Order Code RL33986

CRS Report for Congress

FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective

May 1, 2007

Susan Thaul
Specialist in the Regulation of Prescription Drugs and Biologics
Domestic Social Policy Division

Congressional Research Service

Prepared for Members and Committees of Congress

FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective

Summary

The Best Pharmaceuticals for Children Act (BPCA, P.L. 107-109) and the Pediatric Research Equity Act (PREA, P.L. 108-155) allow the Food and Drug Administration (FDA) to offer financial and regulatory incentives to manufacturers for testing their products for pediatric use. Unless Congress acts, both programs will end on October 1, 2007. FDA has approved for adult use many products never tested in children. Yet clinicians often prescribe them for children believing that the safety and effectiveness demonstrated with adults would hold for younger patients. However, this off-label prescribing results in children receiving ineffective drugs or too much or too little of a potentially useful drug. Some side effects are unique to children, or children of specific ages, including effects on growth and development. Studies show that drugs vary in bioavailability in children, which depends on the maturation and development of organs and other factors.

About 75% of drugs have not had pediatric studies. The market has not been able to overcome the economic, ethical, legal, and mechanical obstacles that make manufacturers reluctant to conduct these tests. FDA had tried to spur pediatric drug research through administrative action. With the FDA Modernization Act of 1997 (FDAMA, P.L. 105-115), Congress provided an incentive: in exchange for a manufacturer's completion of pediatric studies according to an FDA written request, FDA would extend its market exclusivity for that product for six months. BPCA gave this program a five-year reauthorization in 2002. From 1997 through November 2006, FDA sent 338 written requests to patent-holding manufacturers; 44% responded and 91% of those conducted the studies and were granted pediatric exclusivity. This resulted in 118 labeling changes — for 87% of the drugs granted exclusivity, but only 35% of the drugs for which FDA requested studies. BPCA also set up study referral processes through the National Institutes of Health (NIH) for off-patent drugs and on-patent drugs for which the manufacturer declined FDA's request. Those programs have yet to yield labeling changes.

To get pediatric use information on the drugs that manufacturers were not studying, in 1998, FDA published the Pediatric Rule requiring that manufacturers submit pediatric testing data at the time of all new drug applications. In 2002, a federal court declared the rule invalid, holding that FDA lacked the statutory authority to promulgate it. Congress gave FDA that authority with PREA. PREA covers drugs and biological products and includes provisions for deferrals, waivers, and the required pediatric assessment of an approved marketed product. From 2003 through 2006, FDA approved more than 372 drugs and biologics; there have been 63 PREA-related labeling changes.

The FDA Revitalization Act (S. 1082, as reported) contains pediatric research provisions, including the continuing of BPCA and PREA. Updates of this report will reflect legislative activity.

Contents

Introduction 1

Background 1

Manufacturers Have Been Reluctant to Test Drugs in Children 4

The Current Laws Evolved from Earlier Attempts 4
- 1979: Rule on Drug Labeling 4
- 1994: Revised Rule 5
- Food and Drug Administration Modernization Act of 1997 6
- 1997: The Pediatric Rule 6

BPCA and PREA: Laws to Encourage Pediatric Drug Research 7
- The Best Pharmaceuticals for Children Act 7
  - Pediatric Exclusivity 7
  - FDA-NIH Collaboration 7
  - Other Provisions 7
- Pediatric Research Equity Act 8
  - New Applications 8
  - Products on the Market 8
  - Other Provisions 9

BPCA and PREA Have Had Some Impact on Pediatric Drug Research 9
- Best Pharmaceuticals for Children Act 9
  - On-Patent Drugs 9
  - NIH Route for Off-Patent Drugs and On-Patent Drugs for Which Manufacturers Declined FDA's Requests for Study 10
  - GAO Study 11
- Pediatric Research Equity Act 11
- Comparison of BPCA and PREA 12
- FDA Activities 12

Congressional Options 13
- Exclusivity 13
- Cost 14
- Labeling 15
  - Whether Pediatric Information Is Required 15
  - Content of Included Pediatric Information 15
- Enforcement 16
- Sunset 17

Bills in the 110th Congress 17

List of Tables

Table 1. Examples of Differences in Effectiveness, Dosing, and Adverse Events for Children Administered Adult-Tested, FDA-Approved Medications 3
Table 2. Administrative and Statutory Efforts to Encourage Pediatric Drug Research 5
Table 3. Two Ways to Describe the Effect of Pediatric Exclusivity on Pediatric Labeling Changes 10
Table 4. Research Status of Drugs That NIH Deemed In Need of Pediatric Studies, by Patent Status 10
Table 5. Content of PREA-Associated Labeling Changes 11
Table 6. Major Differences in the BPCA and PREA Approaches 12

FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective

Introduction

FDA has approved for adult use many drugs never tested in children. Yet clinicians often prescribe them for children believing that the safety and effectiveness demonstrated with adults probably reasonably transfers to younger patients. The data show that this is not always true. To address this situation, earlier Congresses have offered manufacturers incentives to test drugs in children. Two current statutory programs offering such incentives will cease at the end of this fiscal year if the 110th Congress does not act:

- the Best Pharmaceuticals for Children Act (BPCA, P.L. 107-109) and
- the Pediatric Research Equity Act of 2003 (PREA, P.L. 108-155).

