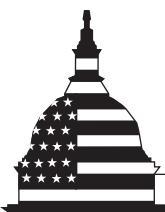


May 2011

PEDIATRIC RESEARCH

Products Studied under Two Related Laws, but Improved Tracking Needed by FDA



G A O

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Why GAO Did This Study

In 2007, Congress reauthorized two laws, the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). PREA requires that sponsors conduct pediatric studies for certain products unless the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) grants a waiver or deferral. Sponsors submit studies to FDA in applications for review. BPCA is voluntary for sponsors. The FDA Amendments Act of 2007 required that GAO describe the effect of these laws since the 2007 reauthorization. GAO (1) examined how many and what types of products have been studied; (2) described the number and type of labeling changes and FDA's review periods; and (3) described challenges identified by stakeholders to conducting studies. GAO examined data on the studies from the 2007 reauthorization through June 2010, reviewed statutory requirements, and interviewed stakeholders and agency officials.

What GAO Recommends

GAO recommends that the Commissioner of FDA track applications during its review process and maintain aggregate data on applications subject to PREA. HHS agreed that better tracking of information is needed but disagreed with GAO's finding that it does not track applications. While FDA is able to identify the status of individual applications during its review, it has not maintained data that would allow it to better manage its review process.

View [GAO-11-457](#) or key components. For more information, contact Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

PEDIATRIC RESEARCH

Products Studied under Two Related Laws, but Improved Tracking Needed by FDA

What GAO Found

At least 130 products—80 products under PREA and 50 under BPCA—have been studied for use in children since the 2007 reauthorization. However, FDA cannot be certain how many additional products may have been studied because FDA does not track and aggregate data about applications submitted under PREA that would allow it to manage the review process. FDA was unable to provide information about some applications that had been submitted to the agency that were subject to PREA. Recent improvements to FDA's data system might assist the agency in tracking future applications. Under PREA, FDA has granted most of the study waivers and deferrals requested by sponsors since the 2007 reauthorization. Under BPCA, FDA granted pediatric exclusivity—an additional 6 months of market exclusivity, which generally delays marketing of generic forms of the product—to the sponsors of 44 of the 50 drugs in exchange for conducting pediatric studies. Because BPCA is voluntary, sponsors may decline FDA's request for pediatric studies. Although BPCA includes provisions to encourage the study of drugs when sponsors have declined FDA's request, few drugs have been studied under these provisions.

Since the 2007 reauthorization, all of the 130 products with pediatric studies completed and applications reviewed under PREA and BPCA had labeling changes that included important pediatric information. The most commonly implemented labeling change expanded the pediatric age groups for which a product was indicated. The next most common type of labeling change indicated that safety and effectiveness had not been established in pediatric populations and provided a description of the study conducted. Additional labeling changes were recommended for products as a result of FDA's monitoring of adverse events associated with products after they had been approved for marketing. FDA officials said they need to complete their review of the application, including all studies, before they can reach agreement with the sponsor on labeling changes.

Stakeholders, including sponsors, pediatricians, and health advocacy organizations, described challenges faced by sponsors that could limit the success of PREA and BPCA. Those challenges included confusion about how to comply with PREA and BPCA due to a lack of guidance from FDA for changes to the laws from the 2007 reauthorization of PREA or BPCA. FDA officials explained that they mitigate this lack of guidance by discussing questions or concerns that sponsors have regarding their pediatric studies with sponsors throughout the process. An additional challenge sponsors described was a lack of economic incentives to study products with no remaining market exclusivity.

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Abbreviations

BPCA	Best Pharmaceuticals for Children Act
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997
FNIH	Foundation for the National Institutes of Health
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
NIH	National Institutes of Health
PAC	Pediatric Advisory Committee
PeRC	Pediatric Review Committee
PIP	paediatric investigation plan
PREA	Pediatric Research Equity Act
PPSR	Proposed Pediatric Study Request

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United States Government Accountability Office
Washington, DC 20548

May 31, 2011

The Honorable Tom Harkin
Chairman
The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Fred Upton
Chairman
The Honorable Henry A. Waxman
Ranking Member
Committee on Energy and Commerce
House of Representatives

Congress and the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) have worked to increase the number of drug and biological products studied for use in children.¹ According to an article by FDA officials, researchers reported in 1999 that 81 percent of products used by children lacked sufficient information or labeling regarding pediatric use.^{2,3} Products not labeled for pediatric use place children at risk of being exposed to ineffective or harmful treatment or receiving incorrect dosing. Since the late 1990s, Congress has passed laws to encourage or require product sponsors, typically the product's manufacturer, to conduct pediatric studies,⁴ including the Pediatric Research Equity Act (PREA)⁵ and the Best Pharmaceuticals for Children

¹Biological products are derived from living sources (such as humans, animals, and microorganisms), unlike drugs, which are chemically synthesized. Biological products include blood, vaccines, allergenic products, certain tissues, and cellular and gene therapies. See 42 U.S.C. § 262(i).

²See D. K. Benjamin Jr., et al, "Safety and Transparency of Pediatric Drug Trials," *Archives of Pediatrics & Adolescent Medicine*, vol. 163, no. 12 (2009).

³Drug or biological product "labeling" includes all labels and other written, printed, or graphic materials on any container, wrapper, or materials accompanying the product. 21 U.S.C. § 321(k), (m).

⁴A drug or biological product sponsor is the person or entity who assumes responsibility for the marketing of a new product, including responsibility for complying with applicable laws and regulations.

⁵21 U.S.C. §§ 355c, 355d.

Act (BPCA).⁶ As a result of these efforts, prior to the most recent reauthorizations of PREA and BPCA, pediatric studies resulted in approximately 250 labeling changes that added or clarified information on pediatric use of the product.

In 2007, as a part of the FDA Amendments Act of 2007 (FDAAA),⁷ Congress reauthorized PREA and BPCA in order to increase the number of products studied for use in children. PREA requires that sponsors conduct pediatric studies for certain drug and biological products before they are marketed unless FDA grants a waiver or deferral for some or all pediatric studies. A waiver removes the requirement that some or all studies be completed, and a deferral allows the sponsor to conduct a study by a specified date after the product has been approved for marketing. BPCA, however, is voluntary for the sponsor; it authorizes FDA to provide an incentive of an additional 6 months of market exclusivity to product sponsors that conduct pediatric studies requested by FDA. This market exclusivity generally delays marketing of generic forms of the product and is known as pediatric exclusivity. Pediatric exclusivity can only be granted to those products that are “on-patent”—that is, those that have patent protection or market exclusivity.⁸ BPCA also includes provisions (1) to allow for the funding of pediatric studies of on-patent drugs that the sponsor declined to study by the Foundation for the National Institutes of Health (FNIH)⁹ and (2) to allow for the conduct of studies of “off-patent” products, which no longer have market exclusivity, through the National Institutes of Health (NIH).¹⁰

The results of pediatric studies conducted under PREA and BPCA are submitted to FDA in an application. The application includes pediatric

⁶21 U.S.C. § 355a; 42 U.S.C. § 284m.

