TRANSITION FROM THE CARROT TO THE STICK: THE EVOLUTION OF PHARMACEUTICAL REGULATIONS CONCERNING PEDIATRIC DRUG TESTING

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Prior to the 1990s, only about twenty percent of all drugs prescribed for children in the United States were ever tested for safety or efficacy.[1] While the Clinton administration examined various aspects of healthcare in the United States, as part of their efforts to create a national healthcare system,[2] Congress became more aware of how drug approval procedures neglected our nation's children.[3] By allowing the pharmaceutical industry to gain Food and Drug Administration ("FDA") approval for drugs that were never tested in pediatric populations, Congress passed the burden of determining the proper pediatric indications and dosing for prescription drugs individually to millions of pediatricians across the nation.[4] Because most drugs were not approved for use on children, pediatricians individually assessed safety risks, efficacy, and dosage for their patients, without guidance from either the manufacturer or the FDA.

By forcing pediatricians to prescribe potentially life-saving pharmaceuticals to children without any guidance or testing, the FDA shifted the risk of liability associated with adverse effects from pharmaceuticals to the prescribing pediatricians.[5] Pediatricians were forced to take this risk in order to treat their patients. Left with choosing between allowing a sick child to go untreated and risking liability for adverse side effects from a prescription, pediatricians relied on their own experience and anecdotal evidence for guidance in deciding whether to prescribe a drug, and if so, what dosage.[6]

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1. S. REP. NO. 107-79, at 1 (2001) ("only 20 percent of prescription medications . . . have been tested and approved for use in children . . .").

2. *See* Note, *Universal Access to Health Care*, 108 HARV. L. REV. 1323 (1994-1995) (noting failure of the Clinton health care plan despite thorough examination).

3. *See* S. REP. NO. 105-43, at 3 (1997) (describing the lack of "systematic means for testing the safety and efficacy of drugs on the pediatric population.").

4. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900 (Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, and 601) ("[t]he absence of pediatric labeling information may sometimes require the physician caring for children to choose between prescribing drugs without well founded dosing and safety information or utilizing other, potentially less effective, therapy.").

5. *Id.*

6. Veronica Henry, *Off-Label Prescribing: Legal Implications*, 20 J. LEGAL MED. 365, 379 (1999) (noting that courts have found that physicians, not drug manufacturers, may be liable for adverse reactions that occur with off-label use, and that many drugs used on children are used off-label). *See also* Lauren Hammer Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 146 (2003) (explaining that pediatricians were forced to estimate proper dosages, expose patients to an unknown risk of adverse effects, and worry that they would improperly medicate their

In the late 1990s, Congress and the FDA began a series of initiatives to relieve the burden placed on pediatricians.[7] These initiatives included motivating drug companies to conduct pediatric clinical trials of their drugs in exchange for extended patent terms, and providing funds to conduct pediatric clinical trials when drug manufacturers were not interested in conducting clinical trials themselves.[8] The initiatives even required pediatric drug testing as a condition for drug approval.[9]

The incentive based program, providing patent term extensions to drug companies for providing pediatric clinical testing data, is heralded as a success for rapidly increasing the number of drugs tested on children.[10] The program, however, is also heavily criticized as a windfall for the pharmaceutical industry because the patent term extensions result in profits that can be thousands of times greater than the cost of conducting the pediatric clinical trials.[11]

This paper briefly summarizes the history of incentive based legislation, focusing on its impact in establishing a pediatric clinical trial infrastructure. While pharmaceutical regulatory efforts directed toward the safety of children rapidly and repeatedly changed in the last ten years, this paper discusses how many of those changes are in form more than in substance. The paper also describes the various legislative attempts to promote more pediatric testing through both incentive and mandatory programs. The transition from voluntary to mandatory pediatric drug testing is explored in terms of the effects on children's safety and economic costs under both regimes. Finally, evolution to a regulatory scheme based exclusively on mandating drug testing in children as a prerequisite to drug approval is endorsed as an appropriate development in response to pubic concern over children's safety and the high cost of prescription drugs for all Americans.

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patients, raising concerns about their own malpractice liability).

7. See Breslow, *supra* note 6, at 148-151 (detailing the history of the legislative and regulatory initiatives).

8. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended in scattered sections of 21 U.S.C. & 42 U.S.C.).

9. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,633 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, and 601); Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. & 42 U.S.C.).

10. 149 CONG. REC. S9811-02 (daily ed. July 23, 2003) (statement of Sen. Kennedy).

11. Rachel Zimmerman, *Child Play: Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids - By Doing Inexpensive Trials, They Gain 6 More Months Free From Generic Rivals - FDA: Law Does Some Good*, WALL ST. J., Feb. 5, 2001 at A1 ("The studies required to gain six more months of marketing exclusivity are relatively small and inexpensive, costing anywhere from $200,000 to $3 million. But the extended exclusivity that results can be very valuable. It will boost drug-company sales by more than $4 billion, by the Journal's calculations, which compare six months of sales while a drug has marketing exclusivity against typical six-month sales of the drug after generic competition hits.").

First, this note presents a brief summary of the social, legislative, and political issues surrounding pediatric drug testing in part I. Part II presents details of the effectiveness of the patent term, or pediatric exclusivity, extensions in motivating the pharmaceutical industry to enthusiastically initiate pediatric testing. The patent term extension serves as a "carrot" to entice cooperation with the government in conducting pediatric clinical trials, but mandatory testing legislation, "the stick," is discussed in part III. Part IV presents an analysis of a proposed transition from a dual regulatory scheme, including both patent term extension incentive and mandatory programs, to a single program that mandates pediatric trial data for drug approval when appropriate. Finally, support for allowing the "carrot" provisions to sunset, as scheduled, in 2007 is proffered in part V.

