manufacturers to fund an appropriate study jointly.¹²⁰

C. Deferrals

For new products seeking approval, FDA may have, on its own initiative or at the request of an applicant, permitted the submission of some or all of the required pediatric information to be deferred until after a product's approval.¹²¹ For example, deferral may have been granted if the product was ready for approval in adults before studies in pediatric patients were complete, or if pediatric studies should have been delayed for ethical or other reasons until additional safety and effectiveness data have been collected. Deferral requests had to be accompanied by a description of the planned or ongoing studies and evidence that the studies were being or would be conducted with due diligence.¹²² FDA could have approved the product for use in adults subject to the requirement that the applicant submit the required pediatric assessments within a specified time.¹²³

FDA stated that it would be less amenable to delays in obtaining pediatric data for products aimed at life-threatening diseases for which adequate therapy does not exist. FDA envisioned studies for such products beginning as soon as preliminary safety data in adults were available.¹²⁴ For less critical products, FDA envisioned studies beginning when additional safety and/or effectiveness data were available from initial well-controlled trials in adults.¹²⁵ FDA did not believe that early study or use in pediatric patients was appropriate for "me too" products in a product class that already contains an adequate number of approved products with pediatric labeling.¹²⁶ FDA may have required that the pediatric use section of the approved labeling of a "me too" product contain a statement recommending preferential use of other drugs that are adequately labeled for pediatric use.¹²⁷

118. 21 C.F.R. §§ 201.23(a), (c)(2)(iv) (2002).

119. 63 Fed. Reg. at 66,654.

120. *Id.*

121. 21 C.F.R. §§ 314.55(b), 601.27(b) (2002).

122. *Id.*

123. 63 Fed. Reg. at 66,642.

124. *Id.* at 66,643.

125. *Id.*

126. *Id.*

127. *Id.*

D. Waivers

In order to obtain a waiver of the study requirement for some or all pediatric age groups, the sponsor of a new product application had to demonstrate that 1) the product did not represent a meaningful therapeutic benefit for pediatric patients over existing treatments, *and* 2) the product was not likely to be used in a substantial number of pediatric patients.¹²⁸ The study requirement would apply if the product offered a meaningful therapeutic benefit, even if it was not used in a substantial number of pediatric patients. The study requirement also would apply if the product was used in a substantial number of pediatric patients, even if the product did not offer a meaningful therapeutic benefit. The holder of a marketed product application seeking a waiver had to satisfy the above criteria *and* show that the absence of adequate labeling could not pose significant risks to pediatric patients. FDA ordinarily would not consider the cost of conducting studies as a factor in determining whether to grant a waiver.¹²⁹

FDA's definition of "meaningful therapeutic benefit" was based on the definition of a "priority" drug used by FDA's Center for Drug Evaluation and Research.¹³⁰ FDA considered a product to have a meaningful therapeutic benefit if it would be a significant improvement in the treatment, diagnosis, or prevention of a disease compared to marketed products that were approved and adequately labeled for that use in the relevant pediatric population.¹³¹ If there were no existing products, the new product would usually be considered to have a meaningful therapeutic benefit. Improvement over existing products would be demonstrated by 1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, 2) elimination or substantial reduction of a treatment-limiting drug reaction, 3) documented enhancement of patient compliance, or 4) evidence of safety and effectiveness in a new subpopulation.¹³² A product would also be considered to provide a meaningful therapeutic benefit if it was in a class of products or for an indication for which there were few products labeled for pediatric use and more therapeutic options were needed, even if the product did not meet FDA's criteria for priority drugs.¹³³

FDA considered a product to be used in a "a substantial number of pediatric patients" if there were 50,000 patients with the disease or condition for which the product was indicated, as determined by physician mentions per year in the IMS National Disease and Therapeutic Index.¹³⁴ A partial waiver would be available

128. 21 C.F.R. §§ 314.55(c)(2)(i), 601.27(c)(2)(i) (2002).

129. 63 Fed. Reg. at 66,647.

130. *Id.* at 66,646.

131. *Id.*

132. *Id.*

133. *Id.*

134. *Id.* at 66,646-47.

for a particular pediatric age group if up to 15,000 patients in that age group were affected by the disease or condition.¹³⁵

FDA would also waive the pediatric study requirement for new and marketed products where: 1) the required studies were impossible or highly impractical (for example, because the population was too small or geographically dispersed), 2) the product was likely to be unsafe or ineffective in pediatric patients, or 3) reasonable efforts to develop a pediatric formulation (if one is needed) failed.¹³⁶

E. Pediatric Use Section of an Application

The final rule required that a new product application contain a pediatric use section. This section briefly summarized the pediatric studies conducted and referenced the full description of each study provided elsewhere in the application.¹³⁷

1. Planning Pediatric Studies

The new rule revised FDA's investigational new drug regulations to provide that all investigational new drug applications (INDs) should contain information on the sponsor's plans for assessing pediatric safety and effectiveness.¹³⁸ FDA would then meet with sponsors at various points in the drug investigation process to discuss plans for the pediatric studies.¹³⁹ FDA emphasized the need for earlier meetings for drugs intended to treat serious or life-threatening diseases or conditions.¹⁴⁰

2. Post-Marketing Reports

Sponsors of approved products were requested to include in their annual reports to FDA the following information: 1) a brief summary of whether labeling supplements for pediatric use had been submitted and whether new studies in the pediatric population to support labeling had been initiated, along with (if possible) an estimate of patient exposure to the product by dosage form with reference to pediatric populations (neonates, infants, children, and adolescents), 2) an analysis

135. *Id.* at 66,648. FDA identified the following particular diseases for which waivers would likely be granted because they rarely occur in pediatric patients, if at all:

Alzheimer's disease, age-related macular degeneration, prostate cancer, breast cancer, non-germ cell ovarian cancer, renal cell cancer, hairy cell leukemia, uterine cancer, lung cancer, squamous cell cancers of the oropharynx, pancreatic cancer, colorectal cancer, basal cell and squamous cell cancer, endometrial cancer, osteoarthritis, Parkinson's disease, amyotrophic lateral sclerosis, arteriosclerosis, infertility, symptoms of menopause. *Id.*

136. 21 C.F.R. §§ 314.55(c)(2)(ii), (3)(iv); §§ 601.27(c)(2)(ii), (3)(iv) (2002).

