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Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry

Kurt R. Karst

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Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry

Keywords

Prescription Drugs, Food and Drug Administration ("FDA"), Pharmaceutical Industry

COMMENTS

PEDIATRIC TESTING OF PRESCRIPTION DRUGS: THE FOOD AND DRUG ADMINISTRATION'S CARROT AND STICK FOR THE PHARMACEUTICAL INDUSTRY

KURT R. KARST*

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* Junior Staff, *American University Law Review*, J.D. Candidate, May 2001, *American University, Washington College of Law*, B.A., 1995, *Marquette University*. I am grateful to Sara Young, David Chavkin, Scott Furst, and Kim Maraviglia for their thoughtful comments on earlier drafts of this Comment. I would especially like to thank my wife, Amanda, my parents, Ralph and Cheryl, my brother, Erik, and most importantly, the Lord Almighty—*Omnia ad majorem Dei gloriam*.

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INTRODUCTION

For more than twenty years, the Food and Drug Administration (“FDA”),¹ the pharmaceutical industry (“Industry”), Congress, and the American Academy of Pediatrics (“AAP”)² have worked to craft substantive and effective proposals³ to provide better pediatric⁴ drug labeling and pediatric drug formulations to reduce off-label drug use.⁵ Efforts have focused on three distinct classes of drugs regulated

1. The FDA established a web page to monitor the progress of various pediatric testing initiatives. See FDA, *Pediatric Medicine* (visited June 1, 2000) <<http://www.fda.gov/cder/pediatric>>. The web page is an excellent resource and contains links to laws, regulations, policies, meetings, presentations, and other sites with pediatric information. See *id.*

2. The AAP is an organization comprised of 50,000 primary care and specialty pediatricians that helps to promote health care issues exclusively for the pediatric population. See AAP, *American Academy of Pediatrics Web Page* (visited June 1, 2000) <<http://www.aap.org>>.

3. See *infra* Part I (elaborating on the various initiatives undertaken by the federal government to address pediatric issues).

4. For the purposes of this Comment, the term pediatric includes neonates (birth to 1 month), infants (1 month to 2 years), children (2 to 12 years), and adolescents (12 to 16 years). See Center for Drug Evaluation and Research (“CDER”), FDA, *Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act* (last modified Sept. 1999) at 6 <<http://www.fda.gov/cder/guidance/index.htm>> (defining appropriate age groups for qualifying pediatric studies).

5. Off-label drug use is the use of a prescription drug in a manner different than that instructed on the drug's labeling. See Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 188 (1999) (defining and discussing off-label drug use). Drug labels, approved by the FDA, indicate the intended uses of a particular product and may also disclaim certain uses of a product. See *id.* at 186-87. If a consumer uses a product in a manner neither approved by the FDA nor tested by the manufacturer, such an act may discharge the manufacturer from liability, provided adequate testing was undertaken in the pre-approval phases of

by the Food, Drug, and Cosmetic Act of 1938 ("FDCA"):⁶ (1) new

development. *See id.* at 224. Approximately 80% of all new drugs and drugs currently on the market have not been adequately tested for use in pediatric populations. *See Reauthorization of the Prescription Drug User Fee Act and Food and Drug Admin. Reform: Hearings before the Subcomm. on Health and Env't of the House Commerce Comm.*, 105th Cong. 10-11 (1997) (testimony of Sanford N. Cohen, Associate Director of the National Institute for Environmental Health Services at Wayne State University on behalf of AAP) (calling for congressional assistance in urging the FDA to require pediatric studies in new drugs expected to be used by children). As a result, physicians must face an ethical dilemma regarding the off-label use of a drug. On the one hand, if a drug's label does not indicate the proper dosage information for use in pediatric patients, and a physician refuses to prescribe the product because of the absence of pediatric dosing information, that physician may be liable for malpractice. On the other hand, a physician places the health of his patient at risk when he prescribes a drug to a patient for whom the product is not approved. *See Committee on Drugs, American Academy of Pediatrics, Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration: Subject Review*, 98 PEDIATRICS 143-45 (1996). In many instances physicians make an educated guess as to the correct dosage for a given drug. Such educated guesses typically do not harm the health of adults, but could have dire consequences for children. Children are not simply small adults, for they absorb and metabolize drugs at different rates than adults. *See SUMNER J. YAFFE, M.D. & JACOB V. ARANDA, M.D., PH.D., F.R.C.P.(C), PEDIATRIC PHARMACOLOGY: THERAPEUTIC PRINCIPLES IN PRACTICE 3* (2d ed. 1992) (describing the increased awareness that drug actions depend on both the intrinsic qualities of the drug and its interaction with the host). In addition, due to the lack of clinical studies in pediatric patients, physicians may not be aware of all possible adverse drug reactions that might occur if the pediatric patient is using other types of medication. *See Charles J. Cote et al., Is the "Therapeutic Orphan" About to Be Adopted?*, 98 PEDIATRICS 118 (1996).

The dearth of pediatric labeling that has led to off-label prescribing practices is, in large part, due to ethical issues that arise when considering whether to enroll children in clinical drug studies, and may present an obstacle to implementing the statute and regulations described in this Comment. *See FDA Considers Ethics of Putting 'Normal' Children in Clinical Trials*, FDA WEEK, July 2, 1999, at 1, 10 (quoting Dianne Murphy, Director, Office of Drug Evaluation IV, the Food and Drug Administration, as saying "ensuring that [clinical] studies are conducted ethically on children is the single greatest barrier to implementation of both the FDA's pediatric rule and [FDAMA Section 111]"). Pediatric patient safety also may be jeopardized by increasing pressure on companies to conduct studies in pediatric patients and competition for pediatric patients to participate in the studies. *See id.* at 10. As children are an especially vulnerable population, they demand greater protection of their rights. *See American Academy of Pediatrics Committee on Drugs: Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286-87 (1995) (arguing that because children are an especially vulnerable subpopulation in the United States, they must be protected from the violation of their individual rights and from undue exposure to risk). Although there are currently ethical guidelines for studying drugs in children, it is necessary to develop research protocols that specifically address children and clinical studies. *See id.* at 287. As the FDA drafts guidance on studying drugs in children, it will have to consider a myriad of issues, including the existence of certain state laws (i.e., California) that prohibit the use of an experimental drug on children unless the drug can maintain or improve the health of the child. *See generally* Memorandum from the Pharmaceutical Research and Manufacturers of America ("PhRMA") 8 (Oct. 5, 1999) (on file with the *American University Law Review*) (commenting on new provisions and rules regarding pediatric drug studies) (enclosed with letter from Marjorie E. Powell, Assistant General Counsel, PhRMA, to Janet Woodcock, M.D., Director, CDER, and Kathryn C. Zoon, Ph.D., Director, Center for Biologies Evaluation and Research, FDA).

6. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 et seq. (1994)) (requiring new drugs to receive premarket approval from the

drugs;⁷ (2) currently marketed drugs;⁸ and (3) off-patent drugs.⁹ As a result of the efforts of the FDA, Industry, and the AAP, Congress has implemented two major policies. First, in November 1997, Congress passed the Food and Drug Administration Modernization Act ("FDAMA"),¹⁰ which included Section 111, Pediatric Exclusivity ("FDAMA Section 111").¹¹ Second, on December 2, 1998, the FDA promulgated a final rule, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" ("Final Rule").¹²

FDAMA Section 111 offers six months of extended patent life¹³ to

FDA).

7. See FDCA § 505A(a); 21 U.S.C. § 355a(a) (Supp. 1997) (discussing the various requirements a new drug must fulfill to receive market exclusivity for pediatric studies).

8. See *id.* § 505A(c), 21 U.S.C. § 355a(c) (Supp. 1997) (discussing various requirements for already-marketed drugs to receive market exclusivity for pediatric studies).

9. Under the FDCA, new and currently-marketed drugs enjoy a period of market exclusivity during which time the life of the product's patent tolls. During the period of exclusivity, the FDA cannot approve a generic copy of the original product, thereby creating a monopoly for the owner of the drug patent. Once a product's patent life expires, it is referred to as off-patent. See generally DONALD O. BEERS, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* § 4.02(A), at 4-3 (5th ed. 1999) (describing provisions that may delay the approval of a competitor's product).

10. Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 301-392 (Supp. 1997)) (intending, among other things, to improve the regulation of food, drugs, devices, and biological products). The FDAMA is a compilation of smaller pieces of legislation meant to reform the FDCA, the two most important of which are the pediatric incentive provision and the reauthorization of the Prescription Drug User Fee Act ("PDUFA"). See Letter from Representatives James C. Greenwood (R-Pa.) and Richard Burr (R-N.C.) to Jane E. Henney, M.D., Commissioner, FDA 1 (May 26, 1999) (on file with the *American University Law Review*) (expressing a desire for the FDA to implement Section 111 which creates incentives for conducting pediatric drug studies). The PDUFA allows drug sponsors to pay user fees to the FDA. In exchange, the FDA hires additional drug application reviewers and implements electronic document submission to expedite the drug approval process. See FY 1998 PDUFA FINANCIAL REPORT 1 (providing an overview of PDUFA II and establishing future initiatives and goals).

11. See FDAMA § 111 (codified at FDCA § 505A, 21 U.S.C. § 355a (Supp. 1997)) (extending market exclusivity for drug manufacturers who identify drugs beneficial to children and conduct pediatric studies).

12. See Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (1998) (codified in scattered sections at 21 C.F.R. (1998)) [hereinafter Final Rule] (requiring manufacturers of certain products to provide data and information to support their directions for use in children).

13. A U.S. patent term runs for either 17 or 20 years. All patents in force or filed as of June 8, 1995 have either a patent for 17 years from the date when the patent was granted, or 20 years from the date of the first filing of the patent application, whichever option is longer. See The Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994) (codified at 35 U.S.C. § 154(c)(1) (1994)). All patents filed after June 8, 1995 have a patent of 20 years. See 35 U.S.C. § 154(a)(2) (1994). Because the FDA will not review applications for generic copies of a drug for six months after its statutory patent life expires, FDAMA Section 111 essentially

innovator drug¹⁴ sponsors who conduct pediatric studies¹⁵ on new and currently-marketed drugs.¹⁶ This provision sunsets in 2002.¹⁷ In contrast, the FDA's Final Rule compels drug sponsors to assess the safety and efficacy of new and currently-marketed drugs and biological products¹⁸ in pediatric populations.¹⁹

The carrot offered in the FDAMA to innovator drug sponsors who conduct pediatric studies complements the FDA's mandatory Final Rule. The former affords the Industry the opportunity to provide new and currently-marketed drug products that should be tested for use among pediatric patients in exchange for patent exclusivity, and the latter allows the FDA to require that all drugs and indications are tested in pediatric populations regardless of their market potential.²⁰

extends the life of the term of the patent by six months. *See generally* BEERS, *supra* note 9, § 4.02(A), at 4-3 (describing various types of market exclusivity).

14. An innovator drug, also referred to as a pioneer drug, is the original version of a patented drug product that the FDA approves for a specific therapeutic purpose. Subsequent versions approved for marketing after the patent term of the innovator drug expires are referred to as generic copies. *See* BEERS, *supra* note 9, § 1.01, at 1-3 (explaining the difference between pioneer drug and generic drug).

15. Pediatric studies entail "at least one clinical investigation (that . . . may include pharmacokinetic studies) in pediatric age groups in which a drug is anticipated to be used." CDER, FDA, *Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act*, at 3 (last modified Sept. 1999) <<http://www.fda.gov/cder/guidance/index.htm>> (citing the definition of pediatric studies under section 505A, which is codified at section 505A(g) of the FDCA). Pharmacokinetics refers to the way in which a human body handles a drug. For example, children metabolize, excrete, and absorb drugs differently than adults. A pharmacokinetic study measures and calculates those differences. *See* Medical Policy Coordinating Committee (MPCC), FDA, *Draft Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*, at 2-4 (Nov. 1998) <<http://www.fda.gov/cder/guidance/index.htm>> (noting the need for pharmacokinetic studies to determine what drug dosage in the pediatric population is as safe and effective as in adults).

16. *See* FDCA § 505A(a), (c); 21 U.S.C. § 355a(a), (c) (Supp. 1997) (describing the patent extension that drug manufacturers may earn by conducting pediatric studies).

17. *See* FDCA § 505A(j); 21 U.S.C. § 355a(j) (Supp. 1997) (stating that this six-month exclusivity period will only apply to drug manufacturers who submit applications for their respective drugs to the FDA on or before January 1, 2002, or if certain other conditions are met).