I. BACKGROUND

A. Children as Therapeutic Orphans

The United States has a complicated history surrounding the use and testing of prescription drugs on children.[12] For the most part, the lack of attention to child safety resulted from the relatively small number of children who took prescription drugs. Historically, children represented such a small patient population that efforts directed to formalizing data on a drug's safety and efficacy in children were viewed as unnecessary.[13]

Additionally, in the absence of data indicating otherwise, physicians often prescribed drugs with the belief that safety, efficacy, and side effects were the same in children as they were in adults. Doctors typically adjusted dosage for a child based on his or her body weight (sometimes instructing a parent to cut a pill in half, or crush a pill and administer a fraction of the powder to the child).[14] Without information to suggest that pharmacokinetics[15] differ between adults and

12. The exploitative history of clinical research on children and the heightened fear of tort liability resulting from adverse effects during clinical testing have discouraged pharmaceutical testing in children. *See* Breslow, *supra* note 6, at 135-144 (describing history of abuses and tort liability surrounding pediatric pharmaceutical testing).

13. *See* Michael S. Labson, *Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients*, 6 J. HEALTH CARE L. & POL'Y 34, 35 (2002) (explaining that in most cases there are comparatively small numbers of pediatric patients with any particular disease, and pharmaceutical use in children is expected to generate little additional revenue).

14. 149 CONG. REC. S3897 (daily ed. Mar. 18, 2003) (statement of Mr. Dewine, for himself, Mrs. Clinton, Mr. Gregg, Dr. Dodd, and Mr. Kennedy).

15. Pharmacokinetics is the "process by which a drug is absorbed, distributed, metabolized and eliminated by the body." THE AMERICAN HERITAGE® DICTIONARY OF THE ENGLISH LANGUAGE 1357 (3d ed. 1992).

children, researchers were well advised not to involve pediatric patients in drug trials, thus avoiding putting the drug trial participants at risk.[16]

Researchers now understand that drug responses can differ significantly between children and adults, and that dosage extrapolation based on body weight often results in severe misadministration of a drug.[17] This understanding surfaced as a result of the many clinical trials undertaken in response to patent term extension incentives.[18]

With little understanding of the importance of clinical drug trial data on children's safety, children were protected from the risks of clinical trials, and few clinical trials were conducted on children.[19] Health care professionals hesitated to engage in clinical testing of drugs on children in part for ethical reasons.[20] Because children lack the legal capacity to consent to clinical trial participation, it was considered unethical to conduct testing on them as non-consenting human subjects.[21]

The government played a critical role in addressing these concerns by instituting extensive regulations and guidelines governing any clinical trial involving children.[22] The safety of the clinical trial participants is protected by detailed rules, governing procedures of consent and monitored by qualified researchers, with special attention directed towards detecting and preventing exploitation and abuse of study participants.[23]

The ethical position against pediatric drug testing transitioned in the face of evidence of different drug response physiology between adults and children. With this evidence, concerns about administering drugs that have never been tested on children outweighed ethical concerns over subjecting children to

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16. Duane Alexander, *Regulation of Research with Children: The Evolution from Exclusion to Inclusion*, 6 J. HEALTH CARE L. & POL'Y 1, 2-3 (2002).

17. 149 CONG. REC. § 9811-02 (daily ed. July 23, 2003) (statement by Sen. Kennedy).

18. Dianne Murphy, Director, Office of Pediatric Therapeutics, Presentation at the DIA Annual Meeting: Impact of Pediatric Initiatives (June 15, 2004), *available at* http://www.fda.gov/oc/opt/presentations/pediatrics.ppt (explaining that studies conducted in response to exclusivity incentives revealed that pharmacokinetics in children are more variable than anticipated).

19. *See* Labson, *supra* note 13, at 35-36 (discussing the many reasons why pediatric studies were not carried out prior to the introduction of patent term extensions).

20. *See* Alexander, *supra* note 16, at 2-3.

21. *Id.*

22. *See* Breslow, *supra* note 6, at 138-139 (discussing legislation that created standards for clinical research in children).

23. See Alexander, *supra* note 16, at 5-6 (describing the development of standards including a protection committee for each protocol involving children to "oversee the selection of individual subjects for research, monitor the continuing willingness of the child and parents to participate in the research, design procedures to intervene in the research if necessary to protect the subject, and evaluate the reasonableness of the parent's and subject's consent.").

controlled clinical trials. In this context, legislation was born to promote, but not mandate, pediatric drug trials.[24]

The FDA acquiesces to drug sponsors when they declare the intended use of drugs in a new drug application.[25] The FDA would approve drugs and the accompanying label information for only those indications listed in the drug approval application.[26] If the manufacturer did not attempt to secure approval for pediatric indications, the FDA submitted to the position that the agency lacked authority to require test data or labeling information relevant to pediatric approval.[27] As a result of this policy, most drug manufacturers did not seek approval for pediatric indications, and therefore, were not required to perform any tests regarding safety or efficacy in children.[28] Because so few drugs contained pediatric indications, pediatricians were not in a position to avoid prescribing a drug merely because the drug was not labeled for pediatric use.

B. Unregulated Off-Label Use of Prescription Drugs Prevalent

Manufacturers have been successful in avoiding involvement in pediatric testing largely because off-label drug use is unregulated.[29] Doctors are free to prescribe drugs however they deem appropriate. Because off-label prescribing is permitted, and in many cases encouraged by drug manufacturers, pharmaceutical companies make their drugs available to all patient populations, even when they seek approval for limited populations and indications.[30]

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24. *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (establishing a six-month patent term incentive to drug manufacturers submitting pediatric testing data).

25. Mitchell Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1280 (2005).

26. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1853-55 (1996).

27. *See* Ass'n of Am. Physicians & Surgeons v. U.S. Food and Drug Admin., 226 F. Supp. 2d 204, 218 (D.D.C. 2002). In holding that the FDA did not have the authority to require manufacturers to provide data for indications they had not requested in the drug approval application, the court relied on statements by the FDA Commissioner saying that the FDA lacked that authority. *Id.* at 218.

28. Christopher-Paul Milne, *Exploring the Frontiers of Law and Science: FDAMA's Pediatric Studies Incentive*, 57 FOOD & DRUG L.J. 491, 493 (explaining that stricter requirements for pediatric drug approval in the 1970s and the permitted practice of "off-label" drug prescriptions combined to create an environment that discouraged drug manufacturers from conducting clinical trials).

29. *Id.* at n.13.