137. 21 C.F.R. § 314.50(d)(7) (2002).

138. *See id.* § 312.23(a)(1)(iii) (2002).

139. *See id.* §§ 312.47, 312.82 (2002).

140. *See id.* § 312.82 (2002).

of available pediatric safety and efficacy data and changes proposed to product labeling based on such data, and 3) a report on the status of any post-marketing pediatric studies that were required or agreed to, including whether the studies were initiated, ongoing (with projected completion date), completed (including completion date), or completed with results submitted to FDA (including date).¹⁴¹

3. *Pediatric Committee*

When it promulgated the Pediatric Rule, FDA announced its intention to convene a panel of pediatric experts to provide advice on a range of issues, including: 1) FDA's implementation of all aspects of the final rule, including its waiver and deferral decisions, 2) identification of marketed products that meet the criteria for requiring studies, 3) identification of diseases or conditions for which additional therapeutic options are needed, 4) consideration of ethical issues raised by clinical trials in pediatric patients, 5) the design of trials and analysis of data for specific products or classes of products, and 6) assessment of the progress of individual studies.¹⁴² The panel was in fact convened and met on these and other issues.

4. *Enforcement*

FDA's main mechanism for enforcing the requirements was the filing of an action in federal court asking the court to find that a product was misbranded or an unapproved new drug, or an unlicensed biologic, and issue an injunction requiring the submission of an assessment of pediatric safety and effectiveness for the product.¹⁴³ Violations of a court-ordered injunction could then result in contempt proceedings and civil or criminal penalties. FDA stated that it did not intend, except in rare circumstances, to disapprove or withdraw approval of a product whose manufacturer violated the requirements imposed under the new rule.¹⁴⁴

VIII. RELATIONSHIP OF THE PEDIATRIC RULE TO FDAMA

FDA's primary reason for finalizing the Pediatric Rule even though FDAMA had been enacted was to address perceived gaps in the statute. As FDA explained, the FDAMA pediatric exclusivity provisions do not apply to products for which no patent or other exclusivity protection is currently in existence that can receive a six-month extension.¹⁴⁵ Biologics and certain antibiotics also are not eligible to receive exclusivity under FDAMA.¹⁴⁶ In addition, the FDAMA provisions are

141. *See id.* §§ 314.81(b)(2), 601.70 (2002).

142. 63 Fed. Reg. at 66,656.

143. *Id.* at 66,655.

144. *Id.*

145. *Id.* at 66,633.

146. *Id.*

voluntary, and FDA was thus concerned that sponsors simply might elect not to respond to a written request even with the potential for earning pediatric exclusivity, or that studies would be pursued but ultimately insufficient to produce needed pediatric labeling.¹⁴⁷

The Pediatric Rule ensured that FDA had a mechanism to obtain pediatric assessments where the FDAMA exclusivity incentive either did not apply or was ineffective. For marketed drugs, FDA made clear that it would provide manufacturers an opportunity to submit studies voluntarily under FDAMA before determining whether it would require any pediatric studies.¹⁴⁸ The Pediatric Rule presumptively applied to all new applications, but any drug studies that were required (whether for new or marketed drugs) were also eligible for extended exclusivity under FDAMA.¹⁴⁹ In this way, the Pediatric Rule reinforced FDAMA to ensure that studies would be undertaken.

In one key respect the Pediatric Rule was actually more limited than FDAMA. FDA was clear that the Pediatric Rule only required pediatric assessments related to adult indications for which the drug sponsor had received or was seeking approval.¹⁵⁰ FDAMA has no such limitation, and written requests can be issued for studies on new or previously unclaimed indications.

A. Ass'n of American Physicians and Surgeons v. FDA

Just as FDA's implementation of the FDAMA exclusivity provisions came under legal attack, so too the Pediatric Rule was challenged in the courts. When FDA issued the rule, it asserted that it possesses the legal authority to require pediatric studies under the following general provisions of the Federal Food, Drug and Cosmetic Act (FDCA) and Public Health Service Act (PHSA):

- Requirement of adequate directions for use and prohibition of false or misleading labeling (including labeling that fails to reveal material facts related to customary or usual use);¹⁵¹
- Authorization to bring enforcement action against a drug not recognized as safe and effective or approved for the conditions prescribed, recommended, or suggested in the labeling;¹⁵²
- Prohibition on misbranding or introducing an unapproved new drug into interstate commerce, and authorization for seizing misbranded or unapproved drugs;¹⁵³

147. *Id.*

148. *Id.* at 66,634.

149. 21 U.S.C.S. § 355a(h) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(h)), formerly 21 U.S.C. § 355a(i) (FDCA § 505A(i)); see also 63 Fed. Reg. at 66,633.

150. 63 Fed. Reg. at 66,634.