This report first provides a background to the development of these laws, including:

- why research on a drug's pharmacokinetics, safety, and effectiveness in children is necessary;
- why the marketplace has not provided sufficient incentive to manufacturers of drugs approved for adult use;
- how the current laws evolved;
- what the current laws — BPCA and PREA — are meant to do; and
- what impact the laws have had on pediatric drug research.

It then outlines some issues that Congress may consider as its discusses how (or whether) to continue the programs beyond September 30, 2007.

Background

A drug cannot be marketed in the United States without Food and Drug Administration (FDA) approval. A manufacturer's application to FDA must include an *Indication for Use* section that describes what the drug does and the clinical condition and population for which drug use is intended. To approve a drug, FDA must find that the manufacturer has sufficiently demonstrated the drug's safety and effectiveness for the specific intended indication (rationale for treatment and its

context) and population specified in the application.[1] The Federal Food, Drug, and Cosmetic Act (FFDCA) prohibits a manufacturer from promoting or advertising a drug for any use not listed in the FDA-approved labeling; only those claims for which FDA has reviewed safety and effectiveness evidence can appear in the labeling. However, the FFDCA does not give FDA authority to regulate the practice of medicine; that responsibility rests with the states and medical professional associations. Once a drug is approved, therefore, a licensed physician may — except in highly regulated circumstances — prescribe it without restriction. A prescription to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling is called off-label use, and is accepted medical practice.

Most of the prescriptions that physicians write for children fall into the category of off-label use. FDA has evaluated the drugs' safety and effectiveness when used to treat adults, but has not seen data relating to their use in children — and thus the labeling does not address indications, dosage, or warnings related to use in children. Faced with an ill child, clinicians must deduce/infer/guess whether the drug might help and what amount of the drug (and frequency of administration) might best balance the drug's intended effect with its anticipated and unanticipated side effects.

Clinicians face an obstacle: children are not miniature adults.[2] At different ages, a body handles a given amount of an administered drug differently, resulting in varying bioavailability. This occurs, in part, because the rate at which the body eliminates a drug (after which the drug is no longer available) varies based on changes in the maturation and development of organs and other factors. Clearance can be quicker or slower in children depending on the age of child, the organs involved, and body surface area.[3]

Errors in prescribing drugs to children, as outlined by the Director of FDA's Office of Pediatric Therapeutics, include unnecessary exposure to ineffective drugs; ineffective dosing of an effective drug; overdosing of an effective drug; undefined unique pediatric adverse events; and effects on growth and behavior.[4] **Table 1**

---

[1] For descriptions and discussions of the FDA procedure for approving new drugs, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul; and FDA, "Drug Approval Application Process," at [http://www.fda.gov/cder/regulatory/applications/default.htm].

[2] David A. Williams, Haiming Xu, and Jose A. Cancelas, "Children are not little adults: just ask their hematopoietic stem cells," *J Clin Invest.*, vol. 116, no. 10, October 2, 2006, pp. 2593-2596; and Stephen Ashwal (Editor), *The Founders of Child Neurology* (San Francisco: Norman Publishing, 1990).

[3] William Rodriguez, Office of New Drugs, FDA, "What We Learned from the Study of Drugs Under the Pediatric Initiatives," June 2006 presentation to the Institute of Medicine, at [http://www.fda.gov/oc/opt/presentations/whatwelearned.ppt].

[4] Dianne Murphy, Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA, "Impact of Pediatric Legislative Initiatives: USA," January 26, 2005 presentation to the European Forum for Good Clinical Practice, at [http://www.fda.gov/oc/opt/presentations/Brussels.ppt]; and Rodriguez, June 2006.

includes some of the examples that FDA scientists have included in recent presentations on pediatric drug development.

Table 1. Examples of Differences in Effectiveness, Dosing, and Adverse Events for Children Administered Adult-Tested, FDA-Approved Medications

Type of difference	Examples of the need for pediatric labeling
Inability to demonstrate effectiveness	• some cancer drugs • buspirone (Buspar) for general anxiety disorder • some combination diabetes drugs
Children require higher doses than adults	• gabapentin (Neurontin) for seizures: in children less than 5 years old • fluvoxamine (Luvox) for obsessive compulsive disorder (OCD): in adolescents (12-17 year olds) • benazepril (Lotensin) for hypertension
Children require lower doses than adults	• famotidine (Pepcid) for gastroesophageal reflux: in patients less than 3 months of age • fluvoxamine (Luvox) for OCD: in 8-11 year old girls
Unique pediatric adverse events	• betamethasone (Diprolene AF, Lotrisone) for some dermatoses: not recommended in patients less than 12 years of age due to hypopituitary adrenal (HPA) axis suppression
Effects on growth and development	• atomoxetine (Strattera) for attention deficit hyperactivity disorder • fluoxetine (Prozac) for depression and OCD • ribaviron/intron A (Rebetron) for chronic hepatitis C

Sources: Presentations by Drs. Dianne Murphy and William Rodriguez, FDA.

Such examples demonstrate the need for studies in children of each drug's pharmacokinetics — uptake, distribution, binding, elimination, and biotransformation rates within the body. Those studies are particularly valuable because doses for some drugs must be *larger* than the adult dose to be effective in children, and because there is great pharmacokinetic variation among children of different ages.

Clinicians need pediatric-specific information in the FDA-approved labeling of drugs to help them decide which, if any, drug to use, in what amount, and by what route to administer the drug. They — and their patients' parents or guardians — need to know what range of adverse events have been noted. That information would come from well-designed and well-conducted studies in children — studies that have been slow to appear.

