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


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December 2, 2008


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

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# Summary

In 2007 Congress reauthorized two laws allowing the Food and Drug Administration (FDA) to offer financial and regulatory incentives to test their products for use in children. Through the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85), Congress extended both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) for five years.

About 75% of drugs have not had pediatric studies. The laws address concerns that clinicians must often prescribe drugs for children that FDA has approved only for adult use. Clinicians often take that step believing that the safety and effectiveness demonstrated with adults would hold for younger patients. But studies show that drugs vary in bioavailability in children, which depends on the maturation and development of organs and other factors. Therefore, this off-label prescribing results in some children's receiving ineffective drugs or too much or too little of a potentially useful drug. It may also result in side effects unique to children, or children of specific ages, including effects on growth and development.

The market has not been able to overcome the economic, ethical, legal, and mechanical obstacles that make manufacturers reluctant to conduct these tests. The reauthorized BPCA and PREA represent ongoing involvement of Congress and FDA to address this need. FDA had tried unsuccessfully to spur pediatric drug research through administrative action before 1997. 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 (P.L. 107-109) gave this program a five-year reauthorization in 2002. 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 (P.L. 108-155). PREA covers drugs and biological products and includes provisions for deferrals, waivers, and the required pediatric assessment of an approved marketed product.

Some of the issues the 110th Congress considered remain of concern. Why offer a financial incentive to encourage pediatric studies when FDA has the authority to require them? How does the cost of marketing exclusivity—including the higher prices paid by government—compare with the cost of the needed research? What percentage of drug labeling includes adequate pediatric information because of BPCA and PREA? Does the law provide FDA with sufficient authority to act and does FDA choose to so act? These kinds of questions—determining what information clinicians and consumers need, how to then develop and disseminate it; how to balance carrots and sticks; and how to consider cost and benefit—could not only help the 111th Congress evaluate BPCA and PREA, but also inform its consideration of healthcare reform.

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# Introduction

The Food and Drug Administration (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 encourage industry to develop drugs and medical devices for pediatric use, Congress has established three programs. The Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85)[1] reauthorized and strengthened two laws addressing drugs—the *Best Pharmaceuticals for Children Act (BPCA) of 2002* and the *Pediatric Research Equity Act (PREA) of 2003*—and enacted a new law addressing devices—the *Pediatric Medical Device Safety and Improvement Act (PMDSIA) of 2007*.

The historical approach of this report allows an understanding of how and why Congress took these steps. Specifically, it:

- ? describes why research on a drug's pharmacokinetics, safety, and effectiveness in children is necessary;
- ? presents why the marketplace has not provided sufficient incentive to manufacturers of drugs approved for adult use;
- ? analyzes how BPCA and PREA evolved from FDA's administrative earlier efforts;
- ? describes how FDAAA amended BPCA and PREA;
- ? analyzes the impact BPCA and PREA have had on pediatric drug research; and
- ? discusses issues, some of which Congress considered leading up to FDAAA, that may form the basis of oversight and evaluative activities.

Other CRS reports address how FDA handles similar issues relating to pediatric use of medical devices.[2]



# Need for Pediatric Labeling

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 it has tested and seeks approval for sale.

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

[1]CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Erin D. Williams and Susan Thaul, presents detailed descriptions of these and other FDAAA provisions.

CRS Report RL32826, *The Medical Device Approval Process and Related Legislative Issues*, and CRS Report RL33981, *Medical Device User Fee and Modernization Act (MDUFMA) Reauthorization*, both by Erin D. Williams.

context) and population specified in the application.[3] The Federal Food, Drug, and Cosmetic Act (FFDCA) allows a manufacturer to promote or advertise a drug only for uses listed in the FDA-approved labeling—and the labeling may list only those claims for which FDA has reviewed (and accepted) safety and effectiveness evidence.