⁷Pub. L. No. 110-85, §§ 401-404, 501-503, 121 Stat. 823, 866-90 (2007).

⁸See 21 U.S.C. § 355a(n)(1)(B); 42 U.S.C. § 284m. For purposes of this report, we refer to drug and biological products that have patent protection or market exclusivity as “on-patent” and those whose patent protection or market exclusivity has ended as “off-patent”. This is the same terminology typically used by government agencies to describe the exclusivity status of a product under BPCA.

⁹FNIH is an independent, nonprofit corporation. The majority of funds that FNIH receives are from the private sector. FNIH funds are used for a variety of purposes, including awards to researchers to conduct studies related to BPCA. See 42 U.S.C. § 290b.

¹⁰NIH is an agency within HHS and is comprised of 27 institutes and centers, each with a specific research agenda.

study results and suggested labeling changes, among other things.¹¹ FDA reviews the application and works to come to agreement with the sponsor on labeling changes, which FDA then approves as part of its approval of the application.¹² PREA and BPCA require that one year after a product's labeling change is implemented, any adverse events reported for that product be reviewed. FDA may require additional labeling changes based on the adverse events.¹³

FDAAA required that we describe the effect PREA and BPCA have had on the study and labeling of drug and biological products for pediatric use.¹⁴ To respond to the requirement in FDAAA that we report our findings to you no later than January 1, 2011, we briefed you on our findings on December 15, 2010. This report contains information we provided during that briefing as well as additional information in which you expressed interest. As discussed with the committees of jurisdiction, we (1) examine how many and what types of drug and biological products have been studied under PREA and BPCA since their 2007 reauthorization; (2) describe the number and type of labeling changes and FDA's review periods for reaching agreement on these changes for the drug and biological products for which studies have been completed since the 2007 reauthorization; and (3) describe challenges identified by stakeholders, including sponsors and other interested parties, to conducting pediatric studies. FDAAA also required that we describe efforts by FDA and NIH to encourage studies in neonates, which are children under the age of one month. We discuss these efforts in appendix I.

¹¹For products studied under PREA or BPCA, sponsors generally submit new drug applications, supplemental new drug applications, biologics license applications, or supplemental biologics license applications to FDA. Before a drug or biological product can be marketed in the United States, the sponsor must submit a new drug application or a biologics license application to FDA containing data demonstrating the safety and efficacy of the product. After a product is marketed, sponsors submit supplemental new drug applications or supplemental biologics license applications to support proposed changes to a product's labeling, a new dosage form or strength of the product, a new patient population or intended use, or changes to the way the product is manufactured. See 21 U.S.C. § 355 (drugs); 42 U.S.C. § 262 (biological products).

¹²Although the product studied might be new to the market and, therefore, its labeling would be new and not a change, FDA characterizes the agreement on labeling as a "labeling change" under PREA and BPCA.

¹³FDA uses the term "adverse event" to refer to any untoward medical event associated with the use of a drug or biological product in humans.

¹⁴Pub. L. No. 110-85, § 404, 121 Stat. 823, 875-76.

To examine how many and what type of drug and biological products have been studied under PREA and BPCA since their 2007 reauthorization, we reviewed FDA and NIH data on products studied in pediatric populations from the date of the 2007 reauthorization of PREA and BPCA through June 30, 2010, the most recent date for which data were available at the time of our analysis.¹⁵ Specifically, we examined data on the number of products for which studies have been completed since the 2007 reauthorization. These studies were generally initiated prior to the reauthorization. We also examined data on the number of products for which studies were initiated since the 2007 reauthorization.¹⁶ These studies are generally still ongoing. We compared FDA's procedures for tracking applications submitted under PREA to the standards described in the *Standards for Internal Control in the Federal Government*.¹⁷ In examining FDA's procedures for tracking data, we examined the agency's ability to locate individual applications and its ability to track aggregate data about applications that would allow FDA to manage the review process, including the total number of applications subject to PREA, whether those applications were complete, and whether PREA applications included pediatric studies or requests for waivers or deferrals at the time of submission. We reviewed FDA data in order to determine the extent to which FDA waived or deferred the requirement for sponsors to submit studies under PREA. We also reviewed FDA data on the therapeutic areas, or conditions treated, for the products

¹⁵The 2007 reauthorization of PREA and BPCA was enacted and went into effect on September 27, 2007.

¹⁶FDA generally reports data to the public on the number of studies conducted under PREA and BPCA, but for the purposes of this report we report on the number of products studied. Since sponsors can conduct multiple studies per product, the number of products studied will be less than the total number of studies conducted. We counted each application submitted by the sponsor to FDA as one product. We counted the following types of applications: new drug applications, supplemental new drug applications, biologics license applications, and supplemental biologics license applications. For studies conducted under BPCA, FDA reports studies by active moiety, or molecule responsible for the physiological or pharmacological action of the drug substance, rather than product. A single moiety could be active in multiple products, such as different strengths of the same dosage form, or a moiety could be present in different dosage forms such as a lotion form and a tablet form. Therefore, because we analyzed the number of products studied, not moieties studied, we may report a different number of products studied than the moieties reported by FDA. For the purposes of our report when we refer to products studied, we are referring to products whose studies have been completed and for whom FDA has completed the application review for the product. In addition, for the purposes of our analyses, we considered all products with biologics license applications as biological products.

¹⁷See GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: November 1999). Internal control comprises the plans, methods, and procedures used to meet missions, goals, and objectives.

studied under PREA and BPCA. In addition, we interviewed officials from FDA, NIH, and FNIH.

To describe the number and type of labeling changes and FDA's review periods for reaching agreement on these changes for drug and biological products for which studies have been completed since the 2007 reauthorization, we analyzed FDA data on all pediatric labeling changes from the date of the 2007 reauthorization of PREA and BPCA through June 30, 2010, the most recent date for which the data were available at the time of our analysis.¹⁸ Specifically, we determined the number and types of labeling changes that have been approved both as a result of pediatric studies and reported adverse events. In addition, we reviewed requirements in PREA and BPCA for reaching agreement on labeling changes and FDA documents on performance goals. We also interviewed FDA officials.

To describe challenges identified by stakeholders to conducting pediatric studies, we interviewed various stakeholders and reviewed articles written by some of these stakeholders. These stakeholders included representatives from five drug and biological product sponsors; three trade groups: the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization,¹⁹ and the Generic Pharmaceutical Association; and several health advocacy organizations, including the American Academy of Pediatrics, the National Organization for Rare Disorders, the Elizabeth Glaser Pediatric AIDS Foundation, the Tufts Center for the Study of Drug Development, the Institute for Pediatric Innovation, and the Pediatric Pharmacy Advocacy Group. In addition, we interviewed officials from FDA, NIH, and FNIH.