151. See 21 U.S.C. §§ 321(n), 352(a), 352(f), 355(d)(7) (FDCA §§ 201(n), 502(a), 502(f), 505(d)(7)); see also 21 C.F.R. § 201.5 (2002).

152. 21 U.S.C. §§ 321(p), 331(a), 331(d), 355(a) (FDCA §§ 201(p), 301(a), 301(d), 505(a)).

- Prohibition on drugs that are dangerous to health when used in the manner suggested in their labeling;¹⁵⁴
- Authorization to impose conditions on the investigation of new drugs, including conditions related to the ethics of an investigation and to require post-marketing reports;¹⁵⁵
- Authorization to issue regulations for the efficient enforcement of the FDCA;¹⁵⁶ and
- Requirement that biological products be safe, pure, and potent.¹⁵⁷

FDA also cited a provision in FDAMA, which states that pediatric studies required by FDA will qualify for extended exclusivity as confirmation of its authority to compel pediatric studies.¹⁵⁸

Notwithstanding the long list of provisions cited by FDA, serious questions exist about FDA's authority to require a study that is not related to an indication or claim sought by the product sponsor. The cited provisions do not give FDA any express power to mandate that studies be performed for indications for which a sponsor has not sought approval. Moreover, FDA had never previously interpreted these provisions in the expansive manner that it was now suggesting, or asserted the open-ended authority that it now claimed to possess. Indeed, in a famous quote, former FDA Commissioner David Kessler stated:

Despite the ardent desire of the FDA to increase pediatric indications, I need to acknowledge the limits of FDA's authority. It is our job to review drug applications for indications suggested by the manufacturer. We do not have the authority to require manufacturers to seek approval for indications which they have not studied Thus, as a matter of law, if an application contains indications only for adults, we're stuck.¹⁵⁹

B. Commissioner Kessler's remarks obviously do not reflect the FDA's current position, as stated in the Pediatric Rule

The question of whether or not FDA has the legal authority to mandate pediatric studies was ultimately presented in the courts. On December 4, 2000, a

153. See *id.* §§ 321(g), 331(a), 331(d), 331(k), 332, 334 (FDCA §§ 201(g), 301(a), 301(d), 301(k), 302, 304).

154. See *id.* § 352(j) (FDCA § 502(j)).

155. See *id.* § 355(i), 355(k) (FDCA § 505(i), 505(k)).

156. See *id.* § 371(a) (FDCA § 701(a)).

157. See Public Health Service Act, Pub. L. ch. 373 § 351(d), § 351, 58 Stat. 702-03 (1944); (codified as amended 42 U.S.C. § 262 (2000)) [hereinafter PHSA].

158. 21 U.S.C.S. § 355a(h) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(h)), formerly 21 U.S.C. § 355a(i) (FDCA § 505A(i)); see also 63 Fed. Reg. 66,633.

159. Remarks by David A. Kessler, at the Annual Meeting of the American Academy of Pediatrics 1, 4 (Oct. 14, 1992) (on file with the Journal of Health Care Law & Policy).

group of not-for-profit organizations filed suit in the United States District Court for the District of Columbia seeking repeal of the Pediatric Rule on the grounds that it exceeds FDA's statutory authority and is otherwise unlawful.¹⁶⁰ The case is *Ass'n of American Physicians and Surgeons v. FDA*, and on October 17, 2002, the district held that FDA exceeded its statutory authority in promulgating the Pediatric Rule, and enjoined FDA from enforcing the Rule.¹⁶¹ The court then proceeded to analyze the text of the FDCA, prior FDA application of the statute, and related statutory provisions, including in particular the pediatric exclusivity provisions from FDAMA and the BPCA.

As to the text of the FDCA, the court concluded that if Congress had intended to grant FDA authority to require drug manufacturers to study their products for unclaimed uses that it "would likely have spoken more clearly."¹⁶² The labeling provisions of the FDCA require that a product's labeling provide directions related to the product's conditions of use, including those that are "customary or usual" and those that are "prescribed, recommended, or suggested" in the product's labeling.¹⁶³ The court held that these provisions regarding labeling do not support FDA's requirement that a drug manufacturer conduct new studies and develop new formulations to support pediatric uses that the manufacturer is not seeking for the product, and may in fact be specifically disclaiming on the label.¹⁶⁴ The court also found that other provisions of the FDCA are in tension with the Pediatric Rule.¹⁶⁵

Next, the court held that the Pediatric Rule contradicts prior FDA tradition, because the agency "has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses."¹⁶⁶ According to the court, if FDA's argument were accepted, "the door would be open to FDA's regulation of all off-label uses, based solely on the manufacturer's knowledge that those uses are common-place."¹⁶⁷ Such an open-ended grant of authority would contravene Congress' intent, the court said, and "would eviscerate the long-established foundation of federal food and drug law, which allows, not the FDA, but the 'manufacturer of the article, through his representations in connection with its sale, [to] determine the use to which the article is to be put.'"¹⁶⁸

160. *Ass'n of Am. Physicians & Surgeons, Inc., et al. v. FDA, et al.*, No. 00-CV-2898 (D.D.C. Dec. 4, 2000).

161. *See Ass'n of Am. Physicians & Surgeons, Inc., et al., v. U.S. FDA, et al.*, No. CIVA.00-02898, 2002 WL 31323411, *7 (D.D.C. Oct. 17, 2002).

162. *Id.* at *8.

163. *Id.* at *7-*9.

164. *Id.* at *8-*11.

165. *Id.* at *11.

166. *Id.*

167. *Id.*

168. *Id.* (quoting S. Rep. No. 73-493, at 3 (1934)).