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 FDA approves a drug, therefore, a licensed physician may—except in highly regulated circumstances—prescribe it without restriction. When a clinician prescribes it to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling, that is called off-label use, which is considered 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, a clinician must deduce/infer/guess whether the drug might help. The doctor must also decide what dose and how often, all to best balance the drug's intended effect with its anticipated and unanticipated side effects.

Such clinicians face an obstacle: children are not miniature adults.[4] At different ages, a body may handle 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, among other things, on changes in the maturation and development of organs. Clearance can be quicker or slower in children depending on the age of child, the organs involved, and body surface area.[5]

Without complete information on which to make these decisions, clinicians sometimes err. Such errors, 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.[6] **Table 1** includes some of the examples that FDA scientists have included in recent presentations on pediatric drug development.



[3] For descriptions and discussions of the FDA procedure for approving new drugs, seeCRS 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.

[4] 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).

[5] 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.

[6] 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.

**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—the 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.

To sum up: 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. Also, 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 BPCA 2002 and PREA 2003, 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."[7]

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.

**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 |

[7] 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.

| Year | Action |
|---|---|
| 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) |
| 2007 | FDA Amendments Act of 2007 (FDAAA, P.L. 110-85) reauthorized BPCA and PREA and enacted the Pediatric Medical Device Safety and Improvement Act |

**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 revised rule attempted to make clear that the "adequate and well-controlled studies" language did not require that manufacturers conduct clinical trials in children. The new rule described how FDA would determine whether the evidence was substantial and adequate. If, for example, clinicians would use the drug to treat a different condition in children than its FDA-approved use in adults, FDA would require trials in children. 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 was 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.[8]

## Food and Drug Administration Modernization Act of 1997

Three years later, Congress took further action. 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. If a manufacturer completed 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.[9] The law required that the Secretary publish an annual list of FDA-approved drugs for which additional pediatric information might produce health benefits. FDAMA also required that the Secretary prepare a report examining whether the new law enhanced pediatric use information, whether the

[8] 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.

[9] 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.

incentive was adequate, and what the program's economic impact was on taxpayers and consumers.

## 1997: The Pediatric Rule

Also in 1997, FDA issued a proposed regulation that came to be called the Pediatric Rule.[10] 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, prompting a lawsuit again FDA by the Competitive Enterprise Institute and the Association of American Physicians and Surgeons. The plaintiffs claimed 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.[11]



# BPCA 2002 and PREA 2003: 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 Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act authorize the programs most focused on pediatric drug research. To maintain the historical organization of this report, descriptions of the laws as initially enacted in 2002 and 2003 appear in this section. The following section describes the changes that FDAAA 2007 made.

## The Best Pharmaceuticals for Children Act of 2002

### 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 2002 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. The provisions applied to both new drugs and drugs already on the market.

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[10] 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.

[11] 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.

### 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 2002, therefore, added provisions to encourage pediatric research in those products.

#### *Off-patent products*

BPCA 2002 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 2002 amended the FFDCA Section 505A to allow their referral by FDA to the Foundation for the National Institutes of Health (FNIH) for pediatric studies, creating a second program of FDA-NIH collaboration.

### Other Provisions

- ? gave priority status to pediatric supplemental applications;
- ? established an FDA Office of Pediatric Therapeutics;
- ? defined pediatric age groups to include neonates;
- ? directed 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.[12] The IOM report to Congress was to include recommendations on best practices relating to research involving children.

## Pediatric Research Equity Act of 2003

Next, Congress turned its attention to the federal court ruling that FDA had overstepped its statutory authority in promulgating the Pediatric Rule. It gave 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 applied only to drugs, PREA applied both to drugs regulated under the FFDCA and to biological products (e.g., vaccines) regulated under the PHSA.

[12] 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.

## New Applications

With PREA, a manufacturer had to submit a pediatric assessment whenever it submitted an application to market a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Congress mandated that the submission be adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and that it support dosing and administration for each pediatric subpopulation for which the product is safe and effective. If the disease course and drug effects were sufficiently similar for adults and children, the HHS Secretary could allow extrapolation from adult study data as evidence of pediatric effectiveness, usually supplemented with other data from children, such as pharmacokinetic studies.