18. A biologic or biological product is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." Public Health Service Act, 42 U.S.C. § 262(i) (1994) (defining biological product). The FDA regulates biological products in conjunction with the Public Health Service Act, and ensures the safety and efficacy of biological products through various licensing requirements. *See* 21 C.F.R. pts. 600-680 (1999) (covering biologics).

19. *See* Final Rule, *supra* note 12, at 66,633 (requiring that manufacturers of both new and marketed drugs and biological products evaluate the safety and effectiveness of their products).

20. *See United States Food and Drug Admin. Anti-Infective Drugs Advisory Comm. Meeting of the Pediatric Subcomm.*, 20-26 (1999) [hereinafter Anti-Infective Drugs

Numerous questions abound, however, as to the future status and implementation of the Final Rule after the FDAMA Section 111 marketing exclusivity incentive expires in 2002.²¹ The Industry fears that once it demonstrates an ability to conduct pediatric studies with a market incentive, and after FDAMA Section 111 sunsets, the FDA will possess only the stick-like Final Rule with which to mandate further pediatric testing.²² Conversely, the FDA is concerned that once FDAMA Section 111 expires, mandatory testing will remain as the only alternative to continue and enhance the availability of drugs for pediatric patients.²³ The FDA's goal, which is to increase the availability of drugs to pediatric patients, does not justify the means chosen by it to reach that end. The implementation of the Final Rule will not increase the availability of drugs to pediatric patients, but rather will stymie the growth of pediatric formulations.²⁴

This Comment argues that the FDA lacks the authority to mandate pediatric testing via the Final Rule.²⁵ Further, this Comment demonstrates that the FDA intends to use FDAMA Section 111 market exclusivity as a carrot for Industry compliance with the Final Rule. This objective is made apparent in the similarity of the FDA's criteria for a drug to qualify for market exclusivity under FDAMA Section 111²⁶ and the criteria that would invoke mandatory testing

Advisory Comm.] (statement of Dianne Murphy, M.D., Associate Director for Pediatrics, FDA) (discussing the FDA's devotion to integrating FDAMA Section 111 and the Final Rule); *see also* Final Rule, *supra* note 12, at 66,634 (noting the FDA's diminished need to require studies of currently-marketed drug products due to the existence of a list that contains approved drugs, which may benefit pediatrics if further information is obtained).

21. *See* Jill Wechsler, *Washington Report: Push & Pull Over Pediatric Medicines*, PHARM. EXECUTIVE, July 1998, at 18, 20 (reporting Industry fear that a voluntary approach to conducting pediatric studies may be delayed in preference for a mandatory approach).

22. *See id.* (discussing the Industry's suspicion of the FDA's approach to implementing FDAMA Section 111 and the Final Rule).

23. *See* Final Rule, *supra* note 12, at 66,632 (discussing the failure of past FDA attempts to persuade drug sponsors to provide pediatric use information on their product's labeling). *But see* Letter from Alan F. Holmer, President, *PhRMA*, to FDA Dockets Management Branch, Docket No. 97N-0165, 2-13 (Nov. 13, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) (noting the success of the FDA's past attempts to increase pediatric information).

24. *See* Letter from Carl B. Feldbaum, President, Biotechnology Industry Organization, to Jane E. Henney, M.D. Commissioner, Food and Drug Administration 1 (June 22, 1999) (on file with the *American University Law Review*) (noting that "[i]ll-advised application of the [Final Rule] could stifle innovation and lead to results quite at odds with the rule's intent").

25. *See infra* Part II.A (arguing that under the FDCA, the FDA lacks the authority to mandate pediatric studies from the Industry).

26. *See infra* notes 141-44 and accompanying text (listing the requirements a drug must fulfill to qualify for FDAMA Section 111).

under the Final Rule,²⁷ the definition of “drug” as active moiety,²⁸ and the lack of expedience the FDA shows in granting market exclusivity from a rather long list of drugs that qualify for pediatric exclusivity under FDAMA Section 111.²⁹ In addition, this Comment explains that an Industry challenge to the FDA’s authority to mandate pediatric studies will coalesce and exacerbate negative public sentiment against the Industry.³⁰ Finally, this Comment recommends that the most prudent option, and the option that best serves the interest of pediatric patients, is a compromise between the Industry and the FDA, whereby the Industry contributes to pediatric studies for off-patent drugs and the FDA agrees to recommend that the United States Congress reauthorize FDAMA Section 111 incentives for an additional five years.³¹

This Comment begins by providing historical information on both the legislative and regulatory attempts to find parents for the “therapeutic orphan”³² that resulted in the passage of FDAMA Section 111 and the promulgation and implementation of the Final Rule. In addition, Part II addresses the unstable statutory foundation upon

27. See *infra* notes 147-51 and accompanying text (listing the requirements a drug must fulfill to qualify for the FDA to mandate pediatric studies under the Final Rule).

28. The active moiety is the part of the drug product or substance that achieves the intended therapeutic or pharmacological effect. See 21 C.F.R. § 314.108(a) (1999) (defining terms related to new drug market exclusivity); see also *infra* Part II.B.2 (noting the effects of recent litigation surrounding FDAMA Section 111).

29. See *infra* Part II.B.3 (arguing that the FDA’s lack of expediency in granting market exclusivity is contrary to its initiative to improve pediatric health and that the FDA intends to lure the Industry into compliance with the Final Rule); see also List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population, 63 Fed. Reg. 27,733 (1998) [hereinafter Priority List] (identifying drugs that require further information for determining whether they may be used safely and effectively in the pediatric population). The official Priority List is located on the FDA’s pediatric web site. See *List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population* (visited Sept. 10, 1999) <<http://www.fda.gov/cder/pediatric/peddrugsfinal.htm>> [hereinafter *Official Priority List*].

30. See *infra* Part II.C (discussing the potential benefits and risks inherent in an Industry challenge to the FDA’s authority to mandate pediatric studies).

31. See *infra* Part III (recommending that the FDA and the Industry cooperate to reauthorize FDAMA Section 111 for an additional timeframe in exchange for studies on off-patent drugs).

32. Children have long been referred to as “therapeutic orphans” among professionals in the pediatric community due to a general lack of medications specifically formulated for their different metabolisms. See, e.g., John T. Wilson, *An Update on the Therapeutic Orphan*, 104 PEDIATRICS 585, 585-86 (1999) (tracing the origin and use of the “therapeutic orphan” concept); see also, e.g., Cote, *supra* note 5, at 120 (citing an article from as far back as 1968, which referred to pediatric patients as “therapeutic orphans”). The former article, written by Dr. Wilson, is part of a supplement to the September 1999 edition of the AAP’s journal *Pediatrics* entitled “the Therapeutic Orphan 30 Years Later.” Each paper considers different aspects of providing information for pediatric use. See generally *The Therapeutic Orphan 30 Years Later*, 104 PEDIATRICS 581-645 (1999).

which the FDA bases its authority to mandate pediatric testing and the difficulty the Industry faces in its challenge of the FDA's authority. Part II examines the consequences the Industry likely will confront when FDAMA Section 111 sunsets in 2002. Part III recommends that the Industry and the FDA reach a compromise to fulfill the needs and goals of the Industry, the FDA, and most importantly the children, which is to ensure that the entire universe of available drugs are available to pediatric populations.

I. PEDIATRIC TESTING: A HISTORICAL PERSPECTIVE OF THE "THERAPEUTIC ORPHAN"

Attempts to protect pediatric health and provide safe and effective products are the hallmarks of change and innovation to the FDCA.³³ Strides in clinical pharmacology have identified how a milieu of factors affect the safety and effectiveness of a drug in different host patients.³⁴ For example, doctors should not consider pediatric patients as "small adults" and prescribe them drugs on an off-label basis.³⁵ Thus, both FDAMA Section 111 and the Final Rule represent a culmination of the most recent initiative to include pediatric labeling on drugs and to adopt the "therapeutic orphan."³⁶

A. *Past Attempts to Acquire Pediatric Labeling*

The initiative to improve pediatric labeling of drugs began in earnest in 1974.³⁷ The FDA and the AAP entered into an agreement

33. In 1938, Congress added safety requirements to the FDCA as a result of numerous deaths, mostly children, resulting from the use of a solvent in an untested drug called Elixir Sulfanilamide. Under the Pure Food Act of 1906, ch. 3915, 1-13, 34 Stat. 768 (repealed 1938), the predecessor of the FDCA, a product did not have to meet safety requirements to be placed on the market. In 1962, Congress added efficacy requirements to the FDCA. *See* Drug Amendments of 1962 (Kefauver-Harris Amendments), Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. (1998)) (changing sections of the FDCA dealing with the safety, effectiveness, and reliability of drugs). The 1962 Kefauver-Harris Amendments were precipitated by thousands of birth defects that occurred as a result of the use of thalidomide by pregnant women to relieve morning sickness. *See* Elizabeth M. Rutherford, *The FDA and "Privatization": The Drug Approval Process*, 50 FOOD & DRUG L.J. 203, 212 (1995) (recounting the thalidomide tragedy).

34. *See* YAFFE & ARANDA, *supra* note 5, at 3 (noting that research has revealed that different stages in pediatric development can affect how a pediatric patient metabolizes a particular drug, and that such metabolization is vastly different from how adults metabolize a drug).

35. *See id.* (noting that drugs may react differently in children than in adults); *see also* Cote, *supra* note 5, at 122 ("The unapproved or off-label use of drugs is not an acceptable alternative to documentation of the safety and efficacy of drugs used by the pediatric population.")

36. *See infra* Part I.B-C (discussing the development of both FDAMA Section 111 and the final rule).

37. *See* Committee on Drugs, American Academy of Pediatrics, *General Guidelines*

to develop a solution for the absence of drugs in the market labeled for pediatric use. The AAP's Committee on Drugs issued general guidelines for the evaluation of drugs to be used in pediatric patients.³⁸ The FDA subsequently adopted these and incorporated them into clinical guidelines in 1977.³⁹ In 1979, the FDA promulgated a "Pediatric Use" regulation that stipulated requirements to which drug sponsors had to adhere in order to include pediatric uses on product labels.⁴⁰ This regulation required drug sponsors to include information on a product's labeling collected from clinical studies performed during a product's safety and effectiveness evaluation.⁴¹ In 1994, the FDA subsequently amended this 1979 regulation,⁴² thereby requiring sponsors to modify drug labels based on an assessment of current pediatric data to seek either a labeling change for pediatric use or to include a statement, such as: "Safety and effectiveness in pediatric patients have not been established."⁴³ Thus, the amended regulation gave the Industry the

for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children (Evanston Ill., 1974), cited in YAFFE & ARANDA, *supra* note 5, at 7.

38. *See id.*

39. *See* U.S. DEPARTMENT OF HEW, PHS, FDA, PUB. NO. 77-3041, GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS IN INFANTS AND CHILDREN (1977) (listing the guidelines for the evaluation of drugs in pregnant women, infants, and children).

40. *See* Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434 (1979) (codified at 21 C.F.R. pts. 201 and 202) (noting that the purpose of the final rule was to establish labeling standards for all prescription drugs).

41. *See id.* at 37,459. The regulation states that:

The 'Clinical Studies' and 'References' sections of the prescription drug labeling are intended to provide health care professionals with basic information on the safe and effective use of the drug that is too detailed for inclusion in the labeling for the drug. [This rule establishes that] at the option of the person responsible for the labeling . . . [c]linical studies and references may also be cited in other sections of prescription drug labeling when the citation is essential to an understandable presentation of the available information A clinical study or reference that is primarily directed to an unapproved use of the drug would not serve [to contribute to an understanding of the labeled uses of the drug, and] would not be appropriately cited in prescription drug labeling.

Id.

42. *See* 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 (1994) (codified at 21 C.F.R. § 201.57(f)(9)(vi) (1994)) (responding to the inadequacy of drug labels in supplying information for use in pediatric populations).

43. *See id.* at 64,241. This regulation required the label to include "any limitations on the pediatric indication, need for specific monitoring, specific hazards of the drug, differences between pediatric and adult responses to the drug, and other information related to the safe and effective use of the drug in pediatric patients." *Id.* Where substantial evidence failed to support a specific pediatric indication or a pediatric use statement for a particular pediatric subgroup, the regulation required the labeling to include a statement characterizing the limitation,

option to conduct pediatric research and include the data on labels.