To assess the reliability of data that FDA and NIH provided, we interviewed agency officials. FDA and NIH officials described how they maintained data on pediatric studies conducted under PREA and BPCA, the resulting labeling changes, and pediatric adverse events. FDA generally maintained the information in separate files rather than centralized databases. To the extent possible, we looked for other sources of

¹⁸We also reviewed data on labeling changes that occurred prior to the 2007 reauthorization in order to provide context to the total number of labeling changes that have occurred as a result of laws providing for pediatric studies, some form of which has been in existence since 1997.

¹⁹The Biotechnology Industry Organization assisted us in convening a panel discussion that included representatives from four drug and biological product sponsors.

information to corroborate or provide perspective on the data FDA supplied. For example, we looked to data that is posted on FDA's Web site and compared it, when possible, to data provided directly by FDA. Although we found that FDA does not maintain certain data on the programs, we generally found the data that FDA maintains to be reliable for our purposes.

We conducted this performance audit from December 2009 through May 2011 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

The FDA Modernization Act of 1997 (FDAMA) established pediatric exclusivity for sponsors that conducted pediatric studies for drugs.²⁰ In 1999, FDA implemented the Pediatric Rule, which required that sponsors include the results of pediatric studies when submitting certain new drug or biological product applications.²¹ However, in 2002, the Pediatric Rule was declared invalid by a federal court.²² In 2002, Congress reauthorized FDAMA's pediatric exclusivity provisions in BPCA, and in 2003, Congress codified much of the Pediatric Rule in PREA, requiring that pediatric studies be conducted and that the results of those studies be included in certain new drug or biological product applications. In September 2007, Congress reauthorized both PREA and BPCA as a part of FDAAA, and in March 2010, Congress extended pediatric exclusivity and applicable BPCA provisions to biological products as a part of the Patient Protection and

²⁰Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305-09.

²¹63 Fed. Reg. 66,632-66,672 (Dec. 2, 1998).

²²Implementation of the Pediatric Rule prompted a lawsuit against FDA by the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert, which claimed that FDA acted outside of its authority in issuing the Pediatric Rule. In 2002, the court ruled that FDA exceeded its authority in issuing the rule and declared the rule invalid. *Association of American Physicians & Surgeons v. FDA*, 226 F. Supp.2d 204 (D.D.C. 2002).

Affordable Care Act.²³ PREA and BPCA are both set to expire on October 1, 2012.²⁴

PREA

PREA requires that sponsors submit the results of pediatric studies in certain drug and biological product applications to FDA. Specifically, PREA applies to drug and biological product applications for any of the following: a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration. In addition, PREA requires that pediatric studies be conducted for the indications described in the application—that is, the indications for which the sponsor plans to market the product—but not for any additional indications.

The 2007 reauthorization of PREA established the Pediatric Review Committee (PeRC), an internal FDA committee responsible for providing assistance in the review of pediatric study results and increasing the consistency and quality of such reviews across the agency.²⁵ The PeRC consists of approximately 40 FDA employees with a range of expertise, including pediatrics, biopharmacology, statistics, chemistry, legal issues, pediatric ethics, and others as pertinent to the pediatric product under review. FDA officials explained that the PeRC is divided into separate subcommittees for PREA and BPCA.

When a sponsor completes all of the required studies for a drug or biological product, it submits an application to FDA.²⁶ The application includes these study results and suggested labeling changes based on the pediatric studies' findings, among other things. If the pediatric studies have not been completed, the application must include a request for a waiver or deferral of the pediatric studies. PREA established certain criteria under which, at the sponsors' request, some or all of the required pediatric studies may either be deferred until a specified date after

²³Pub. L. No. 111-148, § 7002(g)(1), 124 Stat. 119, 819-20 (to be codified at 42 U.S.C. § 262(m)).

²⁴21 U.S.C. §§ 355a(q), 355c(m).

²⁵See 21 U.S.C. § 355d.

²⁶Applications that are subject to PREA are submitted to FDA for approval and undergo a broad application review process that, in addition to reviewing pediatric studies, reviews the results of adult studies and determines whether the application demonstrates that the product is safe and effective for the indicated population.

approval of the product's application or waived altogether by FDA.²⁷ FDA may also grant a deferral or waiver on its own initiative, under specified circumstances. For example, a study required under PREA may be deferred when additional data on the safety and effectiveness of the product in adults is needed before the product can be studied for use in children. If the sponsor requests a deferral, the product's application must include, among other things, a description of the planned pediatric studies and a time frame for completion. The study may be waived when it is determined to be impossible or highly impracticable, such as when the number of pediatric patients with a disease that may be treated with that product is too small to study. Sponsors may conduct multiple studies per product, such as separate studies for subsets of pediatric populations like infants, children, and adolescents. FDA may grant waivers or deferrals for only one type of study, such as in one pediatric age group, or FDA may grant waivers or deferrals for all pediatric studies of the product.

FDA's review of an application under PREA is part of the agency's broader review of the entire application. Once the sponsor submits its application, FDA directs the application to the agency's appropriate division to review the entire application, including all adult study results, the pediatric study results, and requests for a waiver or deferral. FDA may determine that the application is incomplete and more information is necessary from the sponsor. Generally, when this happens, FDA notifies the sponsor and waits to finish reviewing the application until the information is received. According to FDA officials, toward the end of FDA's review, the division provides requests for a waiver or a deferral and a summary of the relevant pediatric data to the PeRC for review. The PeRC provides recommendations on whether or not the pediatric portion of the application satisfies PREA requirements and whether to grant or deny a waiver or deferral. FDA then determines whether or not to approve the application. As a part of the review process, FDA is required by PREA to negotiate and reach an agreement with the sponsor on labeling changes based on pediatric studies within 180 days of the application's

²⁷21 U.S.C. § 355c(a)(3), (4). If a waiver is granted because the product would be ineffective and/or unsafe in children, such information must be included in the product's labeling.

submission.²⁸ If FDA and the sponsor are unable to reach an agreement on labeling changes within 180 days, they are required by PREA to proceed to a formal dispute resolution process. The 2007 reauthorization of PREA provided FDA with authority to make labeling changes on its own initiative when a product has been studied for use in children, including when a study does not determine that the product is safe or effective in pediatric populations. Therefore, FDA can impose a labeling change unilaterally to describe FDA's determination about the study results in the event that the agency cannot reach agreement with the sponsor.