30. Oates, *supra* note 25, at 1280. A drug receives FDA approval only for the particular use for which it was tested, but once the drug is approved for any particular use, the FDA does not regulate how the drug may be prescribed. *See* 21 U.S.C. § 355 (2000). This permits drugs that have been tested and approved only for adult use to be prescribed by a physician for pediatric patients. *See* Ass'n of Am. Physicians and Surgeons, 226 F. Supp. 2d at 217-218.

Although many diseases and ailments are common in both children and adults, many drugs are tested for safety and effectiveness in adults only. As a result, physicians are often forced "to choose between prescribing drugs without well-founded dosing and safety information or utilizing other, potentially less effective, therapy" by prescribing adult-approved drugs to children, but in a smaller dose.[31] This practice is referred to as prescribing "off-label" because the drug is not labeled for pediatric uses.[32]

It is common for physicians to prescribe to children pharmaceuticals only approved for adult use; however, this practice can expose children to various hazards, including giving children an ineffective dose or an overdose, and risking unforeseen or more severe side effects.[33] These hazards exist because:

> Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight . . . or body surface area . . . . Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults.[34]

While the FDA never sanctioned off-label use of prescription drugs, the agency passively endorsed the practice through inaction. Initiatives to encourage and require pediatric drug testing for drugs unlabeled for pediatric use indicates that the FDA now recognizes the practice of off-label prescribing as a serious health concern. These initiatives address health concerns without intruding on a physician's ultimate discretion in treating patients.

C. Recent Pediatric Pharmaœutical Testing Development and Benchmarks

Before Congress acted to legislate, the FDA initiated a response to pediatricians' concerns about the lack of information regarding drug indications for children.[35] The FDA produced the 1992 FDA Proposed Rule on Pediatric Labeling and Extrapolation ("1992 Rule") to encourage manufacturers to provide additional data and analysis that could support pediatric indications, without

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31. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900 (Aug. 15, 1997).

32. *See* Ass'n of Am. Physicians & Surgeons, 226 F. Supp. 2d at 206. "An off-label use is the prescription of a drug by a doctor for a condition not indicated on the label or for a dosing regimen or patient population not specified on the label," and this practice appears to be "generally accepted" in the medical community.

33. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,901 (Aug. 15, 1997).

34. *Id.*

35. Breslow, *supra* note 6, at 151.

requiring manufacturers to undertake costly pediatric clinical trials.[36] The 1992 Rule allowed manufacturers to qualify for a pediatric label without necessarily going through pediatric clinical tests.[37] When the rule was published as the 1994 FDA Final Rule on Pediatric Labeling and Extrapolation ("1994 Rule"), it required any manufacturer who did not submit valid information regarding pediatric safety and effectiveness to include a disclaimer, stating that the drug was not tested for pediatric safety and efficacy.[38]

The FDA hoped the threat of a disclaimer would promote activity on the part of drug sponsors to investigate pediatric indications for drugs, but the 1994 Rule proved to be unsuccessful in promoting a significant response from the industry.[39] The disclaimer simply became an industry standard for most prescription drugs, and pediatricians were still left with the unfortunate choice between prescribing drugs without adequate information concerning efficacy and dosage in children or, leaving sick children unmedicated.[40]

Because the 1994 Rule was unsuccessful at inspiring an industry response, the FDA next moved to force the pharmaceutical industry to be responsible for informing the public about the use of drugs on children. The FDA formulated the 1997 FDA Proposed Rule Requiring Pediatric Studies by the Drug Sponsor ("Proposed Pediatric Rule").[41] The Proposed Pediatric Rule set out to force drug manufacturers to provide information on the safety, efficacy, and use indications in pediatric patients by requiring these data for new drug approval.[42] For drugs already on the market, the Proposed Pediatric Rule would have allowed the FDA

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36. Breslow, *supra* note 6, at 151.

37. *See* Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Proposed Revision of "Pediatric Use" Subsection in the Labeling, 57 Fed. Reg. 47,423, 47,423-24 (Oct. 16, 1992) (codified at 21 C.F.R. pt. 201).

38. *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, 64,241 (Dec. 13, 1994) (codified at 21 C.F.R pt. 201).

39. *See* Breslow, *supra* note 6, at 153. (The FDA requested data from the manufacturers of the ten drugs most prescribed to children, and only one of them submitted results in response to the request).

40. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,900 (stating that "[m]any of the drugs and biological products most widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established").

41. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,902.

42. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,902-43,903 (the proposed rule would require the manufacturer of a new drug to submit safety and effectiveness information on relevant pediatric age groups for the claimed indications prior to approval).

to request pediatric drug trial data from the manufacturers, and failure to comply with the request could result in the drug being deemed misbranded.[43]

Shortly after publishing the Proposed Pediatric Rule, Congress became involved and initiated a new era of pharmaceutical regulations with the Food and Drug Administration Modernization Act ("FDAMA"), which included the Patent Term Extension/Market Exclusivity Provision for Voluntary Pediatric Testing.[44] This legislation introduced a six-month patent term extension when sponsors submitted adequate pediatric testing data.[45] While the patent term extension provision is an incentive for voluntary participation, it appeared that the FDAMA was intended by Congress to work in conjunction with the Proposed Pediatric Rule.[46]

The FDA's activities under the Pediatric Rule[47] were thwarted by legal action. Three organizations, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert (collectively "Plaintiffs"), sued the FDA, claiming the FDA lacked the authority to enact the Pediatric Rule.[48] The Plaintiffs claimed that the Pediatric Rule embodied legislative action outside the administration's authority.[49] In the arguments supporting their position, Plaintiffs pointed to the FDAMA and the Better Pharmaceuticals for Children Act ("BPCA"), stating that Congress had the opportunity to move to a mandatory regime in these pieces of legislation, and instead developed the voluntary regime with attractive incentives to the pharmaceutical industry to elicit participation.[50] Plaintiffs' cited statements by the FDA Commissioner in which

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43. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,902, 43,905.

44. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended in scattered sections of 21 U.S.C. & 42 U.S.C.).

45. *Id.* at 2305.