As the FDA did not mandate the Industry to include pediatric data on labels, both the 1979 "Pediatric Use" regulations and the 1994 modification removed the incentive for drug sponsors to conduct clinical studies.⁴⁴ Even though the purpose of the 1994 amendment to the regulation was to counter this result,⁴⁵ it failed to generate the inclusion of substantive pediatric information on product labels.⁴⁶ As a result, the Industry did not study its products for use in pediatric patients.⁴⁷ Both the Clinton Administration,⁴⁸ through the FDA, and

such as "[s]afety and effectiveness in pediatric patients [below the age of ()] have not been established." *Id.*

44. See Anti-Infective Drugs Advisory Comm., *supra* note 20, at 29-30 (statement of Dianne Murphy, M.D., Associate Director of Pediatrics, FDA) (noting that FDA's efforts in the 1970s and the agency's 1994 effort to include pediatric information on drug labels did not result in sufficient pediatric information because the Industry was given an option to conduct the studies). Drug studies on children often pose significant technical obstacles, such as obtaining informed consent from reluctant parents, and overcoming manufacturers' and clinical investigators' concerns about liability. See *Reauthorization of the Prescription Drug User Fee Act and FDA Reform: Hearing Before the Subcomm. on Health and Env't of the House Comm. on Commerce*, 105th Cong. 83 (1997) (statement of Gordon M. Binder, Chairman and CEO, Amgen Inc.) (listing reasons that drugs are not studied in children). These obstacles deterred pediatric drug studies because sponsors who conducted such studies risked incurring an economic disadvantage against sponsors who did not. See *id.* (implying that sponsors are influenced by economic protection). To offset these disincentives, the Industry receive market protection. See *id.* (arguing that legislation that provides market protection in return for testing in children will provide clear economic incentives for such testing).

45. See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 Fed. Reg. at 64,241 ("The final rule revises the current 'Pediatric use' subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more complete information about the use of a drug in the pediatric population. . . .").

46. See Final Rule, *supra* note 12, at 66,632 (noting that in response to the 1994 "Pediatric use" rule, 430 pediatric labeling supplements were submitted to the FDA, and of those submitted about 75% did not significantly improve pediatric use information); Althea Gregory, *Denying Protection to Those Most in Need: The FDA's Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI. & TECH. 121, 131 (1997) (arguing that the "Pediatric use" regulations did not result in any changes to pediatric testing as evidenced by the fact that at least 71% of drugs still lack adequate pediatric dosing information).

47. The AAP found that between 1984 and 1995, only 20% of new drugs approved by the FDA were indicated for use in children. See *Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearings Before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Gov't Reform and Oversight*, 104th Cong. 109 (1996) (statement of Ralph Kauffman, M.D., Professor of Pediatrics and Pharmacology at the University of Missouri, Kansas City and Director of Medical Research at the Children's Mercy Hospital in Kansas City, on behalf of the AAP) (stating that only approximately 20% of all drugs marketed in the United States have been labeled for use by infants and children and that since 1962, 80% or more of approved drugs have been labeled for adult use with a disclaimer that they are not approved for use by children).

48. See *Remarks by the President at Event on Pediatric Dosage* (last modified Aug. 13, 1997) <<http://www.pub.whitehouse.gov/urires/I2R?urn:pdi://oma.eop.gov.us/>

Congress took steps to remedy this problem. The FDA and Congress, however, each approached the problem from vastly different perspectives. On the one hand, Congress sought to create incentives for drug sponsors,⁴⁹ which resulted in FDAMA Section III. On the other hand, the FDA sought to mandate clinical testing and the subsequent labeling of drugs for pediatric patients, which resulted in the Final Rule.⁵⁰

B. FDAMA Section 111—Pediatric Exclusivity

The first major revision of the FDCA to occur since 1962 is the FDAMA.⁵¹ The development of FDAMA Section 111 began in 1990, when attendees at a workshop at the Institute of Medicine (“IOM”)⁵² suggested market-based incentives to increase pediatric studies and labeling.⁵³ Subsequent to the IOM workshop, Industry

1997/8/13/9.text.1> (announcing the Administration’s proposed rule to mandate pediatric studies); *see also Press Briefing by President’s Principal Health Care Advisor, Chris Jennings* (last modified Aug. 13, 1997) <<http://www.pub.whitehouse.gov.uries/I2R?urn:pdi://oma.eop.gov.us/1997/8/13/3.text.1>> (commenting that because of the decline in pediatric testing and the ineffectiveness of the “Pediatric Use” rule, the Administration believed a mandatory rule was the only solution to increasing pediatric studies).

49. *See infra* Part I.B (discussing the development of FDAMA Section 111).

50. *See infra* Part I.C (discussing the development and implications of the Final Rule).

51. *See infra* notes 57-72 and accompanying text (describing the sponsor market exclusivity and the FDA publication provisions of the FDAMA); *see also* Drug Amendments of 1962 (Kefauver-Harris Amendments), Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. (1998)) (requiring drug sponsors to meet certain requirements with respect to safety, effectiveness and reliability, drug names, advertising, factory inspection, registration of establishments, and patent information to gain FDA approval to market drugs in the United States). *See generally supra* note 33 (discussing the 1938 and 1962 amendments to the FDCA).

52. The Institute of Medicine (“IOM”) is part of the National Academy of Sciences, a private, non-governmental organization. The mission of the IOM is to advance and disseminate scientific knowledge to the government, the corporate sector, the professions, and the public in an effort to improve human health. *See About the Institute of Medicine* (visited Sept. 10, 1999) <<http://www4.nas.edu/IOM/IOMHome.nsf/Pages/About+the+IOM>> (providing general information about the purpose of the IOM).

53. *See* INSTITUTE OF MED., NATIONAL ACADEMY OF SCIENCES, DRUG DEVELOPMENT AND THE PEDIATRIC POPULATION: REPORT OF A WORKSHOP 12 (1991) (“Marion Finkel clarified the industry perspective of the FDA guidelines promoting pediatric drug studies Pharmaceutical industry resources will be required by the initiatives therefore, incentives, such as exclusivity or some patent term extension, would be valuable.”). This author spoke with Marion J. Finkel, M.D., a participant in the IOM workshop. *See* Telephone Interview by Kurt R. Karst with Marion J. Finkel, M.D., Pharmaceutical Clinical and Regulatory Consultant, May 12, 1999. Dr. Finkel noted that the IOM workshop was one of the first substantive discussions suggesting that a period of exclusivity should be offered to pharmaceutical companies that conduct pediatric studies on their products. *See id.* Subsequent to the IOM meeting, Dr. Finkel approached the staff of Senator Nancy Kassebaum (R-Kan.) and recommended the introduction of legislation that would increase pediatric labeling of drugs through market exclusivity incentives. *See id.*

representatives urged Senator Nancy Kassebaum (R-Kan.) to introduce the "Better Pharmaceuticals for Children Act" ("BPCA").⁵⁴ The BPCA was introduced in subsequent sessions of Congress,⁵⁵ and was finally passed and signed into law as part of the FDAMA in 1997.⁵⁶

FDAMA Section 111 provides six months of market exclusivity to innovator drug sponsors who perform clinical studies of specific drugs in pediatric patients.⁵⁷ Moreover, these sponsors can earn an additional six month exclusivity period in certain circumstances.⁵⁸ The six months of additional patent protection is not limited to the specific drug tested, but is applicable to the drug's active moiety,⁵⁹ or, in other words, the part of the drug's make-up that causes its physiological or pharmacological action.⁶⁰ Drug sponsors can earn market exclusivity only for products listed in the "Orange Book"⁶¹ that are eligible for market exclusivity or protected under either the Drug

54. See S. 3337, 102d Cong., 2d Sess. (1992) (proposing deferred effective dates for approval of applications under drug provisions). The purpose of the BPCA was to encourage the innovator Industry to conduct pediatric testing on drug products not solely intended for use in children—e.g. drugs then prescribed on an off-label basis for children—in exchange for six months of market exclusivity. See 138 CONG. REC. S16,998-99 (daily ed. Oct. 5, 1992) (statement of Sen. Kassebaum). Kassebaum stated that:

[T]his legislation creates incentives for drug manufacturers to test the impact of drug products in pediatric populations. . . . The problem . . . is that there is little incentive for manufacturers to perform studies for medications which they do not intend to market for children and which are therefore expected to return little additional revenue from that source.

Id.

55. See H.R. 1727, 105th Cong., 1st Sess. (1997); S. 713, 105th Cong., 1st Sess. (1997); H.R. 4277, 104th Cong., 2d Sess. (1996); S. 2178, 104th Cong., 2d Sess. (1996); H.R. 4427, 103d Cong., 2d Sess. (1994); S. 2010, 103d Cong., 2d Sess. (1994). The 104th Congress also included the BPCA in its initial attempt to reform the FDCA. See S. 1477, 104th Cong., 1st Sess. (1995).

56. See FDCA § 505A; 21 U.S.C. § 355a (Supp. 1997) (providing market exclusivity for sponsors who conduct pediatric studies of drugs). The inclusion of the BPCA in the FDAMA was a priority issue for Congress, second only to the reauthorization of the PDUFA. See *supra* note 10 (noting the importance of FDAMA Section 111 in the passage of the FDAMA).

57. See FDCA § 505A(a), (c); 21 U.S.C. § 355a(a), (c) (Supp. 1997) (extending market exclusivity for certain sponsors who conduct pediatric drug studies).

58. See FDCA § 505A(h); 21 U.S.C. § 355a(h) (Supp. 1997) (providing that drug sponsors may receive an additional six-month period if they satisfy all of the other requirements of this section).

59. See *National Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 39-40 (D.D.C. 1999) (ruling that the term "drug" in FDAMA Section 111 should be interpreted as active moiety).

60. See 21 C.F.R. § 314.108(a) (1999) (defining "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause a drug to be an ester, salt . . . , or other noncovalent derivative . . . , responsible for the physiological or pharmacological action of the drug substance").

61. See FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (CCH 18th ed. 1998) (listing the different types of drug patents that exist and the drugs that are currently protected under those patent categories).

Price Competition and Patent Term Restoration Act,⁶² commonly referred to as the Hatch-Waxman Act,⁶³ or the Orphan Drug Act.⁶⁴ Pursuant to the initiation of clinical studies, the Secretary of the Department of Health and Human Services (“DHHS”), after determining that information about a drug may produce health

62. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified in scattered sections of 15 U.S.C., 21 U.S.C., 28 U.S.C., 35 U.S.C., and 42 U.S.C.) (amending the FDCA to revise procedures for new drug applications, amending Title 35 of the U.S.C., and authorizing the extension of patents for certain regulated products).

63. The purpose of the Hatch-Waxman Act was to amend the pre-marketing approval provisions of the FDCA to expedite the approval of generic copies of FDA-approved innovator products. *See* BEERS, *supra* note 9, § 1.01, at 1-2 to 1-3 (indicating that under the Hatch-Waxman Act, after the FDA first approves use of a chemical entity for specific therapeutic purpose, later FDA approvals of the same chemical entity for the same therapeutic purpose, but sold by different manufacturers, would be expedited). Six exclusivity provisions were added to the Hatch-Waxman Act by the innovator Industry shortly before Congress passed the Act. *See id.* § 4.02(A), at 4-4 (authorizing for human drugs: (1) ten years of market protection for new chemical entities approved between January 1, 1982 and September 24, 1984; (2) two years of protection for already approved entities approved during the above period; (3) five years for new chemical entities approved post-period; (4) three years for new drug applications for already approved drugs when the application “is supported by new clinical investigations, conducted or sponsored by the applicant, that are essential to approval”; (5) three years for supplemental new drug applications that are supported “by new clinical investigations, conducted or sponsored by the applicant, that are essential to approval”; and (6) delay of 180 days when abbreviated new drug applicant challenges innovator product’s patent claims). These exclusivity provisions served to placate the innovator Industry in light of concessions given to the generic industry by extending various types of market protection to innovator products. *See id.* at 4-3 to 4-4 (explaining that exclusivity provisions require generic product manufacturers to include full safety and effectiveness data in their new drug applications and because gathering such data requires time and expense, pioneer manufacturers usually obtain exclusive marketing).

64. Pub. L. No. 97-414, §§ 1-4, 96 Stat. 2049, 2049-56 (1983) (codified in scattered sections of 21 U.S.C., 26 U.S.C., and 42 U.S.C.). The FDCA identifies drugs for rare diseases or conditions. *See* FDCA, Pub. L. No. 75-717, § 526(a)(2)(A)-(B), 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 360bb(a)(2)(A)-(B) (1994)) (defining “rare disease or condition” as one which affects fewer than 200,000 people in the United States or one which affects more than 200,000 people in the United States and for which drug sales are not reasonably expected to exceed drug development costs). As drug manufacturers assume that rare diseases or conditions infect fewer than 200,000 persons, it is not economically viable for them to pursue treatment for such conditions without a market incentive. *See* BEERS, *supra* note 9, § 7.01 (discussing the development of the “orphan drug” designation). To encourage the development of drugs for rare diseases and conditions, the Orphan Drug Act created a seven year market exclusivity provision for drugs which meet statutory and FDA criteria. *See id.* § 7.02 (stating that the first approval of “orphan drug” bars subsequent FDA approval of competitors’ versions for seven years and describing implications of orphan drug exclusivity).