A sponsor can request that a drug or biological product that is required to be studied under PREA be studied under BPCA as well, to allow the sponsor of the product to be eligible to receive pediatric exclusivity.²⁹ According to FDA officials, the sponsor can make this request through a proposed pediatric study request (PPSR). If FDA agrees, it issues a formal written request to the sponsor that outlines, among other things, the nature of the pediatric studies that the sponsor must conduct in order to qualify for pediatric exclusivity. (See fig. 1.) According to FDA officials, the pediatric studies requested under BPCA would generally also fulfill the PREA requirement; however, even if the sponsor does not complete the studies outlined in the BPCA written request, it is still required to complete any studies required under PREA. FDA officials said that pediatric studies conducted under BPCA are generally more extensive than those required under PREA. For example, the written request could

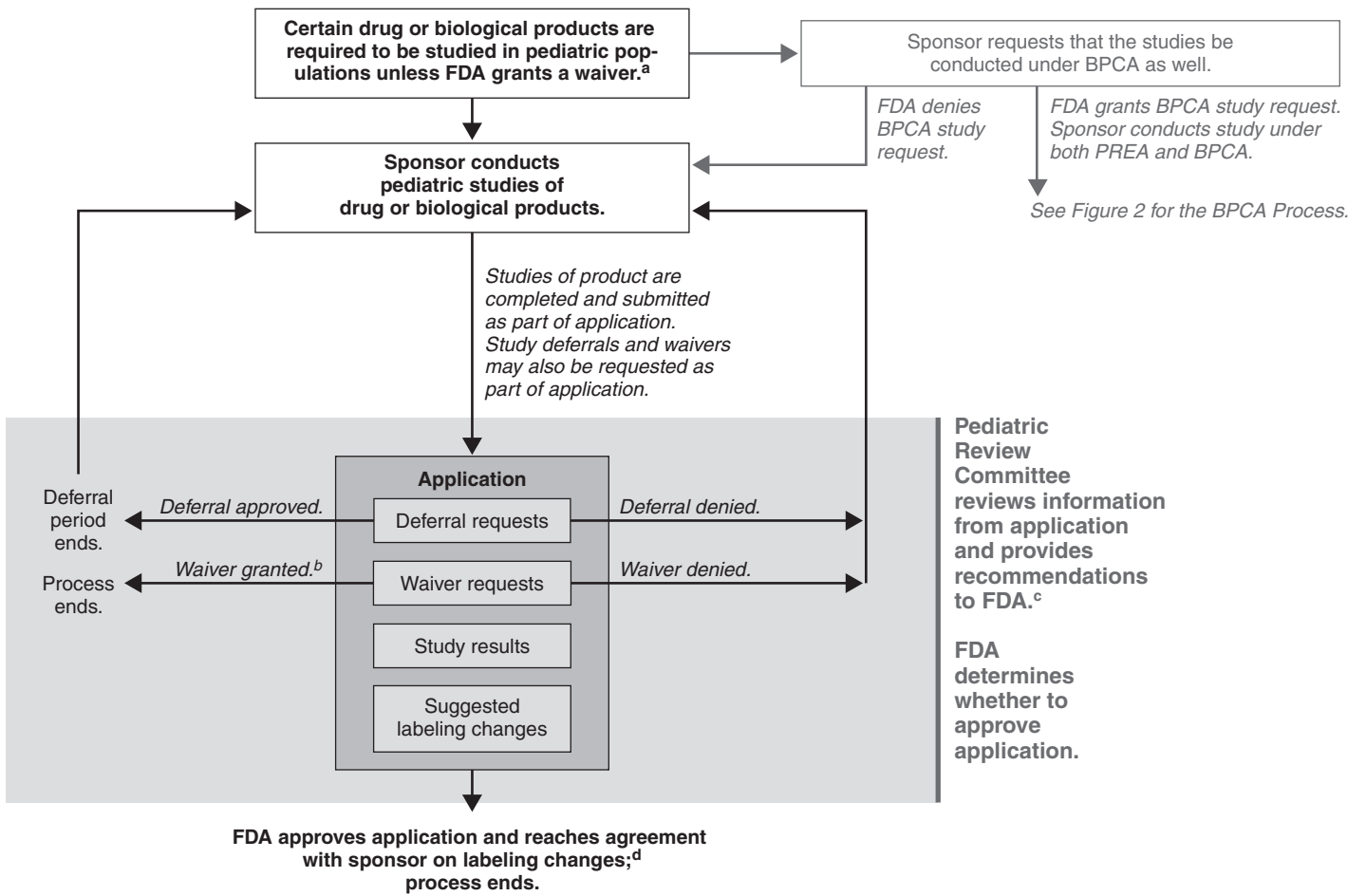
²⁸21 U.S.C. § 355c(g)(1). FDA's review of proposed labeling changes is part of its review of the application. Application review is subject to its own specified time frames. Under the 2007 reauthorization of the prescription drug user fee program as a part of FDAAA, FDA committed to performance goals related to the review of drug applications and biologics license applications, including time frames within which it seeks to review applications. See Pub. L. No. 110-85, § 101(c), 121 Stat. 823, 825 (2007). The performance goals are identified in letters sent by the Secretary of Health and Human Services to the Chairman of the Senate Committee on Health, Education, Labor, and Pensions and the Chairman of the House Committee on Energy and Commerce and are published on FDA's Web site. Each fiscal year, FDA is required to submit a report on its progress in achieving those goals and future plans for meeting them. See 21 U.S.C. § 379h-2(a). Under these performance goals, drug and biological product applications are classified as either priority or standard, and FDA committed to completing its review of 90 percent of priority applications within 180 days of submission and 90 percent of standard applications within 300 days of submission. Applications submitted under PREA may be either priority or standard, depending on the characteristics of the applications.

²⁹For the purposes of this report, we report data on products studied in this manner under BPCA. FDA reports data on these products in a separate category of products studied under both PREA and BPCA.

include studies for indications in addition to those described by the sponsor in its application, such as those that are relevant to children.³⁰

³⁰These additional indications are often referred to as “off-label” indications.

Figure 1: PREA Process



Source: GAO analysis of PREA requirements.

^aPREA applies to drug and biological product applications for any of the following: a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration.

^bIf a waiver is granted because the product would be ineffective and/or unsafe in children, such information must be included in the product's labeling.

^cFDA provides requests for a waiver or a deferral and a summary of the relevant pediatric data to the Pediatric Review Committee for review.

^dPREA requires that FDA and the sponsor enter dispute resolution if the labeling change is not agreed upon within 180 days of the application's submission.

BPCA

Under BPCA, sponsors receive pediatric exclusivity as an incentive to conduct studies of drug and biological products for use in children.³¹ The BPCA process formally begins when FDA determines that information related to the use of the product in a pediatric population may produce health benefits and issues a written request for pediatric studies to the sponsor of a product. Written requests may be issued for new, not previously marketed, drug or biological products or to products that are already on the market but still on-patent. FDA may issue a written request on its own initiative or after it has received and agreed to a PPSR from a sponsor to conduct a study under BPCA. The PeRC reviews all written requests and provides recommendations prior to their issuance to sponsors. According to FDA officials, in the written request, FDA may ask for more than one study of a single drug or biological product, such as studies for multiple indications or separate studies for different age groups, such as infants, children, and adolescents. BPCA requires that FDA take into account adequate representation of children of ethnic and racial minorities when developing written requests.³² (See app. II for information on FDA's efforts to ensure the inclusion of racial and ethnic minorities in pediatric studies.) The sponsor must respond to FDA within 180 days of receiving the written request indicating whether the sponsor agrees to the request and, if so, when the pediatric study will be initiated. If the sponsor does not agree to the request, the sponsor must state the reasons for declining the request.