The law specified situations in which the Secretary might defer or waive the pediatric assessment requirement, such as when the Secretary believes doctors already know that a drug should never be used by children. In those cases, it directed that the product's labeling include any waiver based on evidence that pediatric use would be unsafe or ineffective.



## Products on the Market

When not having pediatric use information on the label could pose significant risks, the Secretary could now require the manufacturer[13] of an approved drug or licensed biologic to submit a pediatric assessment. Such situations could arise when the Secretary found that a marketed product was used by pediatric patients for indications labeled for adults, or that the product might provide children a meaningful therapeutic benefit over the available alternatives. Before requiring the assessment, the Secretary had to issue 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 had to have stated that the NIH funding programs either did or did not have enough funds to conduct that study.

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

## Other Provisions

Seeing PREA and BPCA as complementary approaches to the same goal, Congress, in 2003, 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 continue only as long as BPCA was in effect.

[13] 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.

## 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 3**, adapted from an FDA slide presentation, summarizes the key differences between these two laws.

**Table 3. Major Differences in the BPCA and PREA Approaches**

| BPCA | PREA |
|---|---|
| Added FFDCA Section 505A | Added FFDCA Section 505B |
| Pediatric research | 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.



# Pediatric Provisions in FDAAA 2007

Five years after passing BPCA and PREA, in a year that saw rising concern about drug safety, Congress reauthorized BPCA and thereby also continued PREA. Much of the two laws remained the same, and Congress added provisions to strengthen the programs. What follows groups the changes placed in the FDA Amendments Act of 2007.[14]

## Best Pharmaceuticals for Children Act of 2007

### Pediatric Exclusivity

BPCA 2007 (Title V of FDAAA) again reauthorized the pediatric exclusivity program, amending FFDCA 505A to sunset on October 1, 2012. Its provisions encourage research on off-patent products, strengthen the requirements for labeling changes based on the results of pediatric use studies, and provide for the reporting of adverse events.

#### Internal review committee

[14]CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Erin D. Williams and Susan Thaul, presents detailed tables comparing FDAAA 2007 with BPCA 2002 and PREA 2003, showing both changed and unchanged provisions.

- required that the Secretary establish an internal review committee, composed of FDA employees with specified expertise, to review all written requests; and
- required the Secretary, with that committee, to track pediatric studies and labeling changes according to specified questions.

**Study requirements**

- refined study scope to allow the Secretary to include preclinical studies; and
- required supporting evidence if an applicant turned down a request on the grounds that developing appropriate pediatric formulations of the drug was not possible.

**Reporting, labeling, and timing**

- authorized the Secretary to grant additional marketing exclusivity, for both new drugs and drugs already on the market, only after: a sponsor completed and reported on the studies that the Secretary had requested in writing; the studies included appropriate formulations of the drug for each age group of interest; and any appropriate labeling changes were approved; all within the agreed upon time frames; and
- required that the sponsor propose pediatric labeling resulting from the studies.

**Adverse event reports**

- required applicants to submit, along with the report of requested studies, all postmarket adverse event reports regarding that drug.

**Required public notice**

- expanded the public notice requirement beyond the current notice of an exclusivity decision to include copies of the written request;
- required the Secretary to publicly identify any drug with a developed pediatric formulation that studies had shown were safe and effective for children that an applicant has not brought to market within one year;
- required that, for a product studied under this section, the labeling include study results (if they do or do not indicate safety and effectiveness, or if they are inconclusive) and the Secretary's determination;
- required dissemination of labeling change information to health-care providers; and
- required reporting on the review of all adverse event reports and recommendations to the Secretary on actions in response.

**Dispute resolution**

- established a dispute resolution process to include referral to the Pediatric Advisory Committee.