FDAMA Section 111 exclusivity does not apply to most biological products and antibiotics, which are regulated differently than human drugs. *See* Final Rule, *supra* note 12, at 66,632 (1998) (“[B]ecause FDAMA exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act, it provides no incentive to conduct studies on certain categories of products, including most antibiotics, biologics, and off-patent products.”).

benefits among a pediatric population,⁶⁵ must make a written request to the drug sponsor for pediatric studies.⁶⁶ The drug sponsor is under no obligation to conduct pediatric studies and may do so only to capitalize on the market exclusivity incentive.⁶⁷ Pediatric studies do not have to result in new labeling and do not have to show safety and efficacy in pediatric patients.⁶⁸

FDAMA Section 111 also directs the FDA to develop, publish, and annually update a list of drugs for which additional pediatric information may improve children's health.⁶⁹ For example, the FDA announced the publication of the first list on May 20, 1998.⁷⁰ Moreover, the FDA must report to Congress on the effectiveness and adequacy of FDAMA Section 111, including suggestions for modification, if appropriate, before January 1, 2001.⁷¹ FDAMA

65. See FDCA § 505A(b); 21 U.S.C. § 355a(b) (Supp. 1997) (requiring the DHHS to develop list of drugs which may produce healthy benefits in the pediatric population and, thus, qualify for exclusivity).

66. See FDCA § 505A(d); 21 U.S.C. § 355a(d) (Supp. 1997) (stipulating the various procedures and protocols involved in applications for pediatric exclusivity).

67. See CDER, FDA, *Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act*, at 4 (Sept. 1999) <<http://www.fda.gov/cder/guidance/index.htm>> ("Issuance of a written request to a sponsor does not require the sponsor to conduct pediatric studies described in the written request. It is the sponsor's decision whether to conduct the studies and possibly gain pediatric exclusivity").

68. See Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 203 (1999) (indicating that the goal of the broad grant of exclusivity is to get a maximum amount of useful pediatric information, and make this information public).

The agency is endeavoring to get a maximum amount of useful pediatric information as a result of the grant of exclusivity. The studies that are submitted to gain exclusivity are not required to result in new labeling. They do not have to show that the drug is safe or effective in the pediatric population. FDA's reading of the statute is that the intent of Congress was to make this information public.

Id. See Final Rule, *supra* note 12, at 66,633 (noting that the FDAMA does not guarantee that studies conducted pursuant to FDAMA Section 111 will result in improved pediatric labeling for two reasons: (1) eligibility for exclusivity is based on submitting a study that is consistent with the FDA's written request, not the conclusiveness or usefulness of the results; and (2) sponsors are "not required to obtain approval of a supplement adding the information gained in the study to the drug's label").

69. See FDCA § 505A; 21 U.S.C. § 355a(b) (Supp. 1997) (requiring the Secretary of the DHHS to consult with experts in pediatric research to develop and publish a list of drugs that may qualify for pediatric exclusivity not later than 180 days from the enactment of the FDAMA).

70. See Priority List, *supra* note 29, at 27,733 (indicating the availability of the first draft of the Priority List, the list of drugs for which additional pediatric information may produce health benefits in the pediatric population).

71. See FDCA § 505A(k); 21 U.S.C. § 355a(k) (Supp. 1997) (providing that the FDA shall conduct a study and report to Congress not later than January 1, 2001).

The study and report shall examine all relevant issues, including—(1) the effectiveness of the program in improving information about important pediatric uses for approved drugs; (2) the adequacy of the incentive

Section 111 market incentives currently are scheduled to expire on January 1, 2002.⁷²

C. The FDA's Mandatory Final Rule

After the 1994 voluntary labeling rule failed to increase the number of products on the market with pediatric labeling,⁷³ the FDA sought to guarantee the safety and effectiveness of drugs for pediatric patients by requiring that sponsors both conduct pediatric studies and include the results of those studies on product labels.⁷⁴ The FDA introduced the proposed rule on August 15, 1997.⁷⁵ The promulgation of the Final Rule occurred on December 2, 1998⁷⁶ and took effect on April 1, 1999.⁷⁷

provided under [Section 505A]; (3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and (4) any suggestions for modification that the Secretary determines to be appropriate.

Id.

72. See FDCA § 505A(j); 21 U.S.C. § 355a(j) (Supp. 1997).

A drug may not receive any six-month period . . . unless the application for the drug . . . is submitted on or before January 1, 2002. After January 1, 2002, a drug shall receive a six-month period . . . if—(1) the drug was in commercial distribution as of the date of enactment of the Food and Drug Modernization Act of 1997; (2) the drug was included by the Secretary on the [Priority List] as of January 1, 2002; (3) the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population and that the drug may provide health benefits in that population; and (4) all requirements of [Section 505A] are met.

Id.; see also *FDA Likely to Interpret Pediatric Sunset Provision Broadly*, FDA WEEK, July 9, 1999, at 1 (noting that the FDA plans to interpret the FDAMA Section 111 sunset provision as broadly as possible to maximize pediatric research). The FDA has not been specific as to how it will interpret the sunset provision, but intends to provide detailed plans in an upcoming guidance document that will cover FDAMA Section 111 and the Final Rule. See *id.* (“FDA plans to clarify how the provision will be interpreted in an upcoming guidance document covering exclusivity.”).

73. Both the Proposed and Final Rule note that the 1994 voluntary rule did not remedy the dearth of pediatric labeling. See *Proposed Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients*, 62 Fed. Reg. 43,900, 43,902 (1997) (codified in scattered sections at 21 C.F.R. (1997)) [hereinafter Proposed Rule] (detailing the results of pediatric labeling actions and the need for additional steps); see also Final Rule, *supra* note 12, at 66,632-33 (citing data to indicate that voluntary efforts had not substantially increased the number of products with adequate pediatric labeling).

74. See *Proposed Rule*, *supra* note 73, at 43,902-03 (describing the Proposed Rule); see also Final Rule, *supra* note 12, at 66,633 (stating that the Final Rule requires manufacturers of new and marketed drugs and biological products to conduct clinical studies on pediatric patients).

75. See *Proposed Rule*, *supra* note 73, at 43,900 (indicating date of proposal).

76. See Final Rule, *supra* note 12, at 66,632 (indicating date of issuance of the Final Rule regulations).

77. See *id.* (indicating that the effective date of the Final Rule is April 1, 1999). Although the Final Rule became effective on April 1, 1999, manufacturers do not have to submit any mandated pediatric studies until December 1, 2000. See *id.*

The Final Rule distinguishes new drugs from currently-marketed drugs.⁷⁸ Under the Final Rule, the FDA presumes that sponsors will study all new drugs⁷⁹ in pediatric patients unless they meet two waiver criteria.⁸⁰ The FDA concluded that sponsors with currently-marketed products must conduct pediatric studies if: (1) the use of the product among pediatric patients is great and the absence of labeling would pose significant risks to those patients, and (2) the product's claimed indications would "represent a meaningful therapeutic benefit over existing treatments" if studied in pediatric patients.⁸¹ If the FDA determines that either a new or currently-marketed drug provides a "meaningful therapeutic benefit" for pediatric patients, then the sponsor must develop and test a pediatric formulation.⁸² Drug sponsors can waive this requirement when reasonable attempts to develop a pediatric formulation have failed.⁸³

("Manufacturers must submit any required assessments of pediatric safety and effectiveness twenty months after the effective date of the rule, unless the assessments are waived or deferred by the FDA."). The reason behind the compliance data is that the FDA estimates that manufacturers will need twenty months to conduct pediatric studies. *See id.* at 66,659. The FDA, however, has begun to require pediatric data in certain instances for applications filed and pending as of April 1, 1999. *See* Implementing the FDAMA Pediatric Study Incentive Provisions and the FDA's Mandatory Pediatric Study Rule: Comments of the PhRMA, 25 (Oct. 5, 1999) (unpublished manuscript, on file with the *American University Law Review*) (noting significant confusion among the Industry and the FDA as to the application of the effective date of the Final Rule).

78. *See* Final Rule, *supra* note 12, at 66,634-36 (distinguishing how the Final Rule will apply to new and currently-marketed drugs and detailing the requirements that such drugs must fulfill to comply with the Final Rule).

79. The FDA defined "new drugs" not only as "new chemical entities" or "new (never-before-approved) biological products," but also as currently-marketed drugs with "new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration for which an applicant seeks approval." *Id.* at 66,634. Thus, it recognizes that substantial changes to currently-marketed products can have a significant therapeutic benefit for pediatric patients. *See id.* (explaining that the expansion of scope was based on the observance that changes in already marketed chemical entities can have as much or more therapeutic significance for children than their original counterparts).

80. The two waiver criteria are: (1) the new drug will not be used in a "substantial number of pediatric patients," and (2) the new drug does not provide a "meaningful therapeutic benefit" over currently existing treatments and therefore, the absence of that information will not pose significant risk to pediatric patients. *See id.* at 66,644 (including waiver where the necessary study is impossible, highly impractical, or poses undue risks to pediatric patients).

81. *See id.* at 66,653-54 (noting the final form of the FDA's two requirements that trigger pediatric studies for currently-marketed products).

82. *See id.* at 66,652 (stating that the FDA believes that drugs and biologics that offer meaningful therapeutic benefit to pediatric patients must provide pediatric formulations that ensure the bioavailability and accurate dosing of those products).

83. *See id.* (indicating that the reason for the waiver is that producing pediatric formulation can be difficult or impossible). The FDA will consider a number of variables to determine whether a drug sponsor has made a reasonable attempt to develop a pediatric formulation, including the importance of the product to pediatric patients, the costs of developing a pediatric formulation, and the market

The Final Rule is intended to be product-specific.⁸⁴ Even though FDAMA Section 111 applies to the active moiety of a drug product, the Final Rule is limited to a specific indication for a specific drug product.⁸⁵ Insofar as FDAMA Section 111 and the Final Rule overlap,⁸⁶ the FDA will notify sponsors about the possibility of gaining FDAMA market exclusivity.⁸⁷

II. THE FDA'S QUESTIONABLE AUTHORITY AND INTENT TO MANDATE PEDIATRIC STUDIES

Both FDAMA Section 111 and the Final Rule are meant to co-exist in a symbiotic relationship and complement each another.⁸⁸ The FDA justifies issuing the Final Rule as a means to fill in various gaps

protection status of a drug. *See id.* (noting efforts to develop pediatric formulation should increase with product importance and market protection and decrease with the rise of costs). If a product has significant patent life remaining, then the FDA will assume that a drug sponsor will be able to bear greater pediatric formulation development costs. *See id.* ("FDA will assume that manufacturers can incur greater costs for products that have significant patent life or exclusivity remaining.").

84. *See generally id.* at 66,632 (explaining that the Final Rule applies to manufacturers of "certain" drugs and biologics). The Final Rule applies to each new drug, which is evaluated on an individual basis. *See id.* at 66,640. The FDA has indicated that for currently-marketed drugs, it intends to require studies for specific marketed products. *See id.* at 66,654.

85. *See* Anti-Infective Drugs Advisory Comm., *supra* note 20, at 55 (statement of Dianne Murphy, M.D., Associate Director of Pediatrics, FDA). Dr. Murphy stated that:

[U]nder the rule studies are required. You need to evaluate the need for pediatric information on only the drug product and indication being reviewed at the time that that application is in house, versus FDAMA, the studies are voluntary, you evaluate the need for pediatric information on the entire moiety.

Id.

86. Both FDAMA Section 111 and the Final Rule overlap insofar as they both apply to new and currently-marketed drugs. *See* FDCA § 505A(a), (c); 21 U.S.C. § 355a(a), (c) (1994 & Supp. 1997) (providing market exclusivity for new and already marketed drugs); Final Rule, *supra* note 12, at 66,634-36 (highlighting requirements of the Final Rule with respect to not yet approved products and marketed products).

87. *See* Anti-Infective Drugs Advisory Comm., *supra* note 20, at 52-53 (statement of Dianne Murphy, M.D., Associate Director of Pediatrics, FDA) (noting that where FDAMA Section 111 and the Final Rule overlap, the FDA will notify the manufacturer to explore the possibilities of gaining FDAMA Section 111 exclusivity).