When the pediatric studies are complete, the sponsor submits the results to FDA in an application, which must include any suggested labeling changes resulting from the studies' findings. FDA recommends that the application be submitted 15 months prior to the end of the sponsor's market exclusivity for the product in order to be considered for pediatric

³¹In March 2010, the Patient Protection and Affordable Care Act extended pediatric exclusivity and applicable BPCA provisions to biological products. See Pub. L. No. 111-148, § 7002(g)(1), 124 Stat. 119, 819-20 (codified at 42 U.S.C. § 262(m)).

³²In a 2003 report, we recommended FDA specify in its written requests that sponsors use the standard racial and ethnic categories described in FDA's January 2003 draft guidance. See GAO, *Pediatric Drug Research: Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children*, [GAO-03-950](#) (Washington, D.C.: Sept. 26, 2003), p. 18.

exclusivity.³³ Once the sponsor submits its application, FDA is to review the sponsor's application in order to (1) determine whether or not to approve the application, (2) negotiate and reach an agreement with the sponsor on pediatric labeling changes, and (3) grant or deny pediatric exclusivity. FDA is to grant pediatric exclusivity if the study meets the conditions outlined in the written request, regardless of the study's findings. Specifically, in determining whether to grant or deny pediatric exclusivity, BPCA requires that FDA assess whether the studies fairly responded to the written request, were conducted in accordance with commonly accepted scientific principles and protocols, and were properly submitted.³⁴

During FDA's review of the application, the PeRC may review a summary of relevant pediatric data from the application and provide recommendations to FDA on whether or not to grant pediatric exclusivity. FDA then determines whether or not to approve the application. In addition, if FDA and the sponsor are unable to reach an agreement on the labeling changes within 180 days, they are required by BPCA to proceed to the same formal dispute resolution process that exists for PREA.³⁵ The 2007 reauthorization of BPCA provided FDA with authority to make labeling changes on its own initiative when a product has been studied for use in children, including when a study does not determine that the product is safe or effective in pediatric populations. Therefore, FDA can impose a labeling change unilaterally to describe FDA's determination about the study results in the event that the agency cannot reach agreement with the sponsor.

³³BPCA requires that FDA make the determination that the sponsor has met the study requirements outlined in the written request 9 months prior to the end of the drug or biological product's market exclusivity. 21 U.S.C. § 355a(b)(2), (c)(2). FDA officials explained that because BPCA provides the agency with 180 days to review the study results, FDA recommends that the sponsor submit its results 15 months prior to the end of its market exclusivity. See 21 U.S.C. § 355a(d)(3).

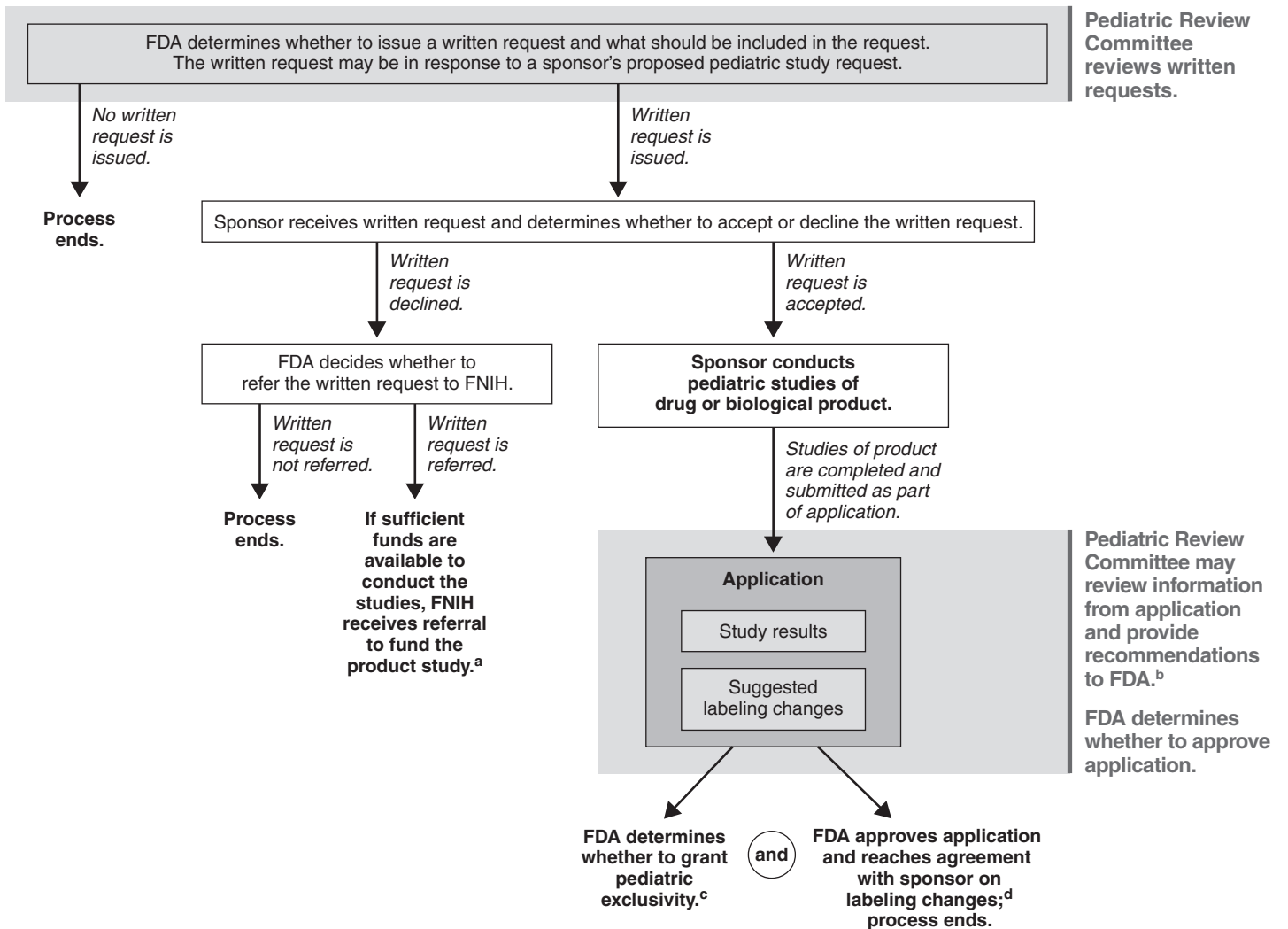
³⁴21 U.S.C. § 355a(d)(3). Pediatric exclusivity applies to all approved uses of the drug or biological product, not just those studied in children. Therefore, if the studies find that the product is not safe for use by children, the product will still receive pediatric exclusivity—that is, extended market exclusivity—for the adult uses of the product.