### FDA-NIH Collaboration

**Off-patent products**

- ? required the Secretary to determine (in consultation with an internal committee required by FDAAA) whether there is a continuing need for pediatric studies. If so, the Secretary must refer those drugs for inclusion on the list of priority needs in pediatric therapeutics that require study;
- ? amended PHSA Section 409I (as discussed earlier), which required that the Secretary, through the NIH Director and in consultation with the FDA Commissioner and pediatric research experts, list approved drugs for which pediatric studies are needed to assess safety and effectiveness. It changed the specifications from an annual list of approved drugs to a list, revised every three years, of priority study needs in pediatric therapeutics, including drugs or indications;
- ? for drugs for which pediatric studies are not completed and for which the Secretary determines there is a need for pediatric information, required the Secretary to determine whether funds are available through the Foundation for the NIH. If yes, required Secretary to issue a proposal to award a grant to conduct such studies. If no, required the Secretary to refer the drug for inclusion on the list established under PHSA Section 409I;
- ? required reports from the Institute of Medicine and the Government Accountability Office; and
- ? included the same authorization of appropriations.

**Sponsor-declined studies**

- ? required the Secretary, after determining that an on-patent drug requires pediatric study, to determine whether the FNIH has sufficient money to fund a grant or contract for such studies. If it does, the Secretary must refer that study to FNIH and FNIH must fund it. If FNIH has insufficient funds, the Secretary may require the manufacturer to conduct a pediatric assessment under PREA. If the Secretary does not require the study, the Secretary must notify the public of that decision and the reasons for it.

### Other Provisions

- ? made ineligible for exclusivity any drug with another exclusivity due to expire in less than nine months.

## Pediatric Research Equity Act of 2007

Next, in order to preserve the carrot and stick approach to encouraging pediatric research, Congress not only reauthorized the Pediatric Research Equity Act (PREA 2007, Title IV of FDAAA) but also amended it to strengthen standards for required tests, explanation of deferrals, labeling, and publicly accessible information.

## New Applications

PREA 2007 required manufacturers to provide documentation of the data used to support extrapolation of effectiveness findings from adult studies to pediatric age groups.

## Products on the Market

PREA 2007 continued the Secretary's authority to require a manufacturer to submit require assessments. It described the circumstances somewhat differently. PREA 2002 applied to a drug used to treat a substantial number of pediatric patients for the labeled indications, and for which the *absence* of adequate labeling could pose *significant risks* to pediatric patients. PREA 2007, however:

- applied to a drug used for a substantial number of pediatric patients for the labeled indications, and for which the *presence* of adequate pediatric labeling "could confer a *benefit* on pediatric patients;" and
- covered a situation in which there was reason to believe the drug would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more of the claimed indications.

Adding to the procedure for when the Secretary grants a *deferral* of some of all of the requirement assessments, PREA 2007:

- required that the applicant include a timeline for the completion of such studies;
- required the Secretary's annual review of each approved deferral, for which the applicant must submit evidence of documentation of study progress; and
- required that all information from that review promptly be made available to the public.

Regarding *waiver* of the requirement to develop a pediatric formulation, PREA 2007:

- required the manufacturer to submit documentation detailing why a pediatric formulation could not be developed; and
- required that submitted materials for granted waivers promptly be made available to the public.

## Other Provisions

PREA 2007:

- required that the Secretary establish an internal committee, composed of FDA employees with specified expertise, to participate in the review of pediatric plans and assessments, deferrals, and waivers;
- required the Secretary to track assessments and labeling changes and to make that information publicly accessible;
- established a dispute resolution procedure, which would allow the Commissioner, after specified steps, to deem a drug to be misbranded if a manufacturer refused to make a requested labeling change;

- ? included review and reporting requirements for adverse events;
- ? required reports from both the Institute of Medicine (IOM) and the Government Accountability Office (GAO); and
- ? continued to link the program's authorization to the five-year authority FDAAA provides to the pediatric exclusivity program.