46. The Senate Report on the Better Pharmaceuticals for Children Act provides: "[The Pediatric Rule] requires the manufacturers of certain new and marketed drugs and biological products to provide adequate labeling for the use of the products in children. The rule is both broader and narrower than the pediatric exclusivity provision enacted by congress [sic] in 1997. When their scopes overlap, Congress provided that pediatric studies required under the rule could also satisfy the requirements for market exclusivity." S. REP. NO. 107-79, at 4 (2001).

47. "The Pediatric Rule" refers to the enacted version of the Proposed Pediatric Rule. The significant features of the Proposed Pediatric Rule remained in the enacted Pediatric Rule. *See* Breslow, *supra* note 6, at 153.

48. *See* Ass'n of Am. Physicians & Surgeons, 226 F. Supp. 2d at 213. ("Plaintiffs argue that 'in no event' do these statutory provisions give the FDA the authority to 'require manufacturers to generate new data and formulations.'").

49. *Id.*

50. *See id.* at 219 (in part, Plaintiffs asserted that Congress demonstrated, through the BPCA, its intention to occupy the field without authorizing the FDA to mandate pediatric testing).

the Commissioner admitted that the FDA is without authority to insist on data outside the indications requested by the manufacturer.[51]

In 2002, the U.S. District Court for the District of Washington D.C. agreed with Plaintiffs and ruled that the 1998 Final Rule was invalid and outside the scope of the FDA's rulemaking authority.[52] During the court proceedings, the patent term extension provisions of the FDAMA sunset, and in its place, the BPCA was enacted.[53] The BPCA extended the patent term extension provision for voluntary pediatric testing and provided a mechanism for obtaining pediatric data when voluntary incentives are ineffective.[54] The BPCA authorizes the FDA to request that the NIH perform clinical drug testing, if funds are available, when a manufacturer declines to voluntarily perform the requested pediatric testing.[55]

Instead of appealing the court ruling on the Pediatric Rule, the FDA asked Congress to codify the Pediatric Rule into law. The result of these efforts is the Pediatric Research Equity Act of 2003 ("PREA").[56] The PREA enables the FDA to require that pediatric testing be performed by either the drug sponsor or a public institution funded by the FDA.[57] The PREA is designed as a last resort in acquiring desired data on pharmaceutical use in children, to be invoked only when the drug sponsors have refused to voluntarily respond to the FDA's request for data.[58]

Like the Pediatric Rule, the PREA was intended to work in conjunction with the patent term extension provisions of the BPCA.[59] Under both provisions, the drug sponsor is, first, requested to voluntarily provide pediatric data.[60] If the patent term extension is not available to the sponsor,[61] or if the extension is not

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51. Ass'n of Am. Physicians & Surgeons, 226 F. Supp. 2d at 217-218 (explaining that "the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses."). *See also id.* at 218 (FDA Commissioner, David Kessler, speaking to the American Academy of Pediatrics, stated the following: "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.").

52. *See id.* at 222.

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

54. *Id.* (in sec. 8, amending FDAMA to extend exclusivity provisions to October 1, 2007; in sec. 3, adding the Program for Pediatric Studies of Drugs.)

55. *Id.*

56. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

57. *See id.*

58. *Id.*

59. *Id.*

60. *See* S. REP. NO. 107-300, at 3 (2002).

61. *Id.* at 6 (patent term extensions are only available during the life of the patent, and only

a sufficient monetary incentive to the sponsor,[62] the FDA may initiate research through the NIH program or employ the provisions of the PREA to require the sponsor to provide the data.

Thus, the current regulatory arena is occupied by a complex assortment of provisions, each designed to promote more clinical drug testing in children. The BPCA is entirely voluntary, providing lucrative patent term extensions where they apply, and if the drug sponsor is not interested in cooperating with the FDA's request for data, the BPCA provides a mechanism for the government to sponsor the clinical testing through grants to third parties.[63] If neither of these mechanisms accomplishes the FDA's goals, then the PREA is invoked, and the drug sponsor can be forced to comply with the requested testing.

D. Political Forces that Influence Regulatory Development

As with most complex issues, there are multiple points of view represented. Consensus exists, although not unanimous, that children suffer from a lack of information on the safety and efficacy of drugs for their use.[64] Children's health advocacy organizations joined the FDA in noting that children's physiology and metabolism are different from adults and that these differences affect drug safety, efficacy, and dosages.[65] Because the differences between adults and children are unpredictable, appropriate pediatric treatment cannot reliably be extrapolated from adult studies.[66]

Even though many agree that pediatric drug testing is important to protect the well-being of the Nation's children,[67] there is little agreement as to whether drug sponsors should be required to supply such data. Pharmaceutical companies have long been reluctant to perform pediatric clinical trials on their drugs because

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one extension can be granted, even if the FDA later asks for additional data, such as for different age groups or formulations that were not available when the initial pediatric studies were performed).

62. S. REP. NO. 107-300, AT 6.(sales of the drug under patent are insufficient to compensate the sponsor for the cost of the requested clinical trials, the sponsor is not obligated to pursue the patent term extension).

63. Best Pharmaceuticals for Children Act, Pub. L. No. 108-155, 115 Stat. 1408 (2002).

64. *See* 149 CONG. REC. H11567-02 (daily ed. Nov. 19, 2003) (statement of Mr. Bilirakis).

65. *See Ass'n of Am. Physicians & Surgeons*, 226 F. Supp. 2d at 205 n.1 (amici curiae, supporting the FDA included the American Academy of Pediatrics, the Elizabeth Glaser Pediatric AIDS Foundation, and the Pediatric Academic Societies).

66. Michelle Meadows, *Drug Research and Children*, FDA CONSUMER, Jan./Feb. 2003, at 12, 14.

67. *But see* Press Release, Association of American Physicians and Surgeons, AAPS Wins Pediatric Drug Case (Oct. 18, 2002), http://www.aapsonline.org/press/nrpedrule.htm (Executive Director Jane M. Orient statement, "Children are not guineas pigs in a regulatory grab for power. . . . We don't want the government requiring drug companies and doctors to expose children to unnecessary risks. Would you volunteer your child for experimental trials?").

the tests are costly to conduct, expose them to increased liability, and raise difficult ethical issues regarding compensation.[68] Despite these many factors, the pharmaceutical industry readily embraced pediatric clinical trials when the six-month patent extension provisions were instituted.[69] Regardless of the complexity of the issues involved, financial motives remain dominant for the pharmaceutical industry.