³⁵21 U.S.C. § 355a(i)(2). FDA's review of proposed labeling changes is part of its review of the application. BPCA requires that all applications submitted under BPCA that propose a labeling change receive priority status and be subject to FDA's performance goals for priority products, under which FDA seeks to complete its review of 90 percent of priority applications within 180 days of submission. See 21 U.S.C. § 355a(i)(1). PREA does not contain this requirement.

BPCA includes provisions for the conduct of pediatric studies even if the sponsor declines the written request. If a sponsor declines a written request by FDA to study an on-patent drug or if a sponsor does not complete studies outlined in an accepted written request, FDA may refer the written request to FNIH if it determines that there is a continuing need for information relating to the use of the drug in the pediatric population. (See fig. 2.) If FNIH is not able to fund all studies, BPCA requires that FDA consider whether to require the studies described in the written request under PREA.³⁶

³⁶Under a provision in BPCA added by the 2007 reauthorization, if FNIH does not have sufficient funds, FDA is required to consider whether to require a sponsor of an on-patent drug already on the market to conduct pediatric studies under PREA. FDA may require studies in this manner if FDA finds that the product is used for a substantial number of pediatric patients for the labeled indication and adequate pediatric labeling could confer a benefit on pediatric patients, the product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for a labeled indication, or the absence of adequate pediatric labeling could pose a risk to pediatric patients. 21 U.S.C. § 355a(n), § 355c(b). FDA has never invoked this provision to require studies of on-patent products for which sponsors have declined written requests.

Figure 2: BPCA Process for On-Patent Drug or Biological Products



Source: GAO analysis of BPCA requirements.

^aIf FNIH does not have sufficient funds, BPCA requires that FDA consider whether to require the studies described in the written request under PREA.

^bFDA may provide a summary of relevant pediatric data to the Pediatric Review Committee for review.

^cAccording to agency officials, FDA can deny a sponsor pediatric exclusivity, but still approve labeling changes based on the studies conducted.

^dBPCA requires that FDA and the sponsor enter dispute resolution if the labeling change is not agreed upon within 180 days of the application's submission.

The process under BPCA for off-patent products differs from the process for on-patent products. To further the study of off-patent products, NIH—in consultation with FDA and experts in pediatric research—is required to develop and publish a list of priority needs in pediatric therapeutics, including products or indications that require study, every 3 years. NIH publishes this list on its Web site and in the *Federal Register*.³⁷ NIH may submit a PPSR to FDA for the study under BPCA of an indication of an off-patent product that is used for one of the pediatric therapeutic areas described on the NIH list of priority needs. FDA is then to determine whether to issue a written request in response to NIH's PPSR to all sponsors of the drug or biological product, including the product's original sponsor as well as any manufacturers of the generic product.³⁸ The PerC reviews all written requests and provides recommendations prior to their issuance to sponsors. If a sponsor were to accept the written request, it would conduct the studies outlined in the request and then submit the study results and any suggested labeling changes to FDA for review. However, according to FDA officials, a sponsor has not accepted a written request to study an off-patent product since the 2007 reauthorization. Off-patent products do not qualify for pediatric exclusivity, so there are few financial incentives to conduct the studies.

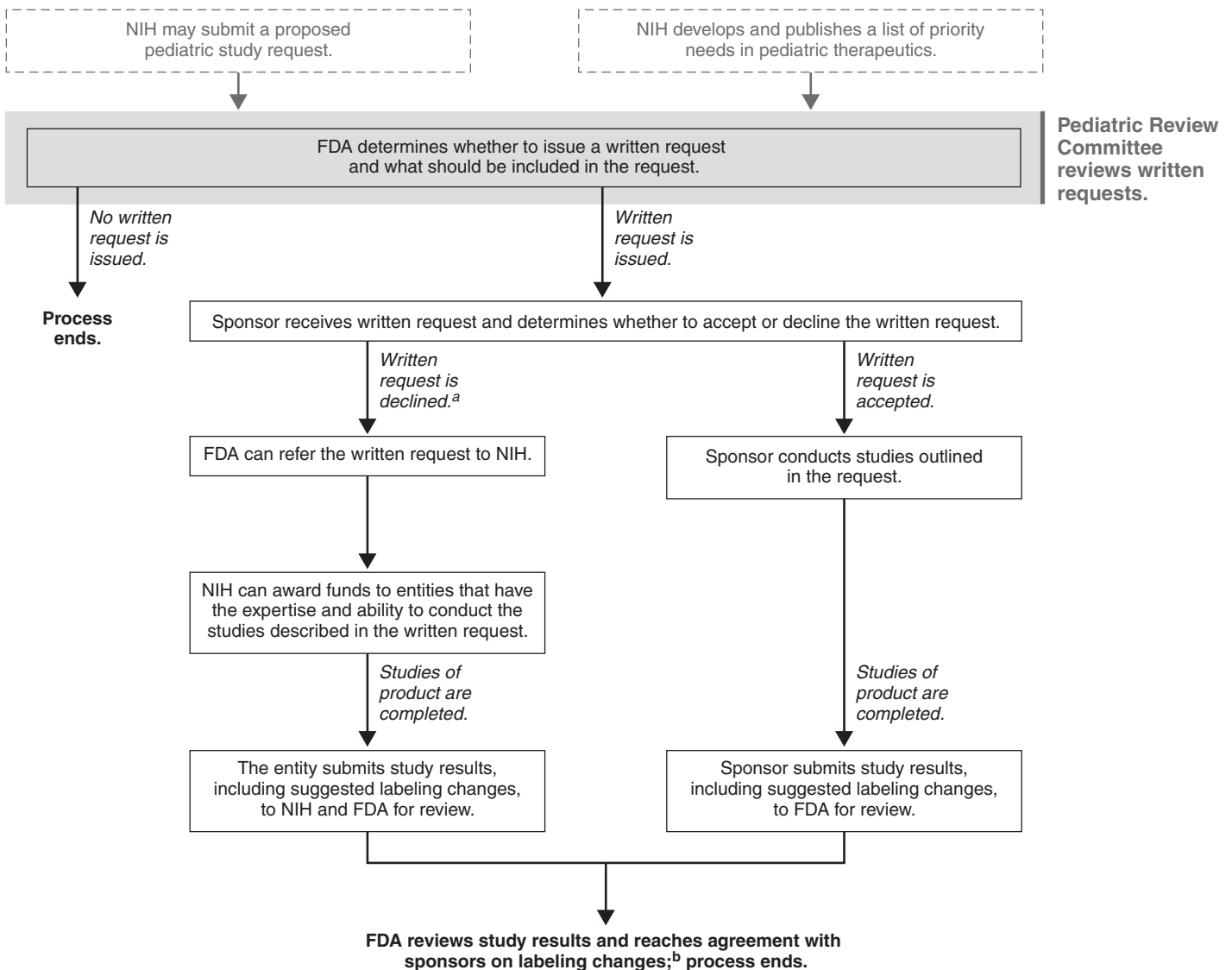
Under the 2007 reauthorization of BPCA, if the sponsors were to decline or fail to respond to the written request for an off-patent product within 30 days, FDA can refer the written request to NIH to publish a request for proposals to conduct the studies. The sponsors of off-patent products are not required to respond to a written request. If within 30 days of FDA's issuance of the written request the sponsors do not accept or decline the request, FDA considers the request declined. NIH can then award funds—for example, through grants or contracts—to entities that have the expertise and ability to conduct the studies described in the written request. When these studies are complete, the entity that completed the studies is to submit the study results to NIH and FDA for review. For off-patent studies conducted by a sponsor or funded by NIH, FDA is to negotiate and reach an agreement with the product's sponsors on appropriate labeling changes resulting from the study findings within 180 days. (See fig. 3.) As is the case with on-patent products studied under

³⁷Prior to the 2007 reauthorization, instead of a list of therapeutic areas, BPCA required NIH to develop an annual list of specific drugs that the agency determined were in need of study in children.