# BPCA and PREA Impact on Pediatric Drug Research

FDA maintains statistics on the two pediatric research encouragement programs on the FDA website.[15]

## Best Pharmaceuticals for Children Act

### On-Patent Drugs

The FDA website offers regularly updated data on activity related to BPCA. **Table 4** uses some of those data.[16] Through October 31, 2008, FDA had issued 360 written requests for pediatric studies to manufacturers holding patent or other exclusivity benefits. The requests, which outlined 854 specific studies, also specified the study purpose: about half of the studies addressed efficacy and safety, and more than a third focused on aspects of pharmacokinetics.

**Table 4. Pediatric Exclusivity Statistics**

| | Number |
|---|---|
| FDA written requests | 360 |
| Exclusivity determinations | 171 |
| Drugs granted exclusivity | 157 |
| Labeling changed | 150 |

**Source:** CRS presentation of FDA data, at http://www.fda.gov/?cder/?pediatric.

Of those 360 written requests, FDA has made exclusivity determinations for 48% (n = 171), noting that the manufacturer has completed and submitted reports on the requested studies. It granted pediatric exclusivity to 92% (n = 157) of those, representing 151 active components. Through November 5, 2008, FDA attributed 157 labeling changes (involving 150 drugs) to BPCA.[17]

[15] FDA, "Pediatric Drug Development," at http://www.fda.gov/?cder/?pediatric.

[16] FDA, "Drugs to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act," updated November 13, 2008, at http://www.fda.gov/?cder/?pediatric/?exgrant.htm; "Pediatric Exclusivity Labeling Changes as of November 5, 2008," at http://www.fda.gov/?cder/?pediatric/?labelchange.htm; "Pediatric Exclusivity Statistics as of October 31, 2008," at http://www.fda.gov/?cder/?pediatric/?wrstats.htm; and "Studies Breakdown Report for Issued Written Requests as of October 31, 2008: Pediatric Exclusivity," at http://www.fda.gov/?cder/?pediatric/?breakdown.htm.

[17] Staff in the FDA Office of Legislation (telephone communication, November 25, 2008) noted the coincidence of 157 products with exclusivity and the 157 labeling changes. Studies can yield information for labeling changes although (continued...)

Of the 360 written requests, 52% (n = 190) have not progressed to an exclusivity determination. For those drugs, studies may be in progress or the manufacturers may have chosen not to accept exclusivity and the pediatric study requirements. Therefore, only 42% of the 360 requests have yielded pediatric labeling changes.

## NIH Route for Off-Patent Drugs and On-Patent Drugs for Which Manufacturers Declined FDA's Requests for Study

Under BPCA, the NIH list has 57 drug-indication entries.[18] NIH has recommended that no studies be pursued for 11 (19%) of those. **Table 5** divides the remaining 46 drugs recommended for pediatric study from 2003 through March 2007 by patent status and whether a study had begun. Thirteen (28%) have progressed to choice of clinical trial sites, an indication that they are funded.

**Table 5. Research Status of Drugs That NIH Deemed In Need of Pediatric Studies, by Patent Status**

| | Clinical trial site chosen | | | Total[Error! Reference source not found.] |
|---|---|---|---|---|
| **Patent status** | **Yes** | | **No** | |
| **On** | 4 | (29%) | 10 | 14 |
| **Off** | 9 | (28%) | 23 | 32 |
| **Total** | 13 | (28%) | 33 | 46 |

a. Total excludes the 11 off-patent products for which NIH does not recommend further study at this time.

**Source:** NICHD, "Table 1: Current Status of Drugs Which Have Been Listed by NIH (NICHD) for BPCA As of March 28, 2007," BPCA, at http://bpca.nichd.nih.gov/?about/?process/?upload/?Drug_Table_2007.pdf.

## GAO Study

In March 2007, the Government Accountability Office (GAO) issued a report that the BPCA legislation had required.[19] 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. The GAO report identified three main categories of labeling change: to inform of ineffective drugs, dosing that was too high or too low, and newly identified adverse events. It juxtaposed those findings with the statement that children take many of these drugs for common, serious, or life-threatening conditions.