Consumer interest groups are vested in the economics of these provisions as well. Any measures to generate pediatric drug testing data will have some cost to the public. Consumer groups and advocates for a conservative government are concerned that the cost of pediatric testing will fall on them, either through taxes or through higher prescription drug prices.[70]

Some children's health advocates, while interested in obtaining safer pharmaceuticals for children, are concerned about protecting children from abuses in clinical testing. They also fear that the creation of a lucrative pediatric testing industry will inevitably lead to abuse and exploitation of vulnerable children and their families.[71]

II. EFFECTIVENESS OF THE CARROT: ANALYSIS OF CHILDREN'S PHARMACEUTICAL SAFETY IMPROVEMENTS THROUGH PATENT TERM EXTENSION INITIATIVES

The six-month patent term extension provisions of the FDAMA and the BPCA prompted several drug companies to initiate pediatric drug trials on their pharmaceutical products that qualified. To qualify for the six-month patent term extension, the drug must (1) have been submitted for approval in a new drug application and (2) be an active moiety for an approved indication that occurs in the pediatric population.[72] The six-month patent term extension is the "carrot"

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68. *See* Milne, *supra* note 28, at 498-504.

69. DEPT. OF HEALTH AND HUMAN SERVS., U.S. FOOD & DRUG ADMIN., THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS 8 (2001), *available at* http://www.fda.gov/cder/pediatric/reportcong01.pdf [hereinafter 2001 STATUS REPORT TO CONGRESS].

70. *See* Zimmerman, *supra* note 11 (explaining that patent term extensions extend the monopoly period, excluding lower priced generics from the market, resulting in higher prescription drug prices due to the absence of generic competition during the monopoly period).

71. *See* Vera Hassner Sharav, *The Impact of the FDA Modernization Act on the Recruitment of Children for Research*, 5 ETHICAL HUM. SCI. & SERV. 83, 108 (2003) ("[T]he shift in public policy since the enactment of the FDA Modernization Act (FDAMA) of 1997 and its financial incentives to industry to test drugs on children, has had a deleterious impact on children's dignity, health and welfare.").

72. U.S. DEPT. OF HEALTH AND HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY: QUALIFYING FOR PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 2 (1999), http://www.fda.gov/cder/guidance/2891fnl.htm [hereinafter

to induce drug companies to pay for costly pediatric testing of pharmaceuticals. This carrot proved to be very attractive to drug sponsors.[73]

While only eleven studies were performed involving pediatric studies in the six years prior to the FDAMA[74], three years after the introduction of the patent extension incentive there were 191 proposals for studies submitted by drug manufacturers.[75] Of those studies proposed, the FDA issued 157 Written Requests.[76] In addition, in its first five years, the patent term extension brought about study results for 107 products.[77] These numbers demonstrate almost a ten-fold increase in the number of pediatric clinical trials performed. For their prompt response to the legislative initiatives, drug manufacturers were richly rewarded, as sixty-three six-month exclusivity periods were granted out of the seventy-one products submitting trials.[78]

Despite the encouraging increase in activity by drug manufacturers in providing much needed pediatric indications for their products, labels for only forty out of the seventy-one products for which data were submitted were changed in the five years following the introduction of patent extensions.[79] Labeling is considered the primary educational tool for the FDA to communicate information concerning the safety, side effects, indications, and appropriate dosage for patients.[80] Prescribing doctors rely on this information, if not from reading the labels themselves, from publications, manuals, and indexes that are commercial compilations of information taken from the product labels.[81] Thus, additional labeling information directed towards pediatric indications, or warnings against pediatric use, may be the best measure of these legislative initiatives' impact on children's safety.

Using the new labeling information as the objective for measuring impact on children's safety, the massive activity in testing, evaluating, and approving exclusivity periods for name-brand drugs may not be resulting in significant

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PEDIATRIC EXCLUSIVITY GUIDANCE].

73. *See* Zimmerman, *supra* note 11 (noting that Eli Lilly gained $831 million in sales during its six-month patent term extension on PROZAC™, and Schering-Plough had an additional $975 million in sales of CLARITIN™ due to the pediatric exclusivity extension).

74. 2001 STATUS REPORT TO CONGRESS, *supra* note 69, at 8.

75. *Id.* at 6.

76. *See also* PEDIATRIC EXCLUSIVITY GUIDANCE, *supra* note 72, at 4-5 (describing a written request as a specific document that requests pediatric information for a product).

77. Murphy, *supra* note 18.

78. Robert Steinbrook, *Testing Medications in Children*, 347 NEW ENG. J. MED. 1462 (2002). As of October 14, 2005, patent term extensions had been granted for 114 drugs under the FDAMA and BPCA. *See* U.S. Food & Drug Admin., Approved Active Moieties to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act, http://www.fda.gov/cder/pediatric/exgrant.htm (last visited Nov. 19, 2005).

79. Steinbrook, *supra* note 78.

80. 149 CONG. REC. H11570-1 (2003) (statements of Rep. Greenwood and Rep. Stupak).

81. Oates, *supra* note 25, at 1279-80.

advancements in safety for children. For example, only forty new labels were issued after drug manufacturers labored to produce and submit 320 detailed study proposals to the FDA.[82] The FDA then expended resources to review and evaluate all of these detailed proposals. In 253 cases, the FDA responded with Written Requests that typically modified and set forth additional requirements for the proposed studies.[83] While the FDA does not report statistics concerning just how many studies were performed, seventy-one products had studies submitted, and of those, a little more than half resulted in changes to labeling.[84]

In addition to the lack of substantive labeling changes, the FDA has been criticized for the long delays between when the sponsor is granted a patent term extension in exchange for submitting pediatric drug use data and when any resulting labeling changes take effect.[85] Patent term extensions are granted when the drug sponsor satisfies the testing requirements set forth in the Written Request, and labeling changes come after the FDA examines and evaluates the submitted data.[86] Many drugs that had label changes received their patent term extension several months before any labeling change took effect, and in some cases, the labeling delay was well over one year.[87] Because the incentive is granted upon completion of the studies, the sponsors have little incentive to work expeditiously to finalize a labeling change in cooperation with the FDA.