³⁸See 42 U.S.C. § 284m(c).

PREA and BPCA, if FDA is unable to reach an agreement on the labeling changes for an off-patent product within that time, FDA is required by BPCA to proceed to the formal dispute resolution process.

Figure 3: BPCA Process for Off-Patent Drug or Biological Products



Source: GAO analysis of BPCA requirements.

^aFDA also considers the written request to be declined if the sponsor does not respond to FDA within 30 days.

^bBPCA requires that FDA and the sponsor enter dispute resolution if the labeling change is not agreed upon within 180 days of the submission of study results.

The Pediatric Advisory Committee

The Pediatric Advisory Committee (PAC) is an FDA advisory committee consisting of 14 voting members, who are appointed by the Commissioner of FDA and are knowledgeable in pediatric research, pediatric subspecialties, statistics, and/or biomedical ethics. The committee includes a representative from a pediatric health organization and a representative from a relevant patient advocacy organization. The PAC is responsible for reviewing reports of all adverse events reported for drug and biological products during a one-year period after a labeling change is made under PREA or BPCA and may review reports of pediatric adverse events in subsequent years. The committee makes recommendations to FDA on how to respond to the adverse events. PAC recommendations can include suggested labeling changes based on the adverse events, continued heightened monitoring of the product, the production or revision of a medication guide for consumers, or a return to routine monitoring of adverse events.

In addition, as required by PREA and BPCA, the PAC is to assist in FDA's dispute resolution if a proposed labeling change is not agreed upon by FDA and the sponsor within 180 days of submission of the application. If a labeling change enters dispute resolution, FDA is to first request that the sponsor make any labeling changes that FDA has determined to be appropriate. If the sponsor does not agree, FDA is to refer the matter to the PAC. The PAC is then to convene to review the results of the pediatric studies and provide recommendations to FDA on appropriate changes to the product's labeling, if any. FDA is then to consider the committee's recommendations and request that the sponsor make any labeling changes recommended by the PAC that FDA has determined to be appropriate. If the sponsor does not make the labeling change, FDA may deem the product misbranded.

Internal Control

The *Standards for Internal Control in the Federal Government* provides the overall framework for establishing guidelines for internal control that help government managers achieve desired objectives.³⁹ Internal control, which is synonymous with management control, comprises the plans, methods, and procedures used to meet missions, goals, and objectives. Internal control is not one event, but a series of actions and activities that occur throughout an entity's operations on an ongoing basis. The responsibility of good internal control rests with managers; they set the

³⁹[GAO/AIMD-00-21.3.1.](#)

objectives, put the control mechanisms and activities in place, and monitor and evaluate these mechanisms and activities. Internal control includes a variety of activities such as ensuring effective information sharing throughout the organization and conducting ongoing monitoring of agency activities.

At Least 130 Products Have Been Studied in Numerous Therapeutic Areas under PREA and BPCA, but FDA Does Not Know If Additional Products Have Been Studied

At least 130 products—80 products under PREA and 50 under BPCA—have been studied for use in children since the 2007 reauthorization. However, FDA does not know if additional products with pediatric studies are included in applications for which FDA reviews under PREA are incomplete. The products studied under PREA and BPCA represent a wide range of therapeutic areas. In addition, few drugs have been studied when sponsors have declined written requests.

FDA Cannot be Certain How Many Additional Products Have Been Studied under PREA; Most Requests for Waivers and Deferrals Have Been Granted

Since the 2007 reauthorization, at least 80 products have been studied under PREA, but FDA cannot be certain how many additional products may have been studied. FDA does not track and aggregate data about applications submitted under PREA until the PeRC has completed its review of information from the application. This generally occurs late in FDA's overall review of the application. Therefore, FDA was unable to provide information about some applications that had been submitted to the agency that were subject to PREA. For example, FDA officials could not provide aggregate data about the total number of applications, whether the applications were complete or incomplete, or whether the application included pediatric studies or requests for waivers or deferrals. Therefore, FDA could not be certain how many additional applications for which it has not yet completed its review under PREA include pediatric studies or requests for waivers or deferrals. This lack of data during the review process about applications subject to PREA, hampers FDA's ability to manage the review process, including whether FDA is meeting statutory requirements and whether the sponsor has complied with PREA's requirements for pediatric studies.

FDA officials said that approximately 830 applications submitted to FDA from September 27, 2007, through June 30, 2010, were subject to PREA, but could not provide a precise number. The PeRC has completed its review of information from 449 of these applications, 80 of which contained the results of pediatric studies. Fifty-nine were drugs and 21 were biological products. FDA could not provide information about the remaining 381 of the approximately 830 applications. Standards for internal control in the federal government provide that managers need certain data to determine whether they are meeting their agencies' missions, goals, and objectives.⁴⁰ This could include whether FDA is meeting PREA requirements and whether the sponsor has complied with PREA's requirements for pediatric studies. FDA officials explained that these 381 applications were submitted to FDA, and were under consideration in the relevant FDA division, but had not yet been reviewed by the PeRC, which advises FDA in its review of pediatric studies or requests for waivers or deferrals. FDA officials said that they could not provide any details about these applications without locating each application individually within the agency and reviewing it to determine whether it included pediatric studies or requests for waivers or deferrals, but stated that it is likely that most of the approximately 381 applications are for products that sponsors plan to market in adult indications and, therefore, would include a request for a deferral of the pediatric studies rather than completed pediatric studies. Although FDA officials could not say how many, they said that some of the approximately 381 applications may be incomplete and awaiting further review upon the sponsor's submission of additional materials, and that some of the applications may have been withdrawn by the sponsor. However, some of the applications could include the results of completed pediatric studies. Therefore, the total number of products with studies completed under PREA may be greater than 80.

HHS officials stated in its comments on a draft of this report that an update to the Document Archiving Reporting and Regulatory Tracking System (DARRTS), completed in May 2011, will provide them with the capability to include a code to indicate whether an application is subject

⁴⁰[GAO/AIMD-00-21.3.1.](#)

to PREA.⁴¹ However, the HHS comments do not state that this data system update would provide the internal controls necessary to track and aggregate data about applications that are currently under review, which would allow FDA to readily retrieve information to manage this program. In addition, HHS states that FDA does not currently plan to code applications retrospectively until they have ensured that there are available resources for such a project. Therefore, unless they do these things, FDA still will not know the status of the 381 applications, including whether the applications were complete or incomplete, or whether the applications included pediatric studies or requests for waivers or deferrals, until the review of those applications is complete.