Finally, the Court concluded that the Pediatric Rule conflicts with the pediatric incentive provisions of FDAMA and the BPCA.¹⁶⁹ The court noted that Congress neither expressly rejected nor endorsed the Pediatric Rule, and found the available legislative history to be contradictory.¹⁷⁰ However, the court concluded that the statutory pediatric exclusivity provisions and the study requirements of the Pediatric Rule are fundamentally incompatible.¹⁷¹ In the court's words, "Congress adopted an incentive scheme while the FDA adopted a command and control approach."¹⁷² FDA had until December 16, 2002 to appeal the court's decision.¹⁷³ In the interim, FDA was subject to the court's injunction prohibiting enforcement of the Pediatric Rule.¹⁷⁴

IX. RECENT DEVELOPMENTS

While the *Ass'n of American Physicians and Surgeons* case was progressing, a bill was introduced in the Congress that would "codify" the Pediatric Rule and provide FDA the express statutory authority to require pediatric trials. Senator Clinton introduced the bill on August 1, 2002, and it has been reported out of the Senate Committee on Health, Education, Labor, and Pensions.¹⁷⁵ Nothing in the *Ass'n of American Physicians and Surgeons* decision on its face, would bar Congress from enacting such a bill.

Senator Clinton introduced the bill after FDA announced in a March 18, 2002 filing in the *Ass'n of American Physicians and Surgeons* case that it intended to "stay" the rule for two years to provide an opportunity to assess how the provisions of the newly enacted BPCA and the Pediatric Rule relate to one another, and "whether, in light of the broader scope of the BPCA, the Pediatric Rule remains necessary."¹⁷⁶ FDA later reversed that position and reaffirmed the validity of the Pediatric Rule.¹⁷⁷ Whether FDA would have ultimately modified the Pediatric Rule in some respect following enactment of the BPCA is unclear, although FDA solicited public comments on how it should proceed.¹⁷⁸ As the next section discusses, the BPCA addresses many of the perceived gaps in the FDAMA exclusivity provisions, including most notably the coverage of off-patent drugs. It

169. *Id.* at *12.

170. *Id.* at *13.

171. *Id.* at *13-*14.

172. *Id.* at *13.

173. See Fed. R. App. P. 4(a)(1)(B).

174. *Ass'n of Am. Physicians & Surgeons*, 2002 WL at *15.

175. S. 2394, 107th Cong. § 505B (2002).

176. Defendants' Motion for Stay of Proceedings, *Ass'n of Am. Physicians & Surgeons*, No. 00-2898 (HHK) at 2.

177. Defendants' Notice of Clarification Regarding Defendants Motion for Stay of Proceedings, *Ass'n of Am. Physicians & Surgeons*, No. 00-2898 (HHK) at 1.

178. Obtaining Timely Pediatric Studies of and Adequate Pediatric Labeling for Human Drugs and Biologics, 67 Fed. Reg. 20,070 (Apr. 24, 2002).

could thus serve some of the same functions that the Pediatric Rule was intended to serve.

*A. The Current Pediatric Initiative Part 3:
The Best Pharmaceuticals for Children Act*

On January 4, 2002, President Bush signed into law the Best Pharmaceuticals for Children Act (BPCA),¹⁷⁹ reauthorizing the pediatric exclusivity provisions of FDAMA until October 1, 2007.¹⁸⁰ The pediatric exclusivity provisions of FDAMA were not without detractors. Some charged that drug sponsors were conducting relatively small pediatric studies in exchange for large windfalls in the form of six months of additional exclusivity, particularly on blockbuster drugs where six months of additional sales without generic competition translates into large dollar amounts.¹⁸¹ Others maintained that studies were not translating into new FDA-approved labeling, because drug sponsors received the additional exclusivity as soon as they submitted responsive studies to FDA, and thus did not have an incentive to make timely labeling changes based on the study results.¹⁸²

For its part, FDA reported to Congress that the FDAMA incentives were working. In the agency's words, "the industry's response has been vigorous and the public health benefits have been extensive."¹⁸³ FDA noted that it had issued 157 written requests for pediatric studies as of September 2000, and sponsors had conducted or planned to conduct 80 per cent or more of the studies FDA requested.¹⁸⁴ Some 58 studies had already been completed and reviewed at least in part by the agency.¹⁸⁵ These studies produced efficacy, safety, and dosing information for a wide range of different therapies, and the information was being captured in new FDA-approved labeling.¹⁸⁶ These public health benefits came at the cost of delayed generic drug approvals, but FDA estimated that the provisions added only one half of one per cent to national spending on pharmaceuticals.¹⁸⁷ Accordingly, FDA recommended that the FDAMA incentives be renewed with

179. Pub. L. No. 107-109, 115 Stat. 1408 (2002).

180. 21 U.S.C.S. § 355a(n) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(n)). In order to be eligible for six months of pediatric exclusivity, before October 1, 2007 there must be an application for the drug accepted for filing and a written request for pediatric studies issued. *Id.* Pediatric studies may then be conducted and submitted after October 1, 2007. *Id.*

181. See, e.g. Rachel Zimmerman, *Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids*, THE WALL ST. J., Feb. 5, 2001, at A1.

182. S. REP. NO. 107-79, at 8-9 (2001).

183. FDA Report to Congress, *supra* note 26, at 8.

184. *Id.*

185. *Id.*

186. *Id.* at 9-12.