88. *See generally id.* at 34-56 (discussing the FDA's views as to the relationship between FDAMA Section 111 and the Final Rule, including how the Final Rule will address gaps left by FDAMA Section 111, and the voluntary nature of FDAMA Section 111 compared to the mandatory nature of the Final Rule). The PhRMA, an industry trade organization, recently requested from the FDA a more detailed guidance document that specifically addresses the interrelationship between FDAMA Section 111 and the Final Rule. *See PhRMA Drafts Letter to FDA Listing Concerns with Pediatric Policy*, FDA WEEK, Aug. 13, 1999, at 1, 10 (expressing the Industry's wish for the FDA to issue a guidance document that will provide details on the interaction between FDAMA Section 111 and the Final Rule).

that FDAMA Section 111 does not address.⁸⁹ The Industry believes that the FDA lacks the legal authority to mandate pediatric studies,⁹⁰ and if left unchallenged, the FDA will expand its authority further after FDAMA Section 111 sunsets on January 1, 2002.⁹¹

A. The FDA's Lack of Authority to Mandate Pediatric Testing

The Final Rule ignores history and precedent and seeks to expand the FDA's regulatory authority beyond the authority granted to it by Congress.⁹² The FDA's statutory justification for mandating pediatric studies is a pastiche of statutory provisions that appears to give legitimacy to the FDA's position.⁹³ Statutory analysis, case law, and even remarks made by FDA officials support the proposition that the FDA lacks the legal authority to mandate pediatric testing.

1. The FDA's misplaced reliance on statutory authority

The FDA relies on section 701(a) of the FDCA to buttress its

89. See Final Rule, *supra* note 12, at 66,633 (stating that the FDA believes the Final Rule is necessary to increase the number of drug and biological products that have adequate labeling, despite the FDA's expectations that FDAMA Section 111 will provide a substantial incentive for sponsors to conduct pediatric studies). The Final Rule identifies four specific gaps to help give legitimacy to the Final Rule: (1) FDAMA exclusivity is limited to specific categories of products and excludes "certain categories of antibiotics, biologics and off-patent products"; (2) the voluntary nature of the FDAMA will leave many drugs and pediatric age groups unstudied, as drug sponsors will target only the most profitable drugs; (3) the FDAMA will not accomplish increased pediatric labeling in neonates, infants, and young children because of the high costs to drug sponsors for clinical studies in those pediatric populations; and (4) the FDAMA does not guarantee that the information discovered in pediatric studies will appear on the product's label, and serves only an informational purpose. See *id.*

90. See *infra* Part II.A (arguing that the FDA lacks the authority to mandate pediatric studies and noting the Industry's concerns regarding the FDA's authority).

91. Various statements made by the FDA and the Industry allude to the Industry's concern that after FDAMA Section 111 expires, the FDA will expand its authority. See, e.g., Anti-Infective Drugs Advisory Comm., *supra* note 20, at 52-53 (statement of Dianne Murphy, M.D., Associate Director of Pediatrics, FDA) (noting the Industry's concern that the Final Rule will overwhelm FDAMA Section 111); Letter from Carl B. Feldbaum, President, *The Biotechnology Industry Organization*, to Jane E. Henney, M.D. Commissioner, Food and Drug Administration 1 (June 22, 1999) (on file with the *American University Law Review*) (urging that the FDA balance and judiciously implement the Final Rule with respect to FDAMA Section 111).

92. Congress granted the FDA the authority to issue regulations for the efficient enforcement of the FDCA. See FDCA § 701(a), 21 U.S.C. § 371(a) (1994 & Supp. 1997). The FDA's authority is limited, however, insofar as any agency actions must reasonably relate to the purposes of the FDCA. See *United States v. Nova Scotia Food Prod. Corp.*, 568 F.2d 240, 246 (2d Cir. 1977) (discussing how a regulation issued under section 701(a) of the FDCA will be sustained so long as it is reasonably related to the purposes of the FDCA).

93. See *infra* Part II.A.1 (arguing that the FDA pieces together numerous statutory provisions to support its asserted authority to mandate pediatric testing).

argument for mandated studies.⁹⁴ This section authorizes the FDA to issue regulations for the “efficient enforcement of the [FDCA].”⁹⁵ Even an expansive interpretation of the FDA’s cited statutory authority to mandate pediatric studies cannot accommodate FDA’s propositions for new or currently-marketed drugs.⁹⁶

a. New drugs

The FDA has historically interpreted section 505 of the FDCA⁹⁷ to allow drug sponsors to select the “conditions of use”⁹⁸ for which a drug will be labeled and marketed.⁹⁹ This statutory interpretation

94. See Final Rule, *supra* note 12, at 66,657 (stating that section 701(a) of the FDCA is the basis of the FDA’s authority to mandate pediatric studies for drug manufacturers). The FDA also relies on section 351 of the Public Health Service Act to require manufacturers of biologics to conduct pediatric studies. See *id.* Section 31 of the Public Health Service Act requires that all biological products be “safe, pure, and potent” to obtain a license to manufacture or prepare biological products. See Public Health Service Act § 351, 42 U.S.C. § 262(a)(2)(B)(i)(II) (Supp. 1997).

95. See FDCA § 701(a); 21 U.S.C. § 371(a) (1994 & Supp. 1997) (“The authority to promulgate regulations for the efficient enforcement of [the FDCA], except as otherwise provided in [section 701 of the FDCA], is hereby vested in the Secretary [of the Department of Health and Human Services].”); See *Nova Scotia Food*, 568 F.2d at 246 (noting that consonant with the Supreme Court’s determination that because the language of the [FDCA] should not be read restrictively, but rather in a manner consistent with the act’s purpose of protecting the public health, a regulation issued under section 701(a) of the [FDCA] will be sustained so long as it is reasonably related to the purposes of the act).

96. See generally Letter from Bonnie J. Goldmann, M.D., Vice President Regulatory Affairs, Merck & Co., Inc., to FDA Dockets Management Branch, Docket No. 97N-0165, at 3 (Nov. 12, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) (arguing that the FDCA does not authorize the FDA to require pediatric studies either for new drugs or currently-marketed drugs); Letter from Alan F. Holmer, President, *PhRMA*, to FDA Dockets Management Branch, Docket No. 97N-0165, at attachment 14 (Nov. 13, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) [hereinafter Holmer Letter] (arguing that because the FDCA does not authorize the FDA to require manufacturers to submit proposed labeling, it lacks the authority to mandate the Industry to conduct safety and effectiveness studies for uses of a drug not selected by the manufacturer). *But see* Letter from Susie Zeegen, *Pediatric AIDS Foundation*, to Michael A. Friedman, M.D., Lead Deputy Commissioner, FDA Docket No. 97N-0165, at 2 (May 13, 1998) (on file at the FDA Dockets Management Branch in Rockville, MD) (“The authority outlined by the FDA along with the proposed rule is a clear articulation of one legal basis for the agency’s actions. . .”).

97. See FDCA § 505; 21 U.S.C. § 355 (1994 & Supp. 1997) (stating the statutory requirements that apply to drugs not yet approved by the FDA for introduction into the U.S. marketplace).

98. *Id.* § 505(d), (e); 21 U.S.C. §§ 355(d), (e) (1994 & Supp. 1997) (stating the conditions under which a new drug application cannot be approved or will be withdrawn if the necessary safety and effectiveness information is not included by the manufacturer for FDA review).

99. See, e.g., *American Pharm. Ass’n v. Mathews*, 530 F.2d 1054, 1055 (D.C. Cir. 1976) (ruling that the FDA was limited to the drug sponsor’s intended uses in the approved labeling to determine the product’s safety and effectiveness). *But see* 37 Fed. Reg. 16,503 (1972) (codified at 21 C.F.R. § 130 (1972)) (stating that the FDA could require NDA sponsors to supplement their applications with research and

receives additional support in subsequent sections of the FDCA, which empower drug sponsors to develop and submit to the FDA labeling information for FDA evaluation and approval “under the conditions prescribed, recommended, or suggested in the [drug sponsor’s] proposed labeling.”¹⁰⁰

The FDA argues that it possesses the authority to mandate pediatric studies or to deem a product without adequate pediatric labeling as mislabeled under sections 502(a),¹⁰¹ 502(f),¹⁰² and 505(d)(7)¹⁰³ of the FDCA, and under sections 201.5¹⁰⁴ and 201.128¹⁰⁵ of the Code of Federal Regulations (“CFR”).¹⁰⁶ Section 502(a) of the FDCA stipulates that product labeling cannot be “false or misleading.”¹⁰⁷ Section 201(n) of the FDCA defines mislabeling as labeling that “fails to reveal factual material . . . with respect to consequences . . . under such conditions for use as are customary or usual.”¹⁰⁸ The FDA contends that drug products prescribed to pediatric patients on an off-label basis become customary and usual conditions under which

investigations necessary to support off-label uses).

100. FDCA § 505(d)(1); 21 U.S.C. § 355(d)(1) (1994 & Supp. 1997); *see also id.* § 505(d)(2), (4), (5); 21 U.S.C. § 355(d)(2), (4), (5) (1994 & Supp. 1997) (noting various subsequent sections of the FDCA that relate to “conditions of use” information required of drug manufacturers when they submit new drug applications to the FDA).

101. *See id.* § 502(a); 21 U.S.C. § 352(a) (1994 & Supp. 1997) (stating that a drug is misbranded if it has a false or misleading label and how the health care economic information should be made available to the Secretary).

102. *See id.* § 502(f); 21 U.S.C. § 352(f) (1994) (noting when the Secretary shall promulgate regulations exempting drugs from having directions for use or warnings on the label).

103. *See id.* § 505(d)(7); 21 U.S.C. § 355(d)(7) (1994 & Supp. 1997) (explaining when the Secretary shall refuse an application for a new drug).

104. *See* 21 C.F.R. § 201.5 (1999) (illustrating how to have adequate directions for use of a drug).

105. *See id.* § 201.128 (explaining how a drug should be labeled with the intended uses of the drug).

106. *See* Final Rule, *supra* note 12, at 66,657 (noting the various statutory provisions under which the FDA has the authority to mandate pediatric studies).

107. *See* FDCA § 502(a); 21 U.S.C. § 352(a) (1994 & Supp. 1997) (“A drug or device shall be deemed to be misbranded—(a) If its labeling is false or misleading in any particular.”).

108. *Id.* § 201(n); 21 U.S.C. § 321(n) (1994). In full, the section states:

If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

Id.

the product is used.¹⁰⁹ The FDA further contends that the absence of information on the customary and usual conditions of use on a product's label denotes false or misleading labeling.¹¹⁰

Sponsors of a New Drug Application ("NDA") cannot predict the customary or usual conditions of use of their product because the drug product is not yet approved.¹¹¹ Following the FDA's logic, drug sponsors will be responsible for predicting all off-label uses of a product and conducting clinical studies so that such information can be included on the product's labeling. Thus, if the drug sponsor fails to study any potential off-label use, then the product will be mislabeled and subject the drug sponsor to FDA enforcement action.¹¹² It clearly is neither the intent nor an acceptable interpretation of section 505 to mandate that drug sponsors predict off-label uses of unapproved new products to gain FDA approval.¹¹³

The FDA unsuccessfully attempts to differentiate off-label uses of a product from pediatric uses.¹¹⁴ In the Final Rule, the FDA commented that it possesses the authority to mandate pediatric studies for customary or usual uses of drugs, but not for conditions a manufacturer does not include in a product's label.¹¹⁵ The customary

109. See Final Rule, *supra* note 12, at 66,657 ("In determining the intended uses of a drug for which it must be adequately labeled, [the] FDA may consider both the uses for which it is expressly labeled and those for which the drug is commonly used.").

110. See *id.* at 66,658 (referring to section 201(n), the FDA stated that "the agency has authority to require a manufacturer to establish the safety and effectiveness of, and adequately label its product for, use of the product in a subpopulation for which the product is not labeled if that use is common or suggested in the labeling").

111. See Holmer Letter, *supra* note 96, at 14 ("Even with unlimited resources, manufacturers cannot study all of the varied uses that physicians might make of prescription drug products.").

112. See, e.g., FDCA §§ 201(p), 301(a), (d), 505(a); 21 U.S.C. §§ 321(p), 331(a), (d), 355(a) (1994 & Supp. 1997) (stating that various provisions of the FDCA that prohibit the introduction of misbranded products into interstate commerce); Final Rule, *supra* note 12, at 66,657 (noting the statutory consequences for violations of the Final Rule).

113. See *American Pharm. Ass'n v. Mathews*, 530 F.2d 1054, 1055 (D.C. Cir. 1976) (ruling that the FDA was limited to the drug sponsor's intended uses in the approved labeling to determine the product's safety and effectiveness); see also James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 78 (1998) (noting various statements made by the FDA where it states that it does not regulate off-label uses).