Manufacturers Have Been Reluctant to Test Drugs in Children

Depending on how one defines the denominator (e.g., all drugs, or all drugs used by children), an estimated 65-80% of drugs have not been tested in children. Why not? The market has not been able to overcome the obstacles — which could be economic, ethical, legal, or mechanical — that make manufacturers reluctant to conduct these tests.

The market for any individual drug's pediatric indications is generally small, providing an economic disincentive for manufacturers to commit resources to pediatric testing. Because young children cannot swallow tablets, the manufacturer might have a mechanical hurdle in developing different formulation (such as a liquid). The ethical and legal difficulties encountered in recruiting adult participants in clinical trials are even greater when seeking children: many parents do not want their children in experiments and liability concerns include not only injury but difficult-to-calculate lifetime compensation.

Congress has offered incentives to manufacturers for pediatric research for two main reasons. First, it is clear that, in treating sick children, doctors will continue prescribing drugs despite insufficient pediatric-use studies. Second, Congress has generally believed that, despite the difficulty in conducting such studies, children could be better served once the research was done.

The Current Laws Evolved from Earlier Attempts

Before the 2002 BPCA and the 2003 PREA, FDA attempted to spur pediatric drug research through administrative action (see **Table 2**).

1979: Rule on Drug Labeling

In a 1979 rule on drug labeling, FDA established a "Pediatric use" subsection. The rule required that labeling include pediatric dosage information for a drug with a specific pediatric indication [approved use of the drug]. It also required that statements regarding pediatric use for indications approved for adults be based on "substantial evidence derived from adequate and well-controlled studies" or that the labeling include the statement "Safety and effectiveness in children have not been established."[5]

Despite the 1979 rule, most prescription drug labels continued to lack adequate pediatric use information. The requirement for adequate and well-controlled studies deterred many manufacturers who, apparently, did not understand that the rule included a waiver option. FDA, therefore, issued another rule in 1994.

---

[5] FDA, "Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs; Final rule," *Federal Register*, vol. 44, no. 124, June 26, 1979, pp. 37434-37467.

Table 2. Administrative and Statutory Efforts to Encourage Pediatric Drug Research

Year	Action
1977	FDA pediatric guidance on "General Considerations for the Clinical Evaluation of Drugs in Infants and Children"
1979	FDA rule on *Pediatric Use* subsection of product package insert: *Precautions* section [21 CFR 201.57(f)(9)] (in 44 Fed. Reg. 37434)
1994	FDA rule revised
1996	FDA guidance on "Content and Format of Pediatric Use Section"
1997	Food and Drug Administration Modernization Act (FDAMA, P.L. 105-115), included the Better Pharmaceuticals for Children Act
1998	FDA Pediatric Rule finalized (effective 1999; invalidated 2002)
2001	Adaptation of HHS Subpart D (pediatric) regulations [45 CFR 36 Subpart D] to FDA-regulated research [21 CFR 50 Subpart D]
2002	Best Pharmaceuticals for Children Act (BPCA, P.L. 107-109)
2003	Pediatric Research Equity Act (PREA, P.L. 108-155)

Source: Adapted from Steven Hirschfeld, Division of Oncology Drug Products & Division of Pediatric Drug Development, Center for Drug Evaluation and Research (CDER), FDA, "History of Pediatric Labeling," presentation to the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, March 4, 2003, at [http://www.fda.gov/ohrms/dockets/ac/03/slides/3927S1_01_Hirshfeld%20.ppt].

1994: Revised Rule

The purpose of the revised rule was to make clear that the "adequate and well-controlled studies" language did not require that clinical trials be conducted in children. The new rule described how FDA would determine whether the evidence was substantial and adequate. A pediatric indication that did not match an approved adult indication (for example, if clinicians would use the drug to treat a different condition in children than its FDA-approved use in adults) would require trials in a pediatric population. However, if the drug would be used in children for the same condition for which FDA had approved its use in adults, the labeling statement regarding effectiveness could be based on adult trials alone. In such instances, FDA might also require pediatric study-based data on pharmacokinetics or relevant safety measures. The 1994 rule continued the 1979 requirement that manufacturers include statements regarding uses for which there is no substantial evidence of safety and effectiveness. It added a requirement that labels include information about known specific hazards from the active or inactive ingredients.[6]

[6] FDA, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection In the Labeling; Final rule," *Federal Register*, vol. 59, no. 238, December 13, 1994, pp.64240-64250.

Food and Drug Administration Modernization Act of 1997

FDAMA (P.L. 105-115), incorporating the provisions introduced as the Better Pharmaceuticals for Children Act, created a Section 505A (21 U.S.C. 355a) in the FFDCA: Pediatric studies of drugs. It provided drug manufacturers an incentive to conduct pediatric use studies on their patented products. In exchange for a manufacturer's completing a pediatric study according to FDA's written request, which included design, size, and other specifications, FDA would extend its market exclusivity for that product for six months.[7] The law required that the Secretary each year publish a list of FDA-approved drugs for which additional pediatric information might produce health benefits. FDAMA also required a report from the Secretary examining whether the new law enhanced pediatric use information, whether the incentive was adequate, and what was the program's economic impact on taxpayers and consumers.