187. *Id.* at 17.

minor modifications: “[The program’s] unprecedented success in generating needed pediatric studies should not be forfeited.”¹⁸⁸

Based perhaps on FDA’s strong endorsement, Congress left the basic features of the pediatric exclusivity provisions essentially intact when it enacted the BPCA. FDA must still issue a written request for pediatric studies, the drug sponsor must conduct the studies in a timely manner and in a way that “fairly responds” to the written request, the drug sponsor still earns six months of exclusivity on all existing patent and exclusivity periods for products containing the active moiety studied, etc. There were proposals in the Congress to amend these basic features of the exclusivity provisions—for example, to create a tiered system of exclusivity with six months of exclusivity for drugs with certain sales, and lesser periods of exclusivity for drugs with greater sales—but these proposals were rejected.¹⁸⁹

At the same time, Congress did address some of the criticisms of FDAMA. In particular, Congress created new programs administered through NIH to address off-patent drugs and other perceived gaps in the FDAMA exclusivity scheme. Congress also added new provisions to ensure that studies conducted under FDAMA would lead to timely labeling changes, even though exclusivity itself would continue to be awarded upon the submission of responsive studies. Following is a summary of these provisions from the BPCA.

B. NIH Funded Pediatric Studies

1. Off-Patent/Off-Exclusivity Drugs

The law creates a new section 409I of the Public Health Service Act, to establish a publicly funded program administered by NIH for awarding contracts to study off-patent/off-exclusivity drugs in pediatric patients.¹⁹⁰ Two hundred million dollars in public appropriations are authorized for contract awards.¹⁹¹ Contracts for these studies will be awarded to third parties (e.g., pediatric research centers), and drug sponsors are not eligible.¹⁹² Based on the third-party study results, FDA will negotiate appropriate labeling changes with the drug sponsors.¹⁹³ In addition, if a

188. *Id.* at 23.

189. The Senate passed the “Best Pharmaceuticals for Children” Act (S. 1789) by voice vote on December 12, 2001. The House of Representatives took up and passed S. 1789 by voice vote on December 18, 2001. Senate bill S. 1789 was the House-Senate conference agreement on the reauthorization legislation. The original Senate bill was S. 838 and passed by voice vote on October 18, 2001. The original House bill was H.R. 2887 and passed under suspension of the rules by a 338-86 vote on November 15, 2001. The primary legislative history for the law consists of Senate Report 107-79 and House Report 107-277.

190. 42 U.S.C.S. § 284m (Law Co-op 1994 & Supp. 2002) (PHSA § 409I).

191. *See id.* § 284m(d) (PHSA § 409I(d)).

192. *See id.* § 284m(b) (PHSA § 409I(b)).

193. *See id.* § 284m(c)(7)-(11) (PHSA § 409I(c)(7)-(11)).

pediatric study completed under a public contract indicates that a formulation change is necessary and FDA agrees, FDA must send a “nonbinding letter of recommendation” to all drug sponsors to that effect.¹⁹⁴ The mechanism for effectuating labeling changes based on publicly funded studies is described in the “dispute resolution” section below.

2. *On-Patent/On-Exclusivity Drugs*

Related provisions exist in the law to study drugs that still have remaining patent or exclusivity protections where the sponsor decides not to perform pediatric studies in response to a written request from FDA. The new law requires that a recipient of a written request under the FDAMA provisions for pediatric studies on an already marketed drug inform FDA within 180 days of receiving the written request whether the recipient will perform the requested studies, and, if so, when the studies will be initiated;¹⁹⁵ previously, no response to a written request was required. If the holder does not agree to do the studies (or fails to respond within 180 days), and FDA determines that there is a continuing need for pediatric information, FDA must refer the drug for study to the Foundation for the National Institutes of Health and give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied under the referral.¹⁹⁶

Under section 499 of the Public Health Service Act, as amended by this law, the Foundation for the National Institutes of Health is authorized to receive gifts, grants, and donations, and to use those funds for the issuance of research grants.¹⁹⁷ After receiving a referral from FDA for pediatric studies, the Foundation must issue a proposal for a grant to conduct the requested studies, unless the Foundation certifies that it does not have the necessary funds.¹⁹⁸ If the Foundation makes such a certification, the drug is referred for inclusion on the list of otherwise off-patent/off-exclusivity drugs to be studied with publicly funded contract awards administered by NIH.¹⁹⁹ Under the law, not all declined written requests must be referred to the Foundation.²⁰⁰

When a pediatric research grant is issued by the Foundation, the recipient of the grant must agree to provide NIH and FDA with reports and data at the conclusion of the studies.²⁰¹ FDA shall then “take appropriate action,” including

194. *See id.* § 284m(c)(12) (PHSA § 409I(c)(12)).

195. 21 U.S.C.S. § 355a(d)(4)(A) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(d)(4)(A)).

196. *See id.* § 355a(d)(4)(B) (FDCA § 505A(d)(4)(B)).

197. 42 U.S.C.S. § 290b (Law Co-op 1994 & Supp. 2002) (PHSA § 499).

198. 21 U.S.C.S. § 355a(d)(4)(C) (FDCA § 505A(d)(4)(C)).

199. *Id.*

200. *See id.* § 355a(d)(4)(E) (FDCA § 505A(d)(4)(E)).