(...continued)

FDA did not grant the product exclusivity.

[18] National Institute of Child Health and Human Development, "Best Pharmaceuticals for Children Act: Status of Drugs Listed by NICHD," at http://bpca.nichd.nih.gov/?about/?process/?status.cfm.

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

## Pediatric Research Equity Act

FDA has approved more than 500 new drug and biologics license applications since the beginning of 2003.[20] For that same period, FDA attributes 88 labeling changes to PREA.[21] **Table 5** indicates the topics of those label changes.

**Table 6. Content of PREA-Associated Labeling Changes**

| Topic of label change | Number of label changes |
|---|---|
| Extended indication | 5 |
| New active ingredient | 14 |
| New dosage form | 26 |
| New dosing regimen | 10 |
| New drug | 5 |
| New indication | 25 |
| New route of administration | 3 |
| **Total number of label changes**[a] | **88** |

a. The 88 changes apply to 76 products; 12 products had two label changes (e.g., Xopenex HFA Inhalation Aerosol had both a new active ingredient and an extended indication).

**Source:** FDA, "PREA Labeling Changes," updated August 8, 2008, at http://www.fda.gov/?CDER/?pediatric/?PREA_label_post-mar_2_mtg.pdf.

## FDA Activities

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

- **Rules and announcements,** such as "Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies; Availability," *Federal Register*, vol. 73, no. 45, March 6, 2008, pp. 12182-12183.
- **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.

[20] 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; "CDER Drug and Biologic Approvals for Calendar Year 2007," at http://www.fda.gov/?cder/?rdmt/?InternetNDA07.htm, and "CDER Drug and Biologic Approvals for Calendar Year 2008, Updated through September 30, 2008," at http://www.fda.gov/?cder/?rdmt/?InternetNDA08.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.

[21] FDA, "PREA Labeling Changes," updated August 8, 2008, at http://www.fda.gov/?CDER/?pediatric/?PREA_label_post-mar_2_mtg.pdf.

- **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."
- **Statistics,** such as "Pediatric Exclusivity Labeling Changes as of November 5, 2008," and "PREA Labeling Changes," updated August 8, 2008.

# Recurring Issues for Congress

Because Congress has reauthorized BPCA and PREA and passed PMDSIA, it may wait for their 2012 reauthorizations before taking further legislative action in this area. Meanwhile, regardless of legislative possibilities, there remain concerns about exclusivity, cost, labeling, enforcement, and sunsets. This report concludes by reviewing each.



## 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, in 2003:

> 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.[22]

In fact, Congress did exactly that: provided an incentive for something that is already a requirement. During the debate on PREA in 2003, Members of the Senate clearly had questions about this contradiction.[23] While Senator Gregg, as committee chair, wrote: "The Pediatric Rule was intended to work as a safety net to (or as a backstop to) pediatric exclusivity;" Senator 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.

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

[22] 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.

[23] S.Rept. 108-84, to accompany S. 650, the Pediatric Research Equity Act of 2003, June 27, 2003.

pediatric exclusivity provisions of section 505A of the Act...." The BPCA and PREA reauthorizations in 2007 did not change their relationship.

The contradiction remained, continued by FDAAA 2007, and is now law. At some point Congress may want to resolve this apparent paradox.

## Cost

In assessing the value of BPCA and PREA, it may be useful to identify the intended and unintended effects—both positive and negative—of their implementation. Let us say FDA grants a manufacturer a six-month exclusivity. Who benefits?

*The manufacturer.* 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.

*Other manufacturers.* 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.

*Government.* 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 insurers*. Private payers also face similar financial costs and benefits as public payers, without the regulatory costs of administering the program.

*Children and their families.* 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 generally 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 led 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.[24] 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.

[24] 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.