1997: The Pediatric Rule

Also in 1997, FDA issued a proposed regulation that came to be called the Pediatric Rule.[8] The Pediatric Rule mandated that manufacturers submit pediatric testing data at the time of all new drug applications to FDA. [Note: This concept is the basis of the Pediatric Research Equity Act, discussed in the next section of this report.] The rule went into effect in 1999. The Competitive Enterprise Institute and the Association of American Physicians and Surgeons filed a lawsuit against FDA, claiming that the agency was acting outside its authority in considering off-label uses of approved drugs. In October 2002, a federal court declared the Pediatric Rule invalid, noting that its finding related not to the Rule's policy value but to FDA's statutory authority in promulgating it:

> The Pediatric Rule may well be a better policy tool than the one enacted by Congress (which encourages testing for pediatric use, but does not require it) ... It might reflect the most thoughtful, reasoned, balanced solution to a vexing public health problem. The issue here is not the Rule's wisdom ... The issue is the Rule's statutory authority, and it is this that the court finds wanting.[9]

---

[7] Although market exclusivity is a characteristic of patent benefit, the FDA-granted exclusivity is not a patent extension; rather, it means that, during the six-month period, FDA would not grant marketing approval to another identical product (usually a generic). For more discussion of pharmaceutical patents and marketing exclusivity, see, for example, CRS Report RL33288, *Proprietary Rights in Pharmaceutical Innovation: Issues at the Intersection of Patents and Marketing Exclusivities*, by John R. Thomas.

[8] FDA, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final rule," *Federal Register*, vol. 63, no. 231, December 2, 1998, pp. 66632-66672.

[9] U.S. District Judge Henry H. Kennedy Jr. quoted in Marc Kaufman, "Judge Rejects Drug Testing on Children; Ruling Finds FDA Overstepped Authority in Forcing Pediatric Studies," *Washington Post*, October 19, 2002, p. A9.

BPCA and PREA: Laws to Encourage Pediatric Drug Research

Although other laws (such as those affecting drug development, safety and effectiveness efforts, and general health care and consumer protection) serve to promote or protect the health of children, the two laws that are scheduled to sunset as FY2007 ends — the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act — authorize the programs most focused on pediatric drug research.

The Best Pharmaceuticals for Children Act

Pediatric Exclusivity. The Best Pharmaceuticals for Children Act (BPCA, P.L. 107-109), in 2002, reauthorized FDAMA's pediatric exclusivity provisions in FFDCA Section 505A (21 U.S.C. 355a). BPCA renewed the agency's authority to give an additional six-month period of marketing exclusivity to a manufacturer in return for FDA-requested pediatric use studies and reports.

FDA-NIH Collaboration. Pediatric exclusivity, however, is not relevant to products that are no longer covered by patent or other marketing exclusivity agreements. Also, a patent-holding manufacturer may decline to conduct the FDA-requested study and, therefore, the exclusivity. BPCA, therefore, added provisions to encourage pediatric research in those products.

Off-patent products. BPCA addressed the first group, which it described as "off-patent," by adding to the Public Health Service Act (PHSA) a new Section 409I (42 U.S.C. 284m). It established an off-patent research fund at NIH for these studies and authorized appropriations of $200 million for FY2002 and such sums as are necessary for each of the five years until the provisions are set to sunset on October 1, 2007.

Sponsor-declined studies. For on-patent drugs whose manufacturers declined FDA's written requests for studies, BPCA amended the FFDCA Section 505A to allow their referral by FDA to the Foundation for the National Institutes of Health for pediatric studies, creating a second program of FDA-NIH collaboration.

Other Provisions. Other BPCA provisions included giving priority status to pediatric supplemental applications; the establishment of an FDA Office of Pediatric Therapeutics; the definition of pediatric age groups to include neonates; and a direction to the HHS Secretary to contract with the Institute of Medicine for a review of regulations, federally prepared or supported reports, and federally supported evidence-based research, all relating to research involving children.[10] The IOM report to Congress was to include recommendations on best practices relating to research involving children.

---

[10] See Institute of Medicine, *Ethical Conduct of Clinical Research Involving Children*, Committee on Clinical Research Involving Children (Washington, DC: National Academies Press, 2004), done with funding from NIH and FDA.

Pediatric Research Equity Act

When a federal court ruled that FDA had overstepped its statutory authority in promulgating the Pediatric Rule, Members of Congress moved to give FDA that authority. The Pediatric Research Equity Act of 2003 (PREA, P.L. 108-155) essentially codified the Pediatric Rule by adding to the FFDCA a new Section 505B (21 U.S.C. 355c): Research into pediatric uses for drugs and biological products. Unlike BPCA, which applies only to drugs, PREA applies both to drugs regulated under the FFDCA and to biological products (e.g., vaccines) regulated under the PHSA.

New Applications. With PREA, a manufacturer submitting an application to market a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must at the same time submit a pediatric assessment. The submission must be adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. If the disease course and drug effects are sufficiently similar for adults and children, the HHS Secretary may allow extrapolation from adult study data as evidence of pediatric effectiveness, usually supplemented with other data from children, such as pharmacokinetic studies.

The law specifies situations in which the Secretary may defer or waive the pediatric assessment requirement, such as when it is known that a drug should never be used by children. In those cases, it directs that the product's labeling include any waiver that was based on evidence that pediatric use would be unsafe or ineffective.