201. 42 U.S.C.S. § 290b(j)(9)(B)(iii) (PHSA § 499(j)(9)(B)(iii)).

negotiating appropriate labeling changes with the holders of approved applications for the drug studied.²⁰²

C. Dispute Resolution for Labeling Changes

The new law creates a special dispute resolution procedure when FDA and drug sponsors do not agree on appropriate pediatric labeling changes. These dispute resolution procedures apply for labeling changes based on both studies conducted by third parties under public contracts awarded by NIH, and based on studies conducted by an NDA holder pursuant to a written request under section 505A of the FDCA. If there is no agreement on appropriate labeling changes within 180 days after the submission of pediatric study reports, then the following procedure is triggered:

- FDA refers the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.
- Not later than 90 days after the referral, the Subcommittee makes a recommendation to FDA as to appropriate labeling changes, if any.
- Within 30 days after receiving the recommendation, FDA makes a request for labeling changes to all sponsors holding approved applications for the drug, if appropriate.
- If a sponsor does not agree to make a requested labeling change within 30 days after receiving the request for the change from the agency, FDA “may deem the drug to be misbranded.”²⁰³

The law states that nothing in these provisions limits the FDA’s authority to bring an enforcement action under the FDCA based on the lack of appropriate pediatric labeling.²⁰⁴

1. Additional Measures to Expedite Pediatric Labeling Changes

The law contains two additional provisions to expedite labeling changes based on pediatric studies conducted under section 505A. First, the user fee waiver that previously applied to pediatric supplements was eliminated, thereby providing FDA with additional resources to review such applications.²⁰⁵ Second, all pediatric supplements submitted in accordance with section 505A will be considered

202. *See id.* § 290b(j)(9)(B)(iv) (PHSA § 499(j)(9)(B)(iv)).

203. 21 U.S.C.S. § 355a(i)(2) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(i)(2)); 42 U.S.C.S. § 284m(c) (7)-(11) (Law Co-op 1994 & Supp. 2002) (PHSA § 4091(c)(7)-(11)). Misbranding is a prohibited act under the FDCA and can lead to FDA enforcement action. *See* 21 U.S.C.S. § 331(b) (FDCA § 301(b)).

204. 21 U.S.C.S. § 355a(i)(2)(E) (FDCA § 505A(i)(2)(E)).

205. *See id.* § 379h(a)(1) (BPCA § 5(a)). Absent a waiver, a fee must be paid when a new drug application or supplement is filed with FDA. *See id.* § 379h(a)(1) (FDCA § 736(a)(1)).

“priority supplements” and will be subject to FDA’s performance goals that apply to priority drugs.²⁰⁶

D. Additional Changes to Section 505A of the FDCA

1. The Pediatric List

The law amends section 505A of the FDCA to eliminate the so-called “pediatric list.”²⁰⁷ Under the old law, a marketed drug had to be on the pediatric list before FDA could issue a written request for pediatric studies.²⁰⁸ Now, FDA may issue written requests for pediatric studies of an already-marketed drug simply if it determines that information relating to the use of the drug in the pediatric population “may produce health benefits in that population.”²⁰⁹ This change reflects FDA’s prior implementation of section 505A. The pediatric list had played no role in practice because FDA deemed every approved drug to be on the pediatric list.²¹⁰

2. Neonates

The law amends section 505A to make clear that written requests may be issued for studies in neonates, where appropriate.²¹¹

3. Racial and Ethnic Minorities

The law requires that FDA take into account adequate representation of children of ethnic and racial minorities when entering into written agreements regarding protocols for studies under section 505A.²¹²

4. Dissemination of Pediatric Information

Under the new law, not later than 180 days after the submission of pediatric reports in response to a written request under section 505A, FDA is required to publish in the Federal Register a summary of FDA’s medical and clinical pharmacology reviews of the completed pediatric studies.²¹³ This information will be published whether or not the application or supplemental application with the

206. See *id.* § 321(kk) (FDCA § 201(kk)). The performance goals that apply to priority supplements and certain other applications are those referred to in section 101(4) of the FDAMA, 111 Stat. 2298 (1997).

207. 115 Stat. at § 2.

208. 21 U.S.C. § 355a(b) (FDCA § 505A(b)); see also *supra* text accompanying note 63.

209. 21 U.S.C.S. § 355a(c) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(c)); 115 Stat. at § 2.

210. 21 U.S.C.S. § 355a(a), (c) (FDCA § 505A(a), (c)); see also *supra* text accompanying notes 64-66.

211. 21 U.S.C.S. § 355a(a) (FDCA § 505A(a)); 115 Stat. at § 4.

212. See 21 U.S.C.S. § 355a(d)(2) (FDCA § 505A(d)(2)); 115 Stat. at § 18.

213. See 21 U.S.C.C. at § 355a(j) (FDCA § 505A(j) as amended by BCPA section 5(b)(2)); 115 Stat. at § 9.

new pediatric data has yet been approved. However, the law provides that it does not alter or amend the public disclosure provisions of the FDCA,²¹⁴ the Freedom of Information Act,²¹⁵ or the Trade Secrets Act,²¹⁶ which do not permit the disclosure of trade secrets and confidential commercial information, among other things.²¹⁷

E. Organizational Changes at FDA

1. Office of Pediatric Therapeutics

The law creates an Office of Pediatric Therapeutics within FDA. The Office will be responsible for oversight and coordination of all agency activities that involve or may have an effect on pediatric issues, and will coordinate with employees of HHS who have responsibilities relating to pediatric therapeutics.²¹⁸ Office staff must include at least one additional individual with expertise in ethical issues raised by the conduct of pediatric research, and at least one additional pediatric expert.²¹⁹

2. Pediatric Pharmacology Advisory Committee

The law establishes an FDA advisory committee on pediatric pharmacology to advise and make recommendations on matters relating to pediatric pharmacology, including the identification of research priorities and the need for additional treatments for specific pediatric diseases or conditions.²²⁰ The advisory committee is to include representatives of pediatric health organizations, pediatric researchers, patient and family organizations, and other experts.²²¹

3. Pediatric Subcommittee of the Oncologic Drugs Advisory Committee The law clarifies the mission of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (the Pediatric Oncology Subcommittee). The Pediatric Oncology Subcommittee is specifically directed to evaluate and prioritize new and emerging pediatric cancer treatments, provide guidance on timely patient access to new therapies, and “advise on ways to improve consistency in the availability of new therapeutic agents.”²²² The Pediatric Oncology Subcommittee must request participation of the following: at least two pediatric oncology specialists from the National Cancer Institute; at least four pediatric oncology specialists from the Children’s Oncology Group, a pediatric oncology consortium sponsored by the

214. 21 U.S.C.S. § 331(j) (FDCA § 301(j)).