114. See Final Rule, *supra* note 12, at 66,658 (noting the applicability of the Final Rule to off-label uses but not to the use of a product for conditions not included in the label).

115. See *id.* Specifically, the FDA noted that it has the authority to require pediatric studies of drugs . . . that have or are expected to have clinically significant use among pediatric patients for the claimed indications. The agency has not examined evidence concerning the use of approved products for diseases or conditions not in the label, and the rule does not apply to those situations.

or usual use in pediatric patients of drugs approved for indications in adults are “use[s] of approved products for diseases or conditions not in the label.”¹¹⁶ Therefore, the FDA admits that it does not possess the authority to mandate pediatric studies of possible off-label uses of new drug products in pediatric populations.

b. Currently-marketed drugs

The FDA’s justification to mandate pediatric studies of new products mirrors its arguments to mandate pediatric studies of currently-marketed drug products.¹¹⁷ Here, the FDA supports its authority on section 505(k) of the FDCA.¹¹⁸ Unlike new products that are in the process of seeking FDA approval, currently-marketed products are FDA-approved and already may have developed “customary or usual”¹¹⁹ off-label uses among medical practitioners.

The same false dichotomy between off-label use and “clinical[ly] significant use among pediatric patients”¹²⁰ discussed in the context of new drugs is applicable to currently-marketed drugs.¹²¹ The FDA noted in the Final Rule that “[t]he agency has not examined [off-label] use of approved drugs . . . and the rule does not apply to those situations.”¹²² Therefore, the FDA’s claim of authority over drug sponsors to mandate pediatric studies in currently-marketed drugs also is misplaced.

Two further objections remain with respect to the FDA’s statutory justification to mandate pediatric studies for currently-marketed products.¹²³ First, the FDA’s reliance on section 201.5 of the CFR is

Id.

116. *Id.*

117. *See id.* at 66,657 (noting the FDA’s statutory authority to mandate pediatric studies for currently-marketed drugs).

118. *See* FDCA § 505(k); 21 U.S.C. § 355(k) (1994) (discussing how an applicant for a new drug has to maintain reports and records and how these records need to be accessible to the Secretary).

119. *See id.* § 201(n); 21 U.S.C. § 321(n) (1994) (evaluating a product’s “customary or usual” use as a factor when determining misleading labeling or advertising).

120. Final Rule, *supra* note 12, at 66,658 (stating the FDA’s distinction between off-label use of a drug and a drug which has a clinically significant use due to customary or usual use).

121. *See supra* Part II.A.1.a (explaining the FDA’s false distinction between off-label use and clinically significant use of a drug for new drugs).

122. Final Rule, *supra* note 12, at 66,658.

123. Not discussed in this Comment is the applicability of the Final Rule to generic copies of approved drugs. With respect to generic drugs, the Final Rule makes apparently contradictory remarks. *See id.* at 66,640-41. The Final rule initially states, “[t]his rule does not impose any requirements on studies submitted in support of applications for generic copies of approved drugs that meet the requirements of section 505(j) of the [FDCA].” *Id.* at 66,640. In a subsequent statement, however, the FDA remarks that:

generally applicable to over-the-counter (“OTC”)¹²⁴ drug products.¹²⁵ Thus, applying those labeling provisions to prescription products is contrary to FDA’s historical application of this provision. Second, the FDA’s alleged authority to remedy omissions or misleading information on drug labeling by appropriating capital from drug sponsors to conduct costly clinical studies through a mandatory rule can be accomplished through less intrusive means. The drug sponsor can remedy label omissions or misleading statements of material facts by simply revealing the material fact.¹²⁶ Both of these objections further demonstrate the FDA’s misplaced reliance on statutory authority to justify mandating drug sponsors to conduct pediatric studies.

2. *FDA officials’ acknowledgment of the FDA’s lack of authority to mandate pediatric testing*

At a 1992 annual meeting of the AAP, former FDA Commissioner David Kessler noted the FDA’s lack of authority to mandate pediatric testing.¹²⁷ Although the FDA does not question the accuracy of

petitions submitted under section 505(j)(2)(C) [of the FDCA] for a change in active ingredient, dosage form, or route of administration may be denied if “investigations must be conducted to show the safety and effectiveness of” the change. Thus, if a petition is submitted for a change that would require a pediatric study under this rule, the petition may be denied.

Id. at 66,641. What these dueling statements appear to do is eviscerate, or pre-empt, parts of the FDCA that apply to generic drugs.

124. OTC drug products are products that do not require a prescription from a physician to be purchased or used. The FDA does not regulate OTC products like prescription drugs. *See generally* BEERS, *supra* note 9, § 1.05[D] (discussing OTC review process and how it differs from prescription drugs).

125. *See* 21 C.F.R. § 201.5 (1999) (setting forth how adequately to give directions for the use of a drug on the label).

126. A statement such as, “[s]afety and effectiveness in pediatric patients have not been established” is sufficient to remedy a section 201.5 violation. *See* Specific Requirements on Content and Format, 59 Fed. Reg. 64,240 (1994) (codified at 21 C.F.R. § 201.57(f)(9)(vi) (1994)).

127. 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 the 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.

Holmer Letter, *supra* note 96, at 13 (citing remarks by David A. Kessler, M.D., *Annual Meeting of the American Academy of Pediatrics*, at 1 (Oct. 14, 1992)). Although not specific to the FDA’s authority to mandate pediatric studies, the FDA, as far back as 1967 said the following:

It should be noted that the burden of proving the safety and effectiveness of a new drug—or of new uses of an already approved drug—rests on the manufacturer. It is the manufacturer who chooses the indications to be investigated and determines the dosage level for which he will seek FDA approval. It is the duty of the Food and Drug Administration under the law

Commissioner David Kessler's remarks, it argues that, under a longstanding policy, informal expressions of opinion made by its employees do not represent the FDA's position and therefore, are not binding on the FDA.¹²⁸

Recent litigation suggests, however, that remarks made by FDA officials, although not binding, are important in considering FDA authority. For example, in *Brown & Williamson Tobacco Corp. v. FDA*,¹²⁹ the Fourth Circuit used statements by former FDA Commissioner Charles Edwards, as well as Congress' intended delegation of powers to the FDA, to help determine the FDA's lack of authority to regulate tobacco as a drug.¹³⁰ The court ruled that the Commissioner's statements carried significant authority, and clarified the FDA's jurisdiction and authority to regulate tobacco.¹³¹ Similarly, a court can consider former Commissioner David Kessler's statements, as well as Congress' intended function of the FDA as reviewer and approver of submitted test results, as indicative of the FDA's lack of statutory authority to mandate drug sponsors to conduct pediatric studies.¹³²

to decide that proposed usages and levels are both safe and effective, based on the data submitted by the manufacturer.

Id. at 13-14 (citing John Jennings, M.D., *The Rx Label: Basis for all Prescribing Information*, 1 FDA Papers 14-15 (Nov. 1967)).

128. See Final Rule, *supra* note 12, at 66,657 (noting that even comments by an FDA Commissioner are not binding on the FDA). The FDA argues that according to 21 C.F.R. section 10.85(k) "[a] statement or advice given by an FDA employee orally . . . is an informal communication that . . . does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed." 21 C.F.R. § 10.85(k) (1999).

129. 153 F.3d 155 (4th Cir. 1998), *aff'd*, 120 S. Ct. 1291 (2000).

130. When Congress later examined the issue of the FDA's jurisdiction during its consideration of tobacco-specific legislation, FDA Commissioner Charles Edwards testified regarding the FDA's lack of authority over cigarettes and stated that "if cigarettes were to be classified as drugs, they would have to be removed from the market because it would be impossible to prove they were safe for their intended [use]." *Id.* at 168 (quoting *Hearings Before the Consumer Subcomm. of the Senate Comm. on Commerce on S. 1454*, 92d Cong., 239 (1972) (alteration in original)). Again in 1989, the FDA Commissioner stated that:

it doesn't look like it is possible to regulate [tobacco products] under the Food, Drug and Cosmetics Act even though smoking, I think, has been widely recognized as being harmful to human health. . . . The above statements evidence the FDA's position . . . that, as a matter of law, it did not have jurisdiction to regulate tobacco products as customarily marketed.

Id. at 169-70 (quoting *Hearings Before the Subcomm. on Rural Dev., Agric., and Related Agencies of the House Comm. on Appropriations*, 100th Cong., 409 (1989) (statement of FDA Commissioner Jere E. Goyan) (alteration in original)). See generally Richard A. Merrill, *The FDA May Not Regulate Tobacco Products as "Drugs" or as "Medical Devices"*, 47 DUKE L.J. 1071, 1074-82 (1998) (analyzing the history of the FDA's assertions that it did not have the authority to regulate tobacco and tobacco products).

131. See *Brown & Williamson*, 153 F.3d at 170-71 (relying on the FDA's numerous testimonies at congressional hearings to clarify whether the FDA has authority to regulate tobacco).

132. Just as the FDA Commissioner's statements persuaded the *Brown &*

B. The FDA's Intention to Expand Pediatric Testing Requirements After FDAMA Section 111 Sunsets

FDAMA Section 111 and the Final Rule are intended to operate in tandem.¹³³ The Industry, however, must carefully monitor the FDA as it continues to fashion the two policies to ensure that the Final Rule does not engulf FDAMA Section 111.¹³⁴ Various indicators exist that can be construed as an attempt by the FDA to use FDAMA Section 111 to lure the Industry with the carrot of market exclusivity to conduct pediatric studies and then, subsequently subject the Industry to the authority of the Final Rule after FDAMA Section 111 sunsets on January 1, 2002.¹³⁵

1. The FDA's issuance of similar criteria for pediatric testing under the mandatory rule and FDAMA Section 111

Although all innovator drug products with current patent exclusivity¹³⁶ are considered candidates for a six month patent extension under FDAMA Section 111,¹³⁷ Congress required the FDA to publish a list of priority drugs that qualify for pediatric exclusivity.¹³⁸ The FDA consulted with experts in pediatric research and other interested parties, and developed a draft list and qualifications.¹³⁹ In June 1998, the FDA published a final list

Williamson court that the FDA does not have the authority to regulate tobacco, *see id.* at 176, a court considering the FDA's authority to mandate pediatric studies might be persuaded by the FDA Commissioner's statements regarding the FDA's lack of authority to mandate pediatric studies.

133. *See* Anti-Infective Drugs Advisory Comm., *supra* note 20, at 122 (statement of Dr. Daniel Notterman) (describing that the Final Rule and the FDAMA complement each other and can be applied in a synergistic fashion); *see also* FDA, Background Paper—Potential Benefits of Pediatric, at 24 (Apr. 1998) (“The interaction of the FDAMA incentives with pediatric rule requirements is likely to be complex and uncertain”) (source available from FDA).

134. The FDA has indicated that it intends to issue a future guidance document that will clarify how FDAMA Section 111 and the Final Rule are to operate together. *See FDA Likely to Interpret Pediatric Sunset Provision Broadly*, FDA WEEK, July 9, 1999, at 1-2.

135. *See* Wechsler, *supra* note 21, at 20 (“[C]ompanies fear that FDAers who prefer the mandatory approach will delay implementing the voluntary program in an effort to ‘run out the clock’ instead of permitting the incentive program to work in its fairly short four-year trial run.”).

136. *See supra* notes 61-68 and accompanying text (clarifying drugs that qualify for patent exclusivity under current law).

137. *See* Final Rule, *supra* note 12, at 66,632 (explaining that FDAMA Section 111 exclusivity can only attach to drugs with current exclusivity under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act).

138. *See* FDCA § 505A(b), 21 U.S.C. § 355a(b) (Supp. 1997) (stating that the FDA should consult with experts in pediatric research to develop and annually update a “list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population”).

139. *See* Notice, 63 Fed. Reg. 12,815 (1998) (giving notice of the FDA's

“Priority List”) that will be updated on an annual basis.¹⁴⁰ The Priority List identifies three criteria for qualification:¹⁴¹ (1) the drug product must be a “significant improvement compared to marketed products;”¹⁴² (2) the drug must be prescribed at least 50,000 times each year;¹⁴³ and (3) the drug must be in a class of drugs with a dearth of pediatric information.¹⁴⁴

“The final rule established a presumption that all new drugs and biologics will be studied in pediatric patients,”¹⁴⁵ but allows waivers in certain circumstances.¹⁴⁶ All currently-marketed drugs that fulfill two criteria are required to conduct pediatric studies:¹⁴⁷ (1) drugs used in a “substantial number of pediatric patients,”¹⁴⁸ defined as 50,000 pediatric patients,¹⁴⁹ and (2) drugs that may provide a “meaningful

development of a draft list of drugs to be considered for pediatric exclusivity).