Products on the Market. The Secretary may require the manufacturer[11] of an approved drug or licensed biologic to submit a pediatric assessment in situations in which not having pediatric use information on the label could pose significant risks. Those situations include a finding by the Secretary that a marketed product is used by pediatric patients for indications labeled for adults, or that the product may provide a meaningful therapeutic benefit over available alternatives for children. Before requiring the assessment, the Secretary must have issued a written request under FFDCA Section 505A (BPCA, pediatric exclusivity) or PHSA Section 409I (NIH funding mechanisms). Further, the manufacturer must not have agreed to conduct the assessment, and the Secretary must have stated that the NIH funding programs either have or do not have sufficient funds to conduct that study.

If the manufacturer does not comply with the Secretary's notice of a required study, the Secretary may consider the product misbranded. Because the Congress wanted to protect adult access to a product under these circumstances, the law sets limits on FDA's enforcement options, precluding, for example, the withdrawal of approval or license to market.

---

[11] The laws refer to the *sponsor* of an application or the *holder* of an approved application. Because that entity is usually the product's manufacturer, this report uses the term *manufacturer* throughout.

Other Provisions. Seeing PREA and BPCA as complementary approaches to the same goal, Congress linked PREA to BPCA. [Note: A discussion of this linkage appears later in this report.] Therefore, rather than specify a sunset date, Congress authorized PREA to remain in effect only as long as BPCA has not sunset.

BPCA and PREA Have Had Some Impact on Pediatric Drug Research

Best Pharmaceuticals for Children Act

On-Patent Drugs. As of February 28, 2007, FDA had issued 338 written requests outlining 782 specific pediatric studies to manufacturers holding patent or other exclusivity benefits.[12] The requests also specify the study purpose: about half of the studies addressed efficacy and safety, more than a third focused on aspects of pharmacokinetics.[13]

The data in **Table 3** illustrate where the pediatric exclusivity provisions in FDAMA and BPCA have helped and where they have not. They show that when FDA granted companies exclusivity for a drug, 87% of those drugs' labeling changed to reflect pediatric information. In other words, the incentive worked. However, those drugs (with labeling changes) make up only 35% of the drugs that FDA asked the manufacturers to study. BPCA did not give FDA any authority to address the remaining 65%, those drugs whose manufacturers chose not to accept exclusivity and the pediatric study requirements.

---

[12] FDA, "Pediatric Exclusivity Statistics as of February 28, 2007," updated March 9, 2007, at [http://www.fda.gov/cder/pediatric/wrstats.htm]; and FDA, "Pediatric Exclusivity," updated January 9, 2007, at [http://www.fda.gov/cder/pediatric/breakdown.htm].

[13] FDA, "Pediatric Exclusivity," updated January 9, 2007, at [http://www.fda.gov/cder/pediatric/breakdown.htm].

Table 3. Two Ways to Describe the Effect of Pediatric Exclusivity on Pediatric Labeling Changes

	Number	% of previous category		% of written requests	
FDA written requests [a]	338	—	100	—	100
Exclusivity determinations	149	(149/338)	44	(149/338)	44
Drugs granted exclusivity [b]	136	(136/149)	91	(136/338)	40
Labeling changed [c]	118	(118/136)	87	(118/338)	35

Sources: FDA, "Approved Active Moieties to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act," updated March 19, 2007; and "Pediatric Exclusivity Labeling Changes as of November 22, 2006," updated Dec. 18, 2006; both at [http://www.fda.gov/cder/pediatric].

a. These 338 written requests entailed 782 studies.
b. These 136 drugs reflect 129 active components.
c. Labeling data go through November 2006, whereas the other data go to mid-March 2007.

NIH Route for Off-Patent Drugs and On-Patent Drugs for Which Manufacturers Declined FDA's Requests for Study. Under BPCA, NIH has put 51 drug-indication entries on its "List of Drugs for Which Pediatric Studies Are Needed."[14] Of those, only nine (17.6%) have progressed to choice of clinical trial sites, an indication that they are funded.

Table 4 shows how the 51 items recommended for pediatric study from 2003 through the first quarter of 2006, are distributed by patent status and whether a study had begun.

Table 4. Research Status of Drugs That NIH Deemed In Need of Pediatric Studies, by Patent Status

	Clinical trial site chosen		
Patent status	**Yes**	**No**	**Total**
On	2 (16.7%)	10	12
Off	7 (17.9%)	32	39
Total	9 (17.6%)	42	51

Source: Adapted from NIH, "List of Drugs for Which Pediatric Studies Are Needed; Notice," *Federal Register*, vol. 71, no. 79, April 25, 2006, pp. 23931-23936.

[14] NIH, "List of Drugs for Which Pediatric Studies Are Needed; Notice," *Federal Register*, vol. 71, no. 79, April 25, 2006, pp. 23931-23936.

GAO Study. In March 2007, the Government Accountability Office (GAO) issued a report that the BPCA legislation had required.[15] Noting that most of the exclusivity-associated studies resulted in labeling changes, GAO calculated the time that elapsed before those changes were completed. The entire process — from initial data submission, through FDA review and frequent requests for additional data, to follow-up submissions and reviews — took an average of nine months. One-third of the drugs' labeling changing took less than three months, while labeling change for one took almost three years. Most of the studies supported labeling changes to inform of ineffective drugs, dosing that was too high or too low, and newly identified adverse events. The GAO report juxtaposed those finding with the statement that children take many of these drugs for common, serious, or life-threatening conditions.