The initial flurry of pediatric drug testing, which was generated immediately following the enactment of the FDAMA, may be a consequence of the Act's sunset provision, as the Act was set to sunset in 2002.[88] Because of the strong support of the FDAMA, the BPCA was passed, essentially reenacting the patent term provisions.

Some of the major developments coming out of these studies include new labeling indications for a variety of drugs. In some cases, the new labels provide guidance to doctors on how to prescribe the drug to pediatric patients, how and what to monitor, and what side effects may occur.[89] Some changes indicate the

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82. *See* Steinbrook, *supra* note 78.

83. *Id.*

84. *Id.*

85. *See* 149 CONG. REC. H11570-1 (2003) (statement of Rep. Stupak).

86. *See id.*

87. *See* U.S. Food & Drug Admin., Pediatric Exclusivity Labeling Changes as of November 23, 2005, http://www.fda.gov/cder/pediatric/labelchange.htm (last visited Jan. 11, 2005). The delay between the grant of exclusivity and labeling changes vary from days to nearly two years. Label changes for Ziagen (for treating HIV infection) occurred three days after exclusivity was granted, whereas labeling changes for Clarinex (a seasonal allergy treatment) occurred nineteen months after exclusivity was granted. *Id.*

88. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

89. *See* U.S. Food & Drug Admin., *supra* note 87.

drug is simply not effective in children, while others indicate that the drug is unsafe and should not be prescribed to children.[90]

Examples of some of the major label changes include fluoxetine, marketed as PROZAC™, which had pediatric indications added to its label.[91] Fluoxetine is a selective serotonin reuptake inhibitor ("SSRI") for treating Major Depressive Disorder ("MDD") and Obsessive Compulsive Disorder ("OCD").[92] Information was added to the fluoxetine label, stating that effectiveness was established for MDD in eight to seventeen year-olds and for OCD in seven to seventeen year-olds.[93] Additional labeling information concerning side effects reported decreased weight gain with the use of fluoxetine as well as with other SSRIs.[94] These label changes were the result of a single nineteen-week clinical trial, in which pediatric patients treated with fluoxetine "gained an average of 1.1cm [sic] less in height . . . and 1.1 kg less in weight . . . than those treated with placebo."[95] The labeling information also indicated that height and weight should be monitored periodically in pediatric patients treated with fluoxetine.[96]

In exchange for their cooperation, PROZAC's manufacturer, Eli Lilly, received a six-month patent term extension, resulting in several hundred million dollars in additional revenue, as lower-priced generic forms of fluoxetine were excluded from the market for six additional months.[97]

Even though Eli Lilly was compensated hugely for its efforts,[98] the public gained information through labeling changes, as a result of the pediatric testing performed. In contrast, a six-month patent term extension was granted on paroxetine, sold by GlaxoSmithKline ("GSK"), under the name PAXIL™ and there were no labeling changes made as a result of the submitted studies.[99] Paroxetine was not approved for use in children, nor was there any information added to the label reflecting a lack of efficacy in children.[100] The submitted data

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90. *Id.*

91. U.S. Food and Drug Admin., *supra* note 87.

92. *Id.*

93. *Id.*

94. *Id.*

95. *Id.*

96. U.S. Food and Drug Admin., *supra* note 87. SSRIs remain controversial drugs for children because of their potential for causing suicidal thoughts and behaviors in a subset of users. Oates, *supra* note 25, at 1286-87.

97. Zimmerman, *supra* note 11.

98. Breslow, *supra* note 6, at 167 (The average pediatric clinical trial costs less than $4 million).

99. *See* U.S. Food & Drug Admin., *supra* note 87 (paxil/paroxetine is not listed, indicating there has been no labeling change); U.S. Food & Drug Admin., *supra* note 78 (paroxetine was granted exclusivity).

100. *See* Paxil Label Information, *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (label indicates that Paxil is not approved for use in pediatric patients, and provides warning that "antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with . . .

indicated that paroxetine was ineffective in patients aged less than eighteen years old.[101] GSK received about $1.6 billion in additional sales from the patent term extension, as low-cost generic competitors were excluded from the market, but in return, pediatricians gained no additional safety information on paroxetine.[102]

Pediatric drug testing data still can be valuable even if the drug is not approved for use in children. Some studies revealed that drugs were ineffective for use in treating pediatric patients.[103] Vinorelbine, sold as NAVELBINE™, is used as a chemotherapy to treat certain types of cancer. While vinorelbine is effective in treating adults with cancer, clinical trials showed there was no meaningful clinical activity in reducing a variety of tumors, including recurrent solid malignant tumors such as rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma, and central nervous system tumors in children.[104] This type of labeling information may prevent children with some of the worst kinds of cancer from enduring torturous chemotherapy treatments that have little chance of reducing their tumor activity. When there is no labeling information indicating that the drug is ineffective in children, doctors may unknowingly prescribe an ineffective drug to pediatric cancer patients. Vinorelbine is an example that demonstrates labeling information is valuable, and worthy of an extended monopoly in trade.

Other new labels add information, indicating that the drug is not safe for children.[105] Studies submitted on sumatriptan, sold as IMITRIX™ by GSK for the treatment of migraine headaches, included five clinical trials evaluating sumatriptan in patients ages twelve to seventeen years old.[106] These studies did not establish safety and effectiveness when compared to a placebo.[107] Importantly, adverse effects that are rarely seen in adults, such as stroke, visual loss, and death, occurred in the pediatric population.[108] The label was changed to specifically indicate that the use of sumatriptan is not recommended in patients younger than eighteen years old.[109] This type of information is critical

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psychiatric disorders").

101. *Anti-Depressant Pediatric Trials: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Energy and Commerce* (2004), *available at* 2004 WL 2030786. (Statement of Janet Woodcock, FDA's Acting Deputy Comm'r Operations that [paroxetine] is among the drugs that have not met FDA standards for effectiveness in children).