Although the BPCA reauthorization in 2007 continued the six-month exclusivity, the Senate bill would have limited the period of exclusivity for a drug to three months if its manufacturer/sponsor had more than $1 billion in annual gross U.S. sales for all its products with the same active ingredient. In future years, Congress might reexamine whether such limits may be in the public interest.

## Labeling

Pediatric studies can produce valuable information about safety, effectiveness, dosing, or side effects when a child takes a medication. Such information benefits children only when it reaches clinicians and others who care for children (including parents). BPCA 2002, PREA 2003, and their 2007 reauthorizations, therefore, included labeling provisions to make the information available.

As a result, FDA now 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;
- ? manufacturer has received pediatric exclusivity after conducting appropriate studies; or
- ? manufacturer has submitted the safety and effectiveness findings from pediatric assessments required under PREA.

In the first case, the labeling includes pediatric use information only if FDA approved the pediatric indication. If FDA turned down or the manufacturer withdrew a request for a pediatric indication, pediatric use information appears nowhere in the product's labeling. In addition, the fact that the manufacturer had made an unsuccessful attempt—and the research findings that blocked approval—would be neither noted in the label nor made public in other ways.

When it comes to exclusivity, the labeling rules 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. The labeling would also make clear 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.

The rules have created measurable change. Still, not all drugs used by children have labeling that addresses pediatric use. As previously noted, FDA approved more than 500 new drug and biologics license applications from the beginning of 2003 through September 2008.[25] Yet, the PREA statistics on labeling note 88 labeling changes over that period.

The PREA and BPCA reauthorizations in 2007 added the third circumstance of required pediatric labeling. Upon determining that a pediatric assessment or study does or does not demonstrate that the subject drug is safe and effective in pediatric populations or subpopulations, the Secretary must order the label to include information about those results and a statement of the Secretary's determination. That is true even if the study results were inconclusive.

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

Labeling is useful if its statements are clear, useful, and read. 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 among:

- ? studies in children found the drug to be ineffective;
- ? studies in children found the drug to be unsafe;
- ? studies in children were not conclusive regarding safety or effectiveness; or
- ? no studies had been conducted concerning pediatric use.

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. BPCA 2007 also strengthened the effect of labeling requirements by mandating the dissemination of certain safety and effectiveness information to health care providers and the public.

Although not included in the pediatric sections, another provision in FDAAA 2007 may yield benefits for pediatric labeling. Regarding television and radio direct-to-consumer (DTC) drug advertisements, the law required that major statements relating to side effects and contraindications be presented in a clear, conspicuous, and neutral manner. It further required that the Secretary establish standards for determining whether a major statement meets those criteria. The fruits of such inquiry could be applied throughout Agency communication.

Finally, BPCA 2003 had required HHS to promulgate a rule within one year of enactment regarding the placement on all drug labels of a toll-free telephone number with which to report adverse events. FDA issued a proposed rule in 2004 but has not yet finalized it. BPCA 2007 required that the 2004 proposed rule take effect on January 1, 2008 unless the Commissioner issued the final rule before then. It limited the rule's application to exclude certain drugs whose packaging already includes a toll-free number for consumers to report complaints to their manufacturers or distributors.[26]



## Enforcement

FDA's postmarket authority regarding pediatric drug use labeling has been limited. Congress had 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 its PREA 2003 bill, the Senate committee noted its intent that the misbranding authority regarding pediatric use labeling not be the basis for criminal proceedings or withdrawal of approval, and

[26] FDA issued the final rule on October 28, 2008. Its effective date is November 28, 2008, and its compliance date is July 1, 2009 (FDA [21 CFR Parts 201, 208, and 209], "Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products; Final rule," *Federal Register*, v. 73, no. 209, October 28, 2008, pp. 63886-63897).

only rarely result in seizure of the offending product.[27] The 2007 reauthorization continues this approach.