Pediatric Research Equity Act

FDA approved more than 372 new drug and biologics license applications from the beginning of 2003 through 2006.[16] For that same period, FDA attributes 63 labeling changes to PREA.[17] **Table 5** indicates the topics of those label changes.

Table 5. Content of PREA-Associated Labeling Changes

Topic of label change	Number of label changes
Extended indication	2
New active ingredient	11
New dosage form	17
New dosing regimen	8
New drug	4
New indication	19
New route of administration	2
Total number of label changes	**63** [a]

Source: FDA, "PREA Labeling Changes," page created March 23, 2007, at [http://www.fda.gov/CDER/pediatric/PREA_label_post-mar_2_mtg.pdf].

a. Eight products had two label changes (e.g., Xopenex HFA Inhalation Aerosol had both a new active ingredient and an extended indication).

---

[15] Government Accountability Office (GAO), *Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act*, Report to Congressional Committees, GAO-07-557, March 2007.

[16] FDA, "CDER Approval Times for Priority and Standard NDAs and BLAs, Calendar Years 1993-2006," January 29, 2007, at [http://www.fda.gov/cder/rdmt/NDAapps93-06.htm]. FDA's Center for Drug Evaluation and Research has, since 2004, covered Biologics License Applications (BLAs) for therapeutic biologics [e.g., monoclonal antibodies for in vivo use; most proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g. thrombolytics), and other novel proteins; immunomodulators; and growth factors]; other BLAs [e.g., vaccines, blood products, and coagulation factors], which are regulated within FDA's Center for Biologics Evaluation and Research, are not included in this tally.

[17] FDA, "PREA Labeling Changes," March 23, 2007, at [http://www.fda.gov/CDER/pediatric/PREA_label_post-mar_2_mtg.pdf].

Comparison of BPCA and PREA

When presenting material about the pediatric research provisions in law, more than one FDA speaker has referred to "the carrot and the stick." BPCA offers a carrot — extended market exclusivity in return for specific studies on pediatric use; PREA follows up with a stick — required studies of a drug's safety and effectiveness when used by children. **Table 6**, adapted from an FDA slide presentation, summarizes the key differences between these two laws.

Table 6. Major Differences in the BPCA and PREA Approaches

BPCA	PREA
Added FFDCA Section 505A Pediatric research	Added FFDCA Section 505B Pediatric assessments
Pediatric studies are voluntary and in exchange for marketing exclusivity	Pediatric studies are mandatory
Applies to drugs	Applies to drugs and biologics
Research and exclusivity to cover all uses of the active drug component	Research to cover the indicated use, dose, and route of administration under FDA review

Source: Adapted from Lisa Mathis, Associate Director, Pediatric and Maternal Health Team, Office of New Drugs, CDER, "Growth and Development of Pediatric Drug Development at the FDA," June 2006 presentation to the Institute of Medicine, the National Academies, at [http://www.fda.gov/oc/opt/presentations/drugdevelopment.ppt].

FDA Activities

In its implementation of the pediatric research laws, FDA has published numerous documents and provides electronic links to these documents on its "Pediatric Drug Development" page, at [http://www.fda.gov/cder/pediatric/]. These include:

- **Rules and announcements,** such as "Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies; Availability," *Federal Register*, vol. 71, no. 201, October 18, 2006, pp. 61484-61485;
- **Final and draft guidances,** such as *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*, issued in 1999; and *How to Comply with the Pediatric Research Equity Act*, draft issued in 2005;
- **Written request templates,** such as "Sample Written Request For Division of Oncology Drug Products";
- **Agenda and transcripts for the meetings of advisory committees,** such as "FDA Pediatric Ethics Working Group Consensus Statement on the Pediatric Advisory Subcommittee's April 24, 2001 Meeting"; and
- **Statistics,** such as "Pediatric Exclusivity Labeling Changes as of November 22, 2006," and "PREA Labeling Changes," March 30, 2007.

Congressional Options

Recent statements by Members of both the House and the Senate make it seem likely that the 110th Congress will preserve the concept and structure of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. There is broad support for some version of these programs that encourage — with carrot and stick — increased research to support accurate labeling information regarding pediatric use of FDA-approved drugs.

But there is also support for change. What issues and options might Congress consider in such an effort?

So far, most discussion in Congress has revolved around five issues: exclusivity, cost, labeling, enforcement, and sunset policy.

Exclusivity

BPCA offers pharmaceutical companies a reward for agreeing to conduct studies on drugs for pediatric populations. But PREA requires pediatric studies. Some may ask why Congress must offer industry a reward for something it requires them to do.

After reviewing the history of pediatric exclusivity during the period when Congress was considering reauthorizing the FDAMA exclusivity provisions in a proposed BPCA, one legal analyst wrote:

> The strongest argument in support of this incentive structure is that without it pharmaceutical companies would not be willing to conduct pediatric tests. This argument depends, however, on a voluntary system of pediatric testing. If Congress had codified the FDA's power to require testing in all new and already marketed drugs, the notion of an incentive or reward for testing would appear ludicrous.[18]

When considering the PREA bill in 2002, Members of Congress debated how the two laws would relate. But the record provides no clear answer.[19] Three years later, in its draft guidance on "How to Comply with the Pediatric Research Equity Act," FDA wrote that "[t]he Pediatric Rule was designed to work in conjunction with the pediatric exclusivity provisions of section 505A of the Act...."