140. See Priority List, *supra* note 29, at 27,733. The Priority List is a list of approved drugs that the FDA believes might produce health benefits in the pediatric population and therefore, for which additional pediatric information is necessary. See *id.*

141. In full, the qualifications are:

The drug product, if approved for use in the pediatric population, 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 . . . ; or,

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

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

Priority List, *supra* note 29.

142. *Id.*

143. See *id.* The requirement that a drug be “mentioned” 50,000 times a year includes numerous prescription refills for a single patient. See Final Rule, *supra* note 12, at 66,647. This method can dilute the actual number of pediatric patients using a particular drug.

144. See Priority List, *supra* note 29.

145. Final Rule, *supra* note 12, at 66,634.

146. See *supra* note 80 and accompanying text (noting the criteria a drug sponsor must fulfill to be exempt from the Final Rule). But see Letter from Arthur J. Ammann, M.D., American Foundation for AIDS Research (“AmFAR”), to FDA Dockets Management Branch, Docket No. 97N-0165, at 1-4 (Nov. 11, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) (arguing that the FDA weakens its authority to mandate pediatric studies by allowing waivers in certain circumstances).

147. In full, the requirements are:

[D]rugs and biological products that: (1) [a]re used in a substantial number of pediatric patients for the claimed indications, and where the absence of adequate labeling could pose significant risks; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients, and the absence of adequate labeling could pose significant risks to pediatric patients.

Final Rule, *supra* note 12, at 66,634.

148. *Id.*

149. See *id.* at 66,647 (“Physician mentions of drugs for pediatric use generally fall either below 15,000 per year or above 100,000 per year FDA has therefore chosen 50,000 as the cut-off for a substantial number of pediatric patients.”).

therapeutic benefit over existing treatments”¹⁵⁰ and would jeopardize a pediatric patient’s health without adequate pediatric labeling.¹⁵¹

The FDAMA’s Priority List qualifications are narrow enough to fall within the broader requirements of the Final Rule.¹⁵² After the FDAMA’s market incentives expire on January 1, 2002, drugs listed on the Priority List that failed to earn six months of market exclusivity due to insufficient time to complete studies or the FDA’s lack of expediency¹⁵³ will be required *de facto* to conduct pediatric studies. Although the original purpose of the Final Rule is to act as a gap-filler for FDAMA Section 111, after market incentives sunset in 2002, the Final Rule will be the only remaining regulation.¹⁵⁴

2. *Expanding the reach of the Final Rule as a consequence of National Pharmaceutical Alliance v. Henney*

In a recent case, *National Pharmaceutical Alliance v. Henney*,¹⁵⁵ the generic industry¹⁵⁶ challenged the FDA’s definition of “drug” in section 355A of the FDCA and sought an injunction to prevent the FDA from issuing written requests for pediatric testing.¹⁵⁷ The plaintiffs contended that the FDA should define “drug” narrowly to

150. *Id.* at 66,634.

151. *See id.* (stating that the Final Rule requires pediatric studies of market drugs and biological products that in the absence of adequate labeling could pose significant risks to pediatric patients).

152. *See* CDER, FDA, *Guidance for Industry: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act*, at 17 (Sept. 1999), available at <<http://www.fda.gov/cder/guidance/index.htm>> (“A sponsor could conduct a study that is adequate to meet the requirements of the pediatric rule but that does not meet the terms of a Written Request.”); *see also Analysis of the Pediatric Rule*, THE FOOD & DRUG LETTER, Oct. 1, 1999, at 2 (noting that “[o]nce that grace period ends, the whip could come down for products now granted exclusivity under [FDAMA]”).

153. *See infra* Part II.B.3 (discussing the FDA’s lack of expediency in granting six months of extended market exclusivity under FDAMA Section 111).

154. The imagery created by the requirements to qualify for FDAMA Section 111 exclusivity and to trigger compliance with the Final Rule is that of two concentric circles. The inner circle is the requirements for FDAMA Section 111 exclusivity. The outer circle is the requirements stipulated in the Final Rule. Once FDAMA Section 111 exclusivity sunsets, the inner circle disappears, leaving the drugs previously subject to FDAMA Section 111 subject to the requirements of the Final Rule.

155. 47 F. Supp. 2d 37 (D.D.C. 1999).

156. The Generic Pharmaceutical Industry Association (“GPIA”) joined The National Pharmaceutical Alliance (“NPA”) as plaintiffs. *See id.* at 37. Both organizations are trade organizations that represent the collective opinion of their membership—manufacturers of generic pharmaceutical products.

157. *See id.* at 38. The generic industry sought to enjoin the FDA from issuing pediatric requests to the Industry because a broad definition of the term “drug” as active moiety would allow the Industry to gain market exclusivity for an entire line of products containing a single active moiety. *See id.* at 39. This would have the effect of preventing the generic industry from introducing any product containing the active moiety identified by the FDA as one that qualifies for FDAMA Section 111 exclusivity.

denote a single pharmaceutical product.¹⁵⁸ The FDA and the Industry¹⁵⁹ argued that “drug” should be defined broadly to mean active moiety.¹⁶⁰ The district court held that under *Chevron v. Natural Resources Defense Council, Inc.*,¹⁶¹ the FDA possessed adequate discretionary authority to interpret “drug” as active moiety rather than as single product.¹⁶²

By defining drug as active moiety under section 355A, the FDA now has the opportunity under the Final Rule to expand pediatric testing to entire classes of currently-marketed drugs and their indications. The Final Rule generally requires pediatric testing for an indication of a specific drug product.¹⁶³ The FDA, however, specifically broadened the scope of the Final Rule to include new drug active moieties.¹⁶⁴ Inherently listed in the Priority List are not only the drugs currently indicated, but all of the drugs in which that active moiety exists. After FDAMA Section 111 sunsets in 2002, the FDA can

158. See Plaintiff’s Memorandum in Support of Plaintiff’s Application for Preliminary Injunction at 2, *National Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37 (D.D.C. 1999) (arguing that the term “drug” is limited to a specific drug product rather than a drug substance, which connotes an active moiety). The FDA’s regulations define “drug product” as “a finished dosage form . . . that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.” 21 C.F.R. § 314.3(b) (1999). The FDA’s regulations also define “drug substance” as “the active ingredient intended to furnish the desired pharmaceutical effect.” *Id.*

159. PhRMA intervened in this case. See *National Pharm. Alliance*, 47 F. Supp. 2d at 38 n.1 (noting that the court granted the PhRMA’s unopposed permissive intervention as a defendant). The AAP also attempted to intervene on behalf of the defendants, but the court denied the AAP’s motion. See *id.* at 41 (holding that the AAP’s interests were adequately represented by existing parties).

160. See Defendant’s Memorandum of Law in Opposition to Plaintiff’s Application for Preliminary Injunction at 10-11, *National Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37 (D.D.C. 1999) (arguing that the “close nexus” between the Hatch-Waxman Act, where “drug” is defined as active moiety, and FDAMA Section 111 implies that “drug” is defined as active moiety under FDAMA Section 111).

161. 467 U.S. 837, 842-45 (1984) (establishing a two-part test to review an agency’s construction of a statute that it administers). The two-part test considers: (1) “whether Congress has directly spoken to the precise question at issue,” and (2) “whether the agency’s answer is based on a permissible construction of the statute.” See *id.* at 842-43. The court in *National Pharm. Alliance* determined that the answer to the first question was no and the answer to the second question was yes. See *National Pharm. Alliance*, 47 F. Supp. 2d at 39-40.

162. *National Pharm. Alliance*, 47 F. Supp. 2d at 40. The District Court’s opinion will likely be the final ruling on the issue of the definition of “drug” in FDAMA Section 111, as the generic industry will not appeal the case. See *NPA, GPIA Decide not to Appeal Ruling Favoring FDA in Pediatrics Case*, FDA WEEK, Apr. 23, 1999, at 1, 10 (discussing both the NPA’s and the GPIA’s decision not to appeal the District Court’s ruling, citing both the high cost of litigation and the small chance that an appeal would result in a different ruling as the reason for their decisions).

163. See Final Rule, *supra* note 12, at 66,634.

164. See *id.* The Final Rule also expands the scope of the rule to include new indications, new dosage forms, new dosing regimens, and new routes of administration. See *id.*

argue successfully that, as all drugs mentioned in the Priority List, which it created with the intent to define “drug” as active moiety, meet the requirements to trigger mandatory pediatric studies,¹⁶⁵ it is only logical that all products containing the active moieties of drugs on the Priority List also meet the requirements that trigger mandatory pediatric studies. Expanding the reach of the Final Rule to include new drug active moieties would strengthen the FDA’s justification for broadening the scope of the Final Rule to incorporate drugs previously covered under FDAMA Section 111.

3. *The FDA’s lack of expediency in granting market exclusivity under FDAMA Section 111*

The FDA is slow to grant the market exclusivity incentives promised in FDAMA Section 111.¹⁶⁶ From November 1997 to May 1999, the FDA granted only five (5) six month patent extensions.¹⁶⁷ This lack of expediency in granting exclusivity has caused the innovator Industry to speculate that the FDA prefers to exhaust the potential of FDAMA Section 111 market incentives and allow the Final Rule to take effect.¹⁶⁸ The FDA’s lack of expediency is attributed to time and budgetary constraints.¹⁶⁹ These excuses, however, are inconsistent with the FDA’s stated priority to provide better health care for children.¹⁷⁰ If the FDA’s priority is to provide better health care for children, then that, instead of time and budgetary concerns, should be the guiding principle behind granting exclusivity.

165. See *supra* Part II.B.1 (asserting that FDAMA Section 111 requirements fall within the Final Rule requirements to mandate pediatric studies).

166. See *Pediatric Exclusivity Statistics* (last modified Oct. 1, 1999) <<http://www.fda.gov/cder/pediatric/wrstats.htm>> (cataloging the number of proposed pediatric study requests (“PPSR’s”), the number of PPSR’s acted upon, and the total PPSR’s pending action for various drugs).

167. See Dianne Murphy, M.D., *Exclusivity Statistics* (last modified July 2, 1999) <<http://www.fda.gov/cder/present/dia-699/mu2-dia99/index.htm>>. The web site refers to a presentation made at the FDA by Dianne Murphy, M.D., Associate Director for Pediatrics, FDA, to update interested parties on the progress of FDAMA Section 111.

168. See Wechsler, *supra* note 21, at 20 (discussing companies’ fear that the FDA prefers the mandatory approach and that this preference will delay the implementation of the voluntary program in an effort to prevent the program from working in its four year trial run).

169. See *Rep. Greenwood Questions FDA Pediatric Review Allocation of Resources*, THE PINK SHEET, May 31, 1999, at 6 (expressing Congressional concern for the FDA’s failure to grant exclusivity under FDAMA Section 111 and attributing it to poor allocation of resources).

170. See Final Rule, *supra* note 12, at 66,632 (discussing the history of FDA initiatives to improve children’s health through more effective labeling and prescription regulations).

C. A Legal Challenge from the Industry Contesting the Validity of the FDA's Authority to Mandate Pediatric Testing Would be Imprudent on the Part of the Innovator Industry

In light of the arguments against the FDA's statutory authority to mandate pediatric studies,¹⁷¹ a strong possibility exists that the innovator Industry will initiate court proceedings against the FDA.¹⁷² Although it is likely to prevail on the merits, an Industry challenge to the FDA's authority may result in a loss of the opportunity to capitalize on any successes FDAMA Section 111 accrues.¹⁷³ Moreover, such a challenge may have the adverse side-effect of coalescing public support against the Industry.¹⁷⁴

1. The FDAMA would likely sunset and no pediatric testing would occur

If the innovator Industry chooses to initiate a legal challenge against the FDA's authority to mandate pediatric studies under the Final Rule, it will harm all parties with interests at stake.¹⁷⁵ Litigation

171. See *supra* Part II.A (arguing that the FDA lacks the authority to mandate pediatric studies).

172. Various comments submitted to the FDA regarding its authority to mandate pediatric studies suggest the possibility that the Industry would seek to enjoin the FDA from implementing the Final Rule. See *supra* note 96 and accompanying text (challenging the FDA's legal basis for mandating pediatric studies under the Final Rule and alluding to the possibility of legal action). In addition, the FDA has acknowledged the likelihood of a legal challenge from the Industry. See Anti-Infective Drugs Advisory Comm., *supra* note 20, at 179 (statements of Mr. Tim Westmoreland, Esq., Public Policy Representative, Elizabeth Glaser Pediatric Aids Foundation) (stating that the PhRMA is considering, or has considered, a lawsuit challenging the FDA's authority to implement the Final Rule).