Again outside its pediatric-specific sections, FDAAA created a new enforcement authority for FDA: civil monetary penalties. Framed in the context of giving FDA tools to create meaningful incentives for manufacturer compliance with a range of postmarket safety activities, the provision listed labeling within its scope. In Senate and House committee discussions of what maximum penalties to allow, proposed one-time penalties were as low as $15,000 and proposed upper levels ranged to $50 million. The final provision says that an applicant violating certain requirements regarding postmarket safety, studies or clinical trials, *or labeling* is subject to a civil monetary penalty of not more than $250,000 per violation, and not to exceed $1 million for all such violations adjudicated in a single proceeding. If a violation continues after the Secretary provides notice of such violation to the applicant, the Secretary may impose a civil penalty of $250,000 for the first 30 days, doubling for every subsequent 30-day period, up to $1 million for one 30-day period, and up to $10 million for all such violations adjudicated in a single proceeding. The Secretary must, in determining the amount of civil penalty, consider whether the sponsor is making efforts toward correcting the violation.

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 can 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.

There are actions, as well, for the Secretary. BCPA 2007 expanded the Secretary's authority and, in some cases, requires action. The Secretary must publish within 30 days of the Secretary's determination regarding market exclusivity and must include a copy of the written request that specified what studies were necessary. The Secretary must also publicly identify any drug with a developed pediatric formulation that studies have demonstrated to be safe and effective for children if its sponsor has not introduced the pediatric formulation onto the market within one year.

## Sunset

Not every law contains a sunset provision. BPCA does, and, although it doesn't use the term, Congress structured PREA 2003 to cease if and when BPCA did. 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."[28]

[27] S.Rept. 108-84.

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

The sunset provision for BPCA's exclusivity incentive to manufacturers has not engendered congressional debate. During PREA consideration in 2003, however, some Members had objected, unsuccessfully, to linking PREA's safety and effectiveness assessment and resulting pediatric labeling to the BPCA sunset. By the committee markups of PREA in 2007, some Members advocated making the mandatory pediatric assessments permanent. If Congress intended the PREA sunset to trigger regular evaluation of the law's usefulness, there may be other legislative approaches that would more directly achieve that.

If, however, the intent was to test the idea of requiring pediatric assessments, the past five years had provided satisfactory evidence.[29] The House-passed bill would have eliminated PREA's link to the BPCA sunset provision; the Senate-passed bill continued it. The enacted bill included the linkage written in the 2003 legislation. At some point, Congress may wish to evaluate the usefulness and effect of that link.

# Concluding Comments

Congress has now repeatedly acted to encourage research into the unique effects of FDA-regulated drugs on children—with both carrots of financial incentive and sticks of required action. It has also required that drug labeling reflect the findings of pediatric research, whether positive, negative, or inconclusive. And, most recently, it has given FDA broader authority to follow up and enforce these requirements.

With each step of legislative and regulatory action over the years, Congress and FDA have tried to balance goals that often conflict:

- drug development to address needs unique to children;
- tools to encourage drug manufacturers to do this, despite the expense, opportunity costs, and liability risk;
- public access to up-to-date and unbiased information on drug safety and effectiveness;
- pharmaceutical industry needs; and
- adequate funding.

Concerns remain, though, about many of the issues discussed during last year's reauthorizations—and in the last section of this paper. Against the backdrop of this fall's financial crisis and the uncertainty about how that will affect the priorities of a new President and Congress, it is hard to predict whether the 111th Congress will wish to address them. They may surface only when reauthorizations are due in 2012.

But the likely legislative debate over health care reform offers Congress opportunities to further ensure safe and effective drugs for children. Some proposed reform elements, such as

[29] 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.

transparency and evidence-based decisions, already appear in BPCA and PREA. For pediatric drugs, using the appropriate dose for the appropriate illness for the appropriate patient is not only good health care but avoids expensive unnecessary, ineffective, or unsafe treatment. Assessing the administrative and research success (or drawbacks) of the BPCA and PREA programs could inform congressional debate over health care organization and financing to help control the cost of reforms that attempt to broaden access to care.

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