---

[18] Lauren Hammer Breslow, "The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing," *Harvard Journal on Legislation*, vol. 40, 2003, pp. 133-191.

[19] S.Rept. 108-84, to accompany S. 650, the Pediatric Research Equity Act of 2003, June 27, 2003. Sen. Gregg, as committee chair, wrote: "The Pediatric Rule was intended to work as a safety net to (or as a backstop to) pediatric exclusivity;" and Sen. Clinton and others wrote in the report's "Additional Views" section: "Neither the intent conveyed by FDA nor FDA's implementation of the [Pediatric] [R]ule supports the report's contention that the rule was intended to work as a 'backstop' to pediatric exclusivity or to be employed only to fill the gaps in coverage left by the exclusivity."

Cost

In assessing the value of BPCA and PREA, identification of the intended and unintended effects — both positive and negative — of their implementation thus far can be useful. One hypothetical product illustrates effects on manufacturers, patients, and the government.

The manufacturer holding pediatric exclusivity incurs the research and development expenses related to the FDA-requested pediatric studies. It then enjoys six months of sales without a competitor product and a potentially lucrative head start on future sales. The manufacturers that do not hold the exclusivity, must wait six months during which they cannot launch competing products. After that, however, they may be able to market generic versions of a drug that has been assessed for pediatric use and has had six months' experience in the public's awareness.

Nonfinancial benefits to government include its progress in protecting children's health. Costs to the government include administrative and regulatory expenses. Because the government also pays for drugs, both directly and indirectly, it must pay the higher price that exclusivity allows for six months. The better pediatric information, however, may yield future financial savings by avoiding ineffective and unsafe uses. Private payers also face the same financial cost and benefit. Some children may incur risks as study subjects; they and others might benefit from more appropriate use of drugs, including accurate dosing.

Although assigning quantitative values to those effects is beyond the scope of this report, some researchers have examined the *financial* costs and benefits faced by manufacturers that receive pediatric exclusivity. One study appeared in February 2007, written by a team lead by Jennifer Li of Duke University's Department of Pediatrics, with co-authors from its Department of Economics and the Duke Clinical Research Institute, as well as from the Office of the Commissioner at FDA.[20] It calculated the net economic benefit (costs minus benefits, after much estimating and adjusting for other factors) to a manufacturer that, in 2002-2004, responded to an FDA request for pediatric studies and received pediatric exclusivity. The median net economic benefit of six-month exclusivity was $134.3 million. The study found a large range, from a net loss to a net benefit of over half a billion dollars.

Are these effects — on manufacturers, pediatric patients and their families, adult patients, others, and on government itself — in line with Congress's intentions in passing the legislation? Might this Congress want to modify the programs to modify the distribution of benefits and costs?

---

[20] Jennifer S. Li, Eric L. Eisenstein, Henry G. Grabowski, et al., "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program," *Journal of the American Medical Association*, vol. 297, no. 5, February 7, 2007, pp. 480-488.

Labeling

Whatever information researchers learn — about safety, effectiveness, dosing, or side effects when a child takes a medication — must reach clinicians and others who care for children (including parents) before a child can benefit. BPCA and PREA, therefore, include labeling provisions. Have they been successful? Could they be modified to be better?

Whether Pediatric Information Is Required. Currently, FDA requires, by law or regulation, pediatric usage labeling in the following circumstances:

- manufacturer has successfully applied (via an original new drug application [NDA] or a supplement) for approval to list a pediatric indication; or
- manufacturer received pediatric exclusivity after conducting appropriate studies.

In the first case, pediatric use information is included in the labeling only if FDA approved the pediatric indication. If FDA turned down or the manufacturer withdrew a request for a pediatric indication, not only does pediatric use information not appear in the product's labeling, the fact that the manufacturer had made an unsuccessful attempt — and the research findings that blocked the approval — are neither noted in the label nor made public in other ways.

The rules for labeling that come with pediatric exclusivity are different. If the studies required for exclusivity support pediatric use or specific limits to pediatric use (different dosing or subgroups), that information would go in the labeling. If the studies did not find the drug to be effective in children or if FDA waived the requirement to study because children should not or would not be given the drug, that information, too, would go in the labeling.

Despite the requirements and the progress that has been made, not all drugs used by children have labeling that addresses pediatric use. As previously noted, FDA approved more than 372 new drug and biologics license applications from the beginning of 2003 through 2006.[21] Yet, the PREA statistics on labeling note 63 labeling changes over that period.

Also, BPCA (January 2002) required HHS to promulgate a rule within one year of enactment (therefore, January 2003) regarding the placement on all drug labels of a toll-free telephone number with which to report adverse events. FDA has not yet issued that rule.

Content of Included Pediatric Information. While an improvement over no mention at all, a statement such as "... effectiveness in pediatric patients has not been established" still deprives a clinician of information that is available. The statement does not distinguish between drugs studied and not studied in children. If no studies were done, effectiveness could not have been established. If studies were

[21] For more information, see [http://www.fda.gov/cder/rdmt/NDAapps93-06.htm].

conducted, were they appropriately designed to test safety and effectiveness? Among drugs that were studied in children, adding "effectiveness in pediatric patients has not been established" to the labeling does not distinguish among the following:

- studied in children, found to be ineffective;
- studied in children, found to be unsafe; or
- studied in children, not found to be effective ... inconclusive.