173. See *infra* notes 175-76.

174. The Industry's reluctance to adhere to the requirements of the Final Rule has already begun to coalesce negative reactions. See, e.g., Letter from Arthur J. Ammann, M.D., AmFAR, to FDA Dockets Management Branch, Docket No. 97N-0165, at 3 (Nov. 11, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) ("It is unfortunate that some members of the pharmaceutical industry are already attempting to incite the public against the pediatric community by suggesting that a requirement for pediatric data will slow drug development for adults. This is offensive.").

175. In the unlikely scenario that the FDA prevails in court, the decision would set a precedent for the FDA to be able to appropriate private funds for any sub-population whose medical treatment needs are not fulfilled by the Industry. For example, the FDA could mandate studies and product labeling for geriatric patients, AIDS patients, or pregnant women. In fact, the FDA has already proposed labeling for geriatric patient populations. See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling, 62 Fed. Reg. 45,313 (1997) (codified at 21 C.F.R. § 201.57 (1997)) (establishing a geriatric use subsection in prescription drug labeling); see also Medical Policy Coordinating Comm. ("MPCC"), FDA, *Draft Guidance for Industry: Content and Format for Geriatric Labeling*, at 1 (Dec. 1998), available at <<http://www.fda.gov/cder/guidance/index.htm>> (providing guidance to the Industry on how to submit geriatric labeling of human prescription drugs and biological labeling under the

is a lengthy and costly initiative for both sides. The Industry would seek to enjoin implementation of the Final Rule during court proceedings until a final decision is rendered. FDAMA Section 111 exclusivity, scheduled to sunset on January 1, 2002, would likely expire before the conclusion of any litigation. In that event, the innovator Industry will lose the opportunity to capitalize on the successes of FDAMA Section 111. Of greatest concern, however, is that without the FDAMA or the Final Rule, drug sponsors will not conduct pediatric studies and children will once again become "therapeutic orphans."¹⁷⁶ Thus, litigation is an imprudent course of action for the Industry to pursue.

2. A legal challenge would coalesce negative public sentiment

A legal challenge to the FDA's authority to mandate pediatric studies under the Final Rule could also have the potential effect of coalescing negative public sentiment against the Industry.¹⁷⁷ The public might interpret Industry opposition to the Final Rule as protecting only market interests while sacrificing pediatric health care.¹⁷⁸ Regardless of whether the Industry's interests in defeating the Final Rule are legally sound, the public likely will compare its willingness to conduct pediatric studies for market incentives to its unwillingness to conduct pediatric studies under a voluntary system.¹⁷⁹ The FDA may argue that without sufficient voluntary compliance, the only alternative that remains in light of the importance of pediatric health is an attempt to mandate pediatric studies.¹⁸⁰ Thus, the overall

newly established geriatric use subsection).

176. Without either FDAMA Section 111 or the Final Rule, the only remaining regulation will be the 1994 "pediatric use" provision, which the FDA has already labeled a failure. *See* Anti-Infective Drugs Advisory Comm., *supra* note 20, at 29-30 (statement of Dianne Murphy, M.D., Associate Director of Pediatrics, FDA) (noting the failure of the 1994 rule based on the fact that 77% of label submissions to the FDA had no improvements in pediatric labeling).

177. Congress has introduced numerous bills caricaturing the Industry as a greedy business. *See, e.g.*, Prescription Drug Fairness for Seniors Act of 1999, H.R. 664, 106th Cong. (1999) (alleging that prescription drug manufacturers engage in discriminatory practices that compel Medicare beneficiaries to pay more for drugs than the drug manufacturers' most favored customers). Numerous bills have also been introduced to create a Medicare drug benefit, which would force drug manufacturers to sell their products at drastically reduced rates. *See, e.g.*, Access to Rx Medications in Medicare Act of 1999, S. 841, 106th Cong. (1999) (proposing the creation of a Medicare drug benefit to cover outpatient prescription drugs).

178. *See* Reply Memorandum in Support of Plaintiff's Application for Preliminary Injunction, at 31-32, *National Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37 (D.D.C. 1999) (arguing that Congress did not create FDAMA Section 111 to establish a substantial economic benefit for innovator companies).

179. *See supra* note 176 and accompanying text (noting the failure of the 1994 rule).

180. *See* Final Rule, *supra* note 12, at 66,632-33 (discussing the failure of the 1994

effect of litigating the FDA's authority to implement the Final Rule would damage the Industry's image by making it look like a health care provider concerned about profits rather than the public's well-being.¹⁸¹

III. RECOMMENDATION

Based on the success of FDAMA Section 111,¹⁸² a more prudent course of action would be for the FDA and Industry members to reach a consensus and seek an extension of FDAMA Section 111 for an additional five years in exchange for assistance with off-patent drug pediatric studies.¹⁸³ Under an agreement designed to gain the FDA's support to re-authorize FDAMA Section 111 in exchange for off-patent drug pediatric studies, the original sponsors of off-patent drug products would work with the AAP and the federally-funded Pediatric Pharmacology Research Units ("PPRUs")¹⁸⁴ of the National Institute of Child Health and Development ("NIHCD")¹⁸⁵ to develop

voluntary rule and concluding that only a mandatory rule will accomplish the FDA's goal of increased substantive pediatric labeling).

181. The fact, however, is that the Industry is a dedicated health care provider. In 1999, the innovator Industry is reportedly developing 207 drugs for children. *See New Medicines in Development for Children*, in PHRMA 1999 SURVEY 1.

182. At a recent conference, FDA officials declared that the impact of FDAMA Section 111 "has been enormous." *Pediatric Studies Proposals Double Under FDAMA Exclusivity*, DICKINSON'S FDA REV., July 1999, at 15. The report continues to note that "[f]rom 1991 to 1997, sponsors submitted 77 proposals for pediatric studies, but in 1998 they submitted 130," and that the dramatic increase in pediatric studies is attributable to the incentives offered in FDAMA Section 111. *See id.*

183. Off-patent drugs are important to pediatric health. For over three decades, the AAP has sought pediatric studies and formulation of new drugs, currently-marketed drugs, and off-patent drugs. *See Reauthorization of the Prescription Drug User Fee Act and Food and Drug Administration Reform: Hearing before the House Commerce Comm. Subcomm. on Health and the Environment*, 105th Cong. at 10-11 (1997) (statement of Sanford N. Cohen, M.D., Associate Director of the National Institute for Environmental Health Services at Wayne State University on behalf of AAP). Whereas new and currently-marketed drugs are manufactured and sold for the benefit of one patent holder, most off-patent drugs may have multiple manufacturers and distributors. Therefore, legislative and regulatory proposals, such as FDAMA Section 111 and the Final Rule, have focused on new and currently marketed drugs. *See, e.g.* Final Rule, *supra* note 12, at 66,663. Many off-patent drugs, however, are used in pediatric patients on an off-label basis. *See Reauthorization of the Prescription Drug User Fee Act and Food and Drug Administration Reform: Hearing before the House Commerce Comm. Subcomm. on Health and the Environment*, 105th Cong. at 11 (1997) (statement of Sanford N. Cohen, M.D., Associate Director of the National Institute for Environmental Health Services at Wayne State University on behalf of AAP). Pediatric studies of off-patent drugs would greatly enhance the array of therapies available to pediatric patients, and would continue to provide incentives for the Industry to conduct pediatric testing. *See id.* at 19.

184. The PPRU's are a cooperative network of organizations that serve as a resource for studies of drug action and disposition in infants, children and adolescents. *See National Institute of Child Health and Human Development* (visited Sept. 10, 1999) <<http://www.nichd.nih.gov/htm>>.

185. The National Institute of Child Health and Development ("NIHCD"), a

a list of important off-patent drugs that should be labeled for pediatric use.¹⁸⁶ The NICHD's PPRUs would compile the information and conduct pediatric studies, the results of which would appear on product labeling.¹⁸⁷

Both FDAMA Section 111 and its legislative history support such a reauthorization.¹⁸⁸ Original versions of the BPCA did not contain a sunset provision¹⁸⁹ and subsequent versions established a sunset date of 2004.¹⁹⁰ Most convincing is the argument that FDAMA Section 111 anticipated the need for reauthorization. FDAMA Section 111 stipulates that before January 1, 2001, the Secretary of the DHHS must report to Congress on the progress made under the FDAMA provision.¹⁹¹ The report should include any recommended

department of the National Institutes of Health ("NIH"), administers numerous research programs, including clinical research in pediatric patients. NIHCD would be an ideal candidate to conduct the necessary research on off-patent drugs. Original drug sponsors could lend assistance by providing the necessary scientific and research information necessary for NIHCD to complete its studies. *See Public Meeting on FDA's Proposed Regulations to Increase Pediatric Use Information for Drugs and Biologics*, Oct. 27, 1997 (visited Oct. 29, 1999) <<http://www.fdc.gov/cder/meeting/transcript/1027.ped.htm>> (discussing novel approaches to obtaining pediatric labeling for off-patent products, including a collaborative agreement between the Industry, the FDA, and the PPRUs).

186. *See* Letter from John D. Siegfried, M.D., *PhRMA*, to FDA Dockets Management Branch, Docket No. 97N-0165, at 4 (Nov. 13, 1997) (on file at the FDA Dockets Management Branch in Rockville, MD) (stating that the PPRU's of the NICHD would be a good resource for developing ways to gather the information for off-patent pediatric drugs).

187. *See generally* Sanford N. Cohen, M.D., *The Pediatric Pharmacology Research Unit (PPRU) Network and its role in Meeting Pediatric Labeling Needs*, 104 *PEDIATRICS* 644 (1999) (providing an excellent overview and description of the history and responsibilities of the PPRU network).

188. In fact, the American Medical Association's ("AMA") House of Delegates supports extending FDAMA's Section 111 incentive and has suggested that Congress award drug manufacturers some type of market exclusivity for conducting pediatric studies for off-patent drugs. *See* The American Med. Ass'n, *H-120.961 Unlabeled Indications of Food and Drug Administration-Approved Drugs*, at 2 (1997) (stating that "[l]egislation should be enacted that provides extensions of marketing exclusivity for the product to manufacturers who complete pediatric studies that lead to pediatric labeling," and urging innovator companies to work with the NIH to ensure that off-patent drugs are studies in pediatric patients).

189. *See, e.g.*, S. 3337, § 2, 102d Cong. (1992) (containing no sunset provision).

190. *See, e.g.*, S. 713, § 3, 105th Cong. (1997) (providing that no market exclusivity be granted for studies commenced after January 1, 2004).

191. *See* FDCA § 505A(a); 21 U.S.C. § 355a(a) (Supp. 1997).

The study and report shall examine all relevant issues, including—(1) the effectiveness of the program in improving information about important pediatric uses for approved drugs; (2) the adequacy of the incentive provided under [Section 505A]; (3) the economic impact of the program on taxpayers and consumers, including the impact of the lack of lower cost generic drugs on patients, including on lower income patients; and (4) any suggestions for modification that the Secretary determines to be appropriate.

Id.

modifications to Section III.¹⁹² Thus, the Secretary's report should include a recommendation that FDAMA Section 111 be re-authorized in exchange for Industry assistance with off-patent drug pediatric studies.

CONCLUSION

Almost eighty percent of all prescription drugs are not indicated for use in pediatric patients. Both the Final Rule and FDAMA Section 111 serve the purpose of increasing the number of prescription drugs specifically indicated for use in pediatric patients. The FDA's solution to remedying the lack of pediatric labeling is to mandate that drug manufacturers conduct pediatric studies. Meanwhile, Congress currently seeks to provide incentives to drug manufacturers, who conduct pediatric studies, by offering the possibility of extended patent life. Both these initiatives, however, are inherently troubled because the FDA does not possess the statutory authority to mandate pediatric studies under the Final Rule and Congress drafted FDAMA Section 111 to expire in 2001. Without the existence of either initiative, the number of prescription drugs indicated for pediatric patients will likely remain unchanged.

The FDA and the Industry should work together to reach a consensus and reauthorize FDAMA Section 111 for an additional five years in exchange for assistance with off-patent drug pediatric studies. The success of FDAMA Section 111 proves that it can act as a vehicle to increase the number of drugs for use in pediatric patients. In exchange for the reauthorization of FDAMA Section 111, the FDA would be able to accomplish its goal of providing pediatric information for the entire universe of drug products—new drugs, currently-marketed drugs, and off-patent drugs. Of greatest importance is that by fostering an atmosphere of cooperation between the FDA and the Industry, children will no longer be treated as “therapeutic orphans.”

192. See FDCA § 505A(k)(4); 21 U.S.C. § 355a(k)(4) (Supp. 1997).