102. *See* Allan Rubin & Harold Rubin, *Patents and Prescription Drugs-Part II* (2005), http://www.therubins.com/legal/patext2.htm (with sales of about $3.2 billion for Paxil in 2002, a six-month exclusivity extension on its patent that provides about $1.6 billion in additional sales, half of the sales for 2002 because generic competition remains excluded from the market).

103. *See* U.S. Food & Drug Admin., *supra* note 87.

104. *Id.*

105. *Id.*

106. *Id.*

107. *Id.*

108. U.S. Food & Drug Admin., *supra* note 87.

109. *Id.*

to the safety of children and worth the cost of extending manufacturers' monopoly by granting a patent term extension.

Of the first forty label changes under the "carrot" legislation, thirty-three percent (12/40) of the newly labeled products had significant changes for dosing or risk, and seventy percent (28/40) had extended age and safety profiles.[110] As of the end of October 2005, the FDA requested 715 drug studies in 309 total written requests, and the projected number of patients involved in the requested studies was over 44,713.[111] Based on the sheer volume of data collected in response to the "carrot" provided in patent term extensions, the legislative initiatives appear to have the desired impact. Certainly the legislation was effective in garnering participation by drug manufacturers in performing pediatric clinical trials.

Drug manufacturers are willing to pay for expensive pediatric studies only when the economics justify the expense. As a result, many important drugs are not tested by the manufacturers, because the economic investment will not likely be returned through sales.

While the BPCA provides a mechanism to gather data on drugs that no longer have patent protection or market exclusivity, the FDA requested pediatric data from sponsors of only ten of these drugs.[112]

IV. USING THE STICK: ANALYSIS OF THE TRANSITION FROM INCENTIVE-BASED TESTING TO MANDATORY TESTING

The FDA and Congress instituted a program to mandate pediatric testing through the Pediatric Rule and PREA, because they recognized the failings of the patent term incentives in achieving all of their pharmaceutical safety goals. The PREA was intended to work in conjunction with the BPCA and not intended to apply to drugs that qualify for a patent term extension under the BPCA or other voluntary provisions under the BPCA.[113] As Senator Kennedy described, the bill requires that the FDA:

> must first provide an opportunity for [pediatric] studies to be conducted under the provisions of the Best Pharmaceuticals for Children Act. However, if a product's manufacturer does not agree promptly to perform such studies voluntarily, and if funds are not sufficient so that the NIH or the Foundation for the NIH does not contract or issue a grant for conduct of the studies within a set period of time, FDA may invoke the authority in this legislation to require the studies. Although FDA

110. U.S. Food & Drug Admin., *supra* note 87.

111. Food & Drug Admin., Studies Breakdown Report for Issued Written Requests (as of November 30, 2005), http://www.fda.gov/cder/pediatric/breakdown.htm (last visited Jan. 2, 2006).

112. U.S. Food & Drug Admin., *supra* note 78.

113. S. REP. NO. 107-79, at 4 (2001).

> never used this authority under its Pediatric Rule, we expect [under the PREA] FDA to use it as necessary to ensure that drugs and biological products that are already approved are studied in children when other mechanisms to get them studied fail.[114]

Legislators also recognized that pediatric testing is not appropriate for all drugs, and allowed manufacturers to escape mandatory testing requirements through provisions in the PREA.[115] For example, drugs designed to treat adult ailments, such as Alzheimer's Disease, would not be required to be tested on children, and would be eligible for partial or complete waivers.[116] Also available under the PREA are deferrals, which specifically address the concern that required pediatric studies delay approval of a beneficial drug to adults.[117] A deferral addresses this concern by allowing a drug to be approved while pediatric tests are pending or expected, thus not delaying the approval for use in adults.[118]

The PREA distinguishes new drugs from already-marketed drugs.[119] Sponsors of new drugs

> may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents . . . ."[120]

Thus, drug manufacturers, under the PREA, may be obligated to study their product on pediatric populations, even if the drug is not explicitly marketed or labeled for children's use. In addition, the "applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit [to such patients] over existing therapies . . . ."[121]

The PREA applies to already-marketed drugs as well, but it has a narrower scope. For already-marketed drugs, the FDA still may require a manufacturer to submit an application containing adequate evidence to support dosage and administration in pediatric populations.[122] The FDA also may require an applicant to develop a pediatric drug formulation for an already-marketed drug.[123]

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114. 149 CONG. REC. S9814 (daily ed. July 23, 2003) (statements by Sen. Kennedy).

115. *See* Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 505B(a)(4), 117 Stat. 1936.

116. *Id.*

117. 21 U.S.C. § 355(c)(a)(3) (2005).

118. *Id.*

119. 21 U.S.C. § 355(a)(b); 21 U.S.C. § 355(a)(c) (2005).

120. 21 C.F.R. § 201.23(a) (1998).

121. *Id.* The term "meaningful therapeutic benefit" is defined as "a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population."

122. 21 U.S.C. § 355a(c) (2005).

123. 21 C.F.R. § 201.23(a) (1998).

For an already-marketed drug, the FDA can require pediatric testing only if the lack of adequate labeling poses significant risks to pediatric patients; and either (1) the drug is "used in a substantial number of pediatric patients for the labeled indications"[;] or (2) "[t]here is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications . . . ."[124]

The PREA is well equipped to compel compliance. If a manufacturer fails to provide the required information, the FDA is authorized to seek a federal court injunction to declare that the product is "misbranded or an unapproved new drug . . . ."[125] The FDA may request other injunctive relief or seizure of misbranded products.[126] Lastly, the FDA may withdraw approval of the drug or biological product; however, this action is appropriate only in rare cases.[127]

While there has been surprisingly little activity reported under the PREA, the FDA began several actions under the Pediatric Rule, which was largely adopted in the PREA. Between April 1999 and December 2002, the FDA received 517 New Drug Applications.[128] From these 517 applications, the FDA issued 264 waivers, absolving the applicant drug manufacturers from conducting pediatric clinical trials.[129] The FDA granted 206 deferrals, and received 129 applications with completed studies, although only sixty-seven of those applications with completed pediatric studies were not covered by the patent term extension incentive.[130]

Under the Pediatric Rule, out of 517 applications filed, 470 applications were granted waivers of deferrals; thus, ninety percent of applications were excepted from satisfying the Pediatric Rule requirements.[131] Before any pediatric drug testing initiatives, about eighty percent of drugs were approved without any pediatric clinical testing data.[132] After the incentive programs were instituted, that figure fell to about seventy-five percent of approved drugs.[133] At this point, "mandatory" pediatric testing has not dramatically improved the percentage of drug applications undergoing pediatric testing.