If studies suggest that safety, effectiveness, or dosage reactions vary by age, condition to be treated, or patient circumstances, then detailed information could be included in the labeling.

Enforcement

Congress has given FDA limited authority regarding pediatric drug use labeling, similar to the FDA's situation with direct-to-consumer (DTC) prescription drug advertising. FDA is charged to regulate direct-to-consumer (DTC) prescription drug advertising, but without the authority, except in egregious situations, to require that a manufacturer change an ad's content. For both situations — pediatric labeling and DTC advertising, Congress has given FDA the authority to use its sledgehammer — deeming a product to be "misbranded" and thereby gaining the authority to pull it from the market — but has not given the agency authority to require less drastic actions, such as labeling changes.

To pull from the market a drug on which many consumers rely would be, according to some health care analysts, akin to throwing out the baby with the bathwater. In its report accompanying the PREA bill, the Senate committee specifies that the misbranding authority regarding pediatric use labeling should not be the basis for criminal proceedings or withdrawal of approval, and could only rarely result in seizure of the offending product.

Enforcement scenarios: What options should FDA have if a manufacturer that has already received the six-month pediatric exclusivity then refuses or delays making an appropriate labeling change? For studies that result in labeling changes, when should FDA make study results available to the public?

In considering whether to strengthen FDA's enforcement authority within the context of pediatric research and labeling, Congress has the option to address manufacturers' actions at many points in the regulatory process, if and when, for example,FDA notes: a manufacturer's reluctance to accept the agency's requested study scope, design, and timetable; that a study's completion is clearly lagging or overdue; that a manufacturer does not complete such a study; or does not release its results to FDA, peer-reviewed publications, or the public; or that procedures to incorporate pediatric study results into a drug's labeling have not proceeded appropriately.

Sunset

Not every law contains a sunset provision. BPCA does, and PREA, although the term is not used, essentially is set to cease if and when BPCA does. By including an end date or another indication of a predetermined termination date, Congress provides "an 'action-forcing' mechanism, carrying the ultimate threat of termination, and a framework or guidelines for the systematic review and evaluation of past performance."[22]

Although the concept of a sunset is apparently accepted for BPCA (which offers pediatric exclusivity as a financial incentive to manufacturers), whether it is appropriate for PREA (which seeks to ensure that the labeling of all drugs that clinicians prescribe for children's use includes information about safety, effectiveness, and dosing in relevant subsets of children) is again a topic of debate.[23]

If proponents of a PREA sunset intend it as a trigger for regular evaluation of the law's usefulness, there may be other legislative approaches that would more directly achieve that. If, however, the intent is to use PREA to test the idea of requiring pediatric assessments, that would likely engender a different focus of debate.

Bills in the 110th Congress

- S. 830, Pediatric Medical Device Safety and Improvement Act of 2007, introduced March 8, 2007, by Senator Dodd.

- H.R. 1494, Pediatric Medical Device Safety and Improvement Act of 2007, March 13, 2007, by Representative Markey. [This bill includes all these provisions in S. 830 and would also require an annual review by FDA's Pediatric Advisory Committee.]

- S. 993, the Pediatric Research Improvement Act, introduced March 28, 2007, by Senator Clinton.

- S. 1082, the Food and Drug Administration Revitalization Act, introduced April 10, 2007, by Senator Kennedy.[24] The bill includes

---

[22] CRS Report RS21210, *Sunset Review: A Brief Introduction*, by Virginia A. McMurtry.

[23] See Senator Clinton's comments at the Senate Committee on Health, Education, Labor, and Pensions hearing, "Ensuring Safe Medicines and Medical Devices for Children," March 27, 2007, at [http://www.cq.com/display.do?dockey=/cqonline/prod/data/docs/html/transcripts/congressional/110/congressionaltranscripts110-000002481833.html@committees&metapub=CQ-CONGTRANSCRIPTS&searchIndex=0&seqNum=13]; and S.Rept. 108-84, Additional Views.

[24] Other provisions in S. 1082, as reported, are prescription drug and medical device user fee program reauthorizations, drug safety, clinical trial databases, and conflicts of interest. See related CRS reports, including CRS Report RL33914, *The Prescription Drug User Fee Act*

(continued...)

three sets of related provisions in its Title IV: "Pediatric Medical Products."

S. 1082 includes, as Subsection A of Title IV, the Best Pharmaceuticals for Children Amendments of 2007. Subsection B is the Pediatric Research Improvement Act, which includes the provisions of S. 993, except for one. S. 993 would eliminate the provision in the Pediatric Research Equity Act that linked authorization to the sunset provision in the Best Pharmaceuticals for Children Act. As reported, S. 1082 allows for the sunset on October 1, 2012. Subsection C is the Pediatric Medical Device Safety and Improvement Act of 2007. It includes many of the provisions of S. 830.

The Senate Committee on Health, Education, Labor, and Pensions, on April 24, 2007, reported the Chairman's April 16, 2007 mark of S. 1082, with amendments. This FDA Revitalization Act is scheduled for Senate floor consideration.

The House Energy and Commerce Committee has held hearings on pediatric drug safety, but has not yet considered any specific bill.

---

[24] (...continued)
(PDUFA): Background and Issues for PDUFA IV Reauthorization, by Susan Thaul; CRS Report RL33981, *Medical Device User Fee and Modernization Act (MDUFMA) Reauthorization*, by Erin D. Williams; CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul; and CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin D. Williams.