215. Pub. L. No. 89-554, 80 Stat. 383 (1966) (codified as amended 5 U.S.C. §§ 552 et seq. (2000)).

216. 62 Stat. 791 (1948) (codified as amended 18 U.S.C. § 1905 (2000)).

217. 21 U.S.C.S. § 355a(m)(2) (LEXIS 1997 & Supp. 2002) (FDCA § 505A(m)(2)).

218. 115 Stat. at § 6.

219. *See id.* § 6(c).

220. *See id.* § 14.

221. *See id.* § 14(c).

222. *See id.* § 15(a).

National Cancer Institute (e.g., the Pediatric Brain Tumor Consortium), or elsewhere with pediatric research expertise; at least two representatives of patients or families; one representative of the nursing community; at least one statistician; and at least one industry representative.²²³

F. Additional Provisions re: Pediatric Oncology

In addition to clarifying the mission of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, the law contains the following provisions intended to spur research on pediatric cancer therapies:

- The law amends section 413 of the Public Health Service Act to direct the National Cancer Institute to expand research on the development of preclinical models for potential pediatric cancer therapies, and coordinate such activities with those of other NIH research institutes and agencies.²²⁴
- The law amends the FDCA to require that applications to conduct new clinical investigations (investigational new drug applications, or INDs) include a statement of whether the sponsor has plans for assessing pediatric safety and efficacy.²²⁵
- The law amends section 402(j) of the Public Health Service Act to require that sponsors of studies required to be included in a clinical trial databank previously established by FDAMA include a description for the databank of whether and through what procedures the sponsor will respond to requests to expand research protocols to allow broader use of a drug under study, particularly for children.²²⁶ FDAMA previously required that NIH establish a databank of information on clinical trials of drugs for serious or life-threatening diseases and conditions.²²⁷

G. Adverse-Event Reporting

The law requires that FDA promulgate a final rule within one year, requiring that the labeling of each drug approved under section 505 of the FDCA (regardless of the date of approval) include the toll-free number maintained by FDA for

223. *See id.* § 15(a)(2)(B).

224. 42 U.S.C.S. § 285a-2 (Law Co-op 1994 & Supp. 2002).

225. 21 U.S.C.S. § 355(i)(1)(D) (LEXIS 1997 & Supp. 2002) (FDCA § 505(i)(1)(D)) (requiring the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy).

226. 42 U.S.C.S. § 282(j) (Law Co-op 1994 & Supp. 2002) (PHSA § 402(j)).

227. *See id.*; *see also* Draft Guidance for Industry, Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank; Availability 65 Fed. Reg. 16,620 (March 29, 2000); *see generally* CTR. FOR DRUG EVALUATION & RES. (CDER) AND CTR. FOR BIOLOGICS EVALUATION & RES. (CBER), FDA DRAFT GUIDANCE FOR INDUSTRY, INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE-THREATENING DISEASES: IMPLEMENTATION PLAN (2001).

adverse event reporting.²²⁸ The rule must be crafted in a manner that FDA considers most likely to reach the broadest consumer audience, and must seek to minimize the costs of the rule on the pharmacy profession.²²⁹

The law also requires that during the one-year period following a grant of pediatric exclusivity, any adverse event report regarding the drug received by FDA be referred to the new Office of Pediatric Therapeutics.²³⁰ The Office of Pediatric Therapeutics must provide for review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.²³¹ Nothing in the provision restricts FDA's authority to continue such procedures after the end of the one-year period.²³²

H. Interaction with Other Exclusivity Periods

The BPCA clarified how pediatric exclusivity grants interact with certain other available exclusivity periods. One such other type of exclusivity is available to the first generic drug applicant to challenge the patents of an innovative drug sponsor.²³³ This is often referred to as "180 day exclusivity." The BPCA makes clear that 180-day generic exclusivity periods do not start to run until an innovative drug sponsor's pediatric exclusivity period has expired.²³⁴ This ensures that generic drug sponsors entitled to 180-day exclusivity will not lose a portion of that exclusivity due to the overlap with a pediatric exclusivity period.

The BPCA also addresses the interaction of pediatric exclusivity and the three years of marketing exclusivity innovative drug sponsors can earn when they file supplemental applications that contain new clinical investigations essential to approval of the application.²³⁵ Drug sponsors who perform pediatric studies in response to a written request under section 505A and who also obtain approval of new pediatric labeling based on those studies are eligible to receive not only six additional months of pediatric exclusivity for the drug as a whole, but also three years of marketing exclusivity for the new pediatric labeling. That is, a generic would not be able to include the new protected pediatric labeling for three years.

The BPCA provides that a generic drug shall not be considered ineligible for approval or misbranded if the labeling for the generic drug omits a pediatric

228. 115 Stat. at § 17(a).

229. *Id.*

230. *See id.* § 17(b).