The PREA may not be prompting the massive drive to pediatric testing as the patent-term extension incentive has, but it has provided important information

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124. 21 C.F.R. § 201.23(b) (1998).

125. 21 C.F.R. § 201.23(d) (1998).

126. *See* 21 U.S.C. § 332 (2005) (injunction proceedings) and 21 U.S.C. § 334 (2005) (seizure).

127. 21 C.F.R. § 201.23(d) (1998).

128. Food & Drug Admin., Pediatric Rule Update, http://www.fda.gov/cder/pediatric/rulestats.htm (last visited Nov. 20, 2005).

129. *Id.*

130. *Id.*

131. *See id.*

132. 145 CONG. REC. S2576-02 (daily ed. Mar. 11, 1999).

133. *See* Breslow, *supra* note 6, at 159.

on several drugs that would have otherwise remained untested. Some of the drugs that underwent clinical studies are drugs that have long been prescribed to children, although never formally studied for safety, side effects, or dosage indications. These drugs include Acculate, for the treatment of asthma, Humalog, an insulin injectable for treating juvenile diabetes, and Ritalin, for treating attention deficit hyperactivity disorder.[134] These drugs were found safe for children, and information concerning appropriate indications and use of drugs are now available.[135] For example, Acculate was tested in children as young as five years old, but was approved for use only in children aged seven years and older.[136] For Humalog, labeling changes included additional information about the appropriate dilution of the drug for pediatric patients.[137] Lastly, Ritalin was approved only for use in patients six to twelve years old, as a result of its clinical testing.[138]

Information from the clinical trials required by the PREA certainly contributes to the safety of children who are being prescribed or would have been prescribed the drugs in the absence of the information, but there is a serious cost for this information.

The PREA has been law only for a short amount of time, so it is difficult to detect its impact on the early stages of drug development. Drug innovators may be factoring in the costs of mandatory pediatric drug trials when deciding on which diseases to spend precious research dollars. One concern is that an unintended consequence of the PREA will be that our drug innovation "pipeline" will be filled with drugs to treat erectile dysfunction, infertility, and Alzheimer's disease, while drug manufacturers try to avoid being subject to the PREA by failing to affect a substantial number of pediatric patients.

IV. TRANSITION FROM DUAL VOLUNTARY AND MANDATORY REGIME TO SINGULAR MANDATORY REGIME.

The patent term extension incentives played a critical role in motivating the pharmaceutical industry to participate in long avoided and dreaded pediatric studies. All previous efforts to entice drug companies to conduct pediatric tests were unsuccessful in overcoming the industry's reluctance to swallow pediatric drug testing as a part of doing business in the pharmaceutical industry. Patent term extensions provided the economic windfall necessary to persuade the industry to participate.

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134. *See* Food & Drug Admin., *Pediatric Rule Labeling Changes, available at* http://www.fda.gov/cder/pediatric/pedrule_labelchange.htm (last visited Feb. 14, 2006).

135. *Id.*

136. *Id.*

137. *Id.*

138. *Id.*

The pharmaceutical industry, the FDA, and the public understand the importance of data gathered under the incentives to the safety of children. While the significance of the data is appreciated more now that tests demonstrated significant differences between children and adults in pharmacokinetics, the public is bearing a disproportionate share of the costs for these data. Under the current dual system of the BPCA and PREA, the public bears a disproportionate cost by paying higher prices for drugs protected under patent six months longer than they otherwise would be. This can cost prescription drug users hundreds of millions of dollars per drug.[139]

When the drug does not enjoy large sales, the drug company may avoid bearing the cost of pediatric testing while continuing to benefit from the sales the drug produces. Because the pharmaceutical industry is willing to perform the tests to receive a patent term extension, the industry should be able to bear the costs of testing less profitable drugs.

As the industry and the public grow to expect and demand pediatric drug testing respectively, a regime of mandated pediatric tests is preferred. The costs of all pediatric testing will be absorbed into the price of all drugs, including the blockbuster drugs with billions in sales, as well as the less profitable products. Now that a pediatric testing infrastructure is established, and expertise has been generated in the community,[140] it is appropriate for pediatric clinical trials to be demanded of all appropriate drugs.

V. CONCLUSION

The patent term extension incentives are utilized disproportionately by the sponsors of high selling drugs, resulting in enormous profits to manufacturers, even though these drugs may be prescribed infrequently to children. In contrast, requests for pediatric data on inexpensive, off-patent drugs, such as antibiotics that are frequently prescribed to children, may (1) be rejected by the manufacturer; (2) denied by the NIH and associated Foundation if funding is insufficient; and (3) required, but enforceable, only through court order.

The incentive provisions were essential in preparing the pharmaceutical industry and the government for a regime of mandatory testing. The potential windfall for the industry motivated drug manufacturers to develop an infrastructure for conducting pediatric testing. The windfall has come at the expense of all prescription drug users. With the pediatric infrastructure established, the elimination of the patent term extension incentive and a transition to a mandatory testing regime is appropriate. The patent term

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139. *See* Breslow, *supra* note 6, at 168 (estimated additional revenue from granted exclusivity includes $975 million for Claritin, $831 million for Prozac, $648 million for Glucophage, $290 million for Pepcid, and $1.4 billion for Prilosec).

140. *See* 2001 STATUS REPORT TO CONGRESS, *supra* note 69, at ii.

extension provision of the BPCA will sunset in 2007,[141] providing a default opportunity to transition to a mandatory regime, allowing the mandatory testing regime set forth in the PREA to dictate drug approval and regulation.

141. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (sec. 8, extending exclusivity provisions to October 1, 2007).