231. *Id.*

232. *Id.*

233. 21 U.S.C.S. § 355(j)(5)(B)(iv) (LEXIS 1997 & Supp. 2002) (FDCA § 505(j)(5)(B)(iv)); 115 Stat. at § 3; *see also*, *Mova Pharm. Corp v. Shalala*, 140 F.3d 1060, 1064-65 (D.C. Cir. 1998).

234. 21 U.S.C.S. § 355a(k) (FDCA § 505A(k)); 115 Stat. at § 10.

235. *See* 21 U.S.C.S. §§ 355(c)(3)(D)(iii); 355(j)(5)(D)(iii) (FDCA §§ 505(c)(3)(D)(iii); 505(j)(5)(D)(iii)); 115 Stat. at § 10; *see also*, *Upjohn Co. v. Kessler*, 938 F.Supp. 439, 441 (W.D. Mich. 1996) (explaining three-year market exclusivity provisions).

indication or other aspect of labeling related to pediatric use that is protected by patent or by three-year market exclusivity.²³⁶ Where such labeling is omitted, FDA may require that the labeling contain any necessary pediatric contraindications, warnings, or precautions, as well as a statement that the generic is not labeled for pediatric use because of marketing exclusivity for the pioneer.²³⁷ These provisions do not otherwise affect pediatric exclusivity, market exclusivity for pediatric formulations (as opposed to pediatric labeling), or the ability of generic drugs to omit other labeling protected by exclusivity.²³⁸ This provision of the law was drafted in order to prevent a pioneer company from using three-year market exclusivity for pediatric labeling to affect approval of a generic for adult indications.²³⁹

I. Government Reports

1. Institute of Medicine Report on Protections for Research Subjects

The law directs the Secretary of HHS to contract with the Institute of Medicine to review a variety of issues related to the protection of pediatric research subjects and federal support for pediatric research.²⁴⁰ Among the issues the Institute of Medicine is to review are the process of obtaining informed consent and assent, payments to children or parents for participating in research, the monitoring of compliance with legal requirements, and the roles of institutional review boards.²⁴¹ A report of the Institute of Medicine will be submitted to Congress within 2 years.²⁴² The report is to include recommendations on best practices relating to research involving children.²⁴³

2. Comptroller General Report on Pediatric Exclusivity Program

The law requires that the Comptroller General, in consultation with the Secretary of HHS, submit a report to Congress by October 1, 2006 that addresses (1) the effectiveness of the new law in ensuring that medicines are appropriately tested and labeled for pediatric use, (2) the economic impact of the law (savings from the more effective use of medicines, increased costs to consumers and the government, increased sales for pioneer drugs), (3) the nature and type of studies

236. 21 U.S.C.S. § 355a(l) (FDCA § 505A(l)); 115 Stat. at § 11.

237. 21 U.S.C.S. § 355a(l)(2) (FDCA § 505A(l)(2)).

238. See *id.* § 355a(l)(3) (FDCA § 505A(l)(3)).

239. See H.R. REP. NO. 107-277 at 30.

240. 115 Stat. at § 12.

241. *Id.*

242. *Id.*

243. *Id.*

conducted to earn pediatric exclusivity, (4) any recommendations for modifications to the pediatric exclusivity program, (5) the increase in public and private research capacity associated with the law, (6) the number of written requests and additional letters of recommendation issued by FDA, (7) the prioritized list of off-patent drugs for which FDA issues written requests, and (8) the efforts made by FDA to increase the number of studies conducted in neonates (and the results of those efforts).²⁴⁴

3. General Accounting Office Report on Racial and Ethnic Minorities

The law also directs the General Accounting Office to conduct a study and report to Congress by January 10, 2003 on (1) the extent to which children of ethnic and racial minorities are adequately represented in pediatric studies conducted under section 505A of the FDCA, (2) whether FDA has appropriate systems to monitor the representation of children of ethnic and racial minorities in such studies, and (3) whether drugs for diseases that disproportionately affect racial and ethnic minorities are being studied under section 505A.²⁴⁵

4. FDA Report on Access to New Pediatric Cancer Therapies

By January 31, 2003, FDA, in consultation with NIH, must report to Congress on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.²⁴⁶

5. FDA Implementation

Neither NIH nor FDA has yet implemented the primary provisions of the BPCA. It is therefore not clear how the new public study programs for off-patent and other drugs will operate in relation to the FDAMA exclusivity provisions or the Pediatric Rule.

X. CONCLUSION

The available record demonstrates that the new pediatric initiative is working. Drugs are being studied and labeled for use in different pediatric age groups, and the capacity in the public and private sectors to perform pediatric research is vastly expanded. This growth in the amount of pediatric research brings its own challenges, including, in particular, a heightened imperative to ensure that the rights of pediatric patients enrolled in studies are protected. There is no reason why these additional challenges cannot be met and new research conducted within appropriate legal and ethical bounds.

244. *See id.* § 16.

245. *See id.* § 17(b).

246. *See id.* § 15(d).

There are, therefore, grounds for significant optimism at this point in the evolving story of pediatric drug development. The federal government's efforts at both the legislative and administrative levels over the past five years to expand research on the use of medicines in pediatric patients have yielded unprecedented results. The government has employed multi-pronged solutions to a complex problem, using an innovative mixture of private market incentives, regulatory mandates, and publicly funded research programs. Officials have shown a willingness to try new approaches after prior attempts failed, and to continue to refine even those programs that have worked, as reflected in the steps Congress recently took when it reauthorized the pediatric exclusivity incentives while also creating brand new pediatric programs at NIH. The challenge will be to maintain that spirit of open-minded problem solving. As Dr. Shirkey's call echoes still in our ears, if ever so slightly fainter, this is no time to stop the good work that has begun.