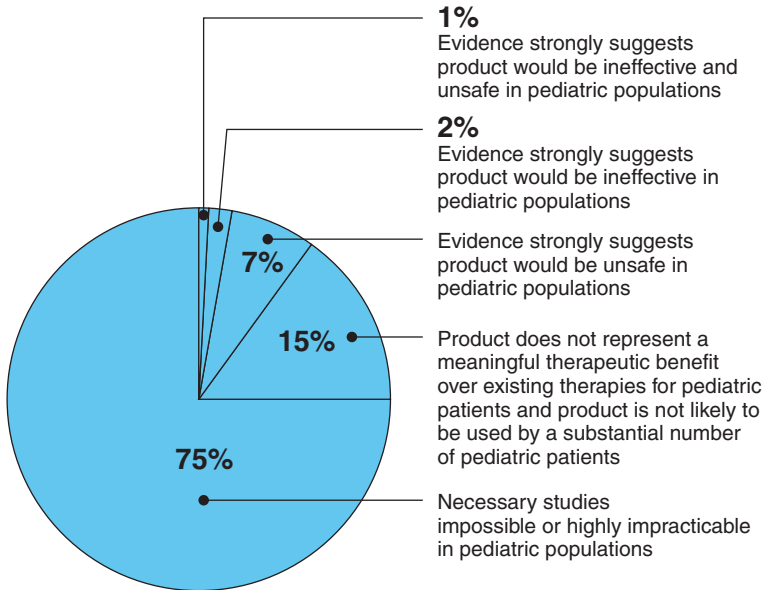
FDA has granted a full or partial waiver or deferral to more than half of the applications that it has reviewed under PREA. According to FDA officials, of the 449 applications for which FDA has completed its review, FDA granted sponsors 237 waivers and 131 deferrals. FDA officials noted that, generally, most sponsors request deferrals of pediatric studies in the product's application rather than conduct the pediatric studies prior to submitting the product's application. FDA sometimes granted a full or partial waiver and a deferral to a single application, therefore a single application could be included in both totals. FDA officials could not provide additional information about the remaining 381 applications submitted to FDA during this period but not reviewed by the PeRC.

Waivers and deferrals were granted for multiple reasons. The reason most frequently cited for granting a waiver was that the drug or biological product studies were found to be impossible or highly impracticable. Waivers may be granted for this reason because, for example, the number of patients in that age group is too small. Most deferrals were granted because the product was ready to be approved for use in adults before pediatric studies had been completed. (See fig. 4).

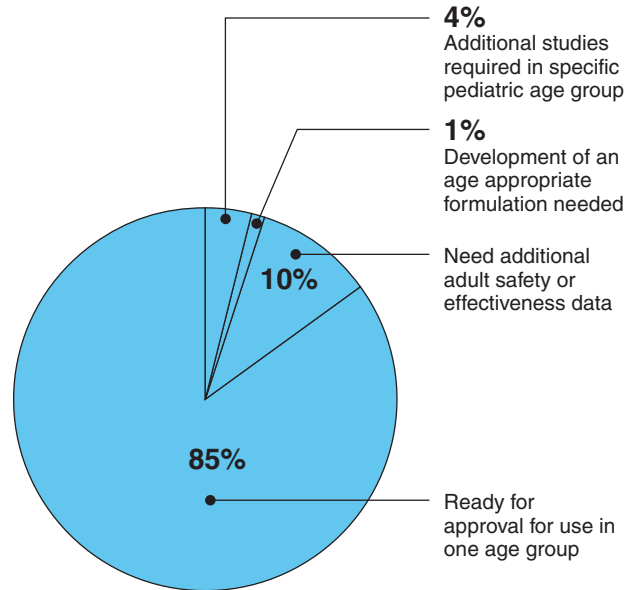
⁴¹According to FDA, DARRTS is intended to be a flexible, integrated, fully electronic workflow tracking and information management system to receive, log, track, assign, process, and manage official submissions with internal and external stakeholders. FDA is releasing DARRTS in stages. The first version was released in January 2006. Updates to the system, which incorporate additional types of FDA data into DARRTS, have been periodically implemented.

Figure 4: Reasons Applications Were Granted a Waiver or Deferral, September 27, 2007, through June 30, 2010

Reasons studies were granted a waiver



Reasons studies were granted a deferral



Source: GAO analysis of FDA data.

Note: PREA contains categories of reasons for FDA to use when granting waivers and deferrals and the figure above reflects all of these reasons. However, FDA has never granted a waiver for the reason, “applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.”

FDA officials also could not say how many studies are ongoing under PREA because the agency does not maintain a count of those studies. According to FDA, sponsors inform FDA of their plans for studies currently being conducted under PREA, but FDA does not aggregate data for these products until the sponsor completes the studies and the results are submitted to FDA for review.

50 Products Have Been Studied under BPCA since Its 2007 Reauthorization

Fifty products have been studied under BPCA from the 2007 reauthorization through June 30, 2010; FDA has reviewed applications for 50 of these products, none of which were biological products.⁴² As noted earlier, sponsors submit studies to FDA as part of an application. According to FDA officials, FDA granted pediatric exclusivity to the

⁴²Studies for all but two of these products were initiated prior to the 2007 reauthorization.

sponsors of 44 of the 50 drugs.⁴³ Sponsors of five of the six drugs that did not receive exclusivity submitted only partial responses to the written request. FDA officials explained that FDA reviews study results as they are submitted, but does not make a pediatric exclusivity determination until it receives a full response to the written request. Therefore, although FDA completed its review of the applications, the pediatric exclusivity determination is pending the completion of the remainder of the studies FDA requested. FDA officials stated that FDA denied pediatric exclusivity for one of the products prior to the 2007 reauthorization because the studies completed by the sponsor did not meet the conditions of the written request.⁴⁴ Additionally, FDA officials told us that two additional drugs were studied between September 27, 2007, and June 30, 2010, but those studies were still undergoing FDA review.

Since the 2007 reauthorization, according to FDA officials, FDA has issued 37 written requests for on-patent drug and biological products to sponsors under BPCA, 25 of which originated from a PPSR submitted to FDA by the sponsor since the 2007 reauthorization of BPCA.⁴⁵ Sponsors agreed to 35 of the written requests. (See fig. 5.) FDA officials stated that the sponsors completed studies for two of the written requests; studies for the remaining 33 written requests are ongoing.⁴⁶ The two other written requests were declined because the sponsors stated they would be unable to finish the studies by the completion date outlined in the written

⁴³Thirty-one of the 50 drugs with completed and reviewed studies were required to be studied under PREA, but sponsors requested and received written requests for the products to be studied under BPCA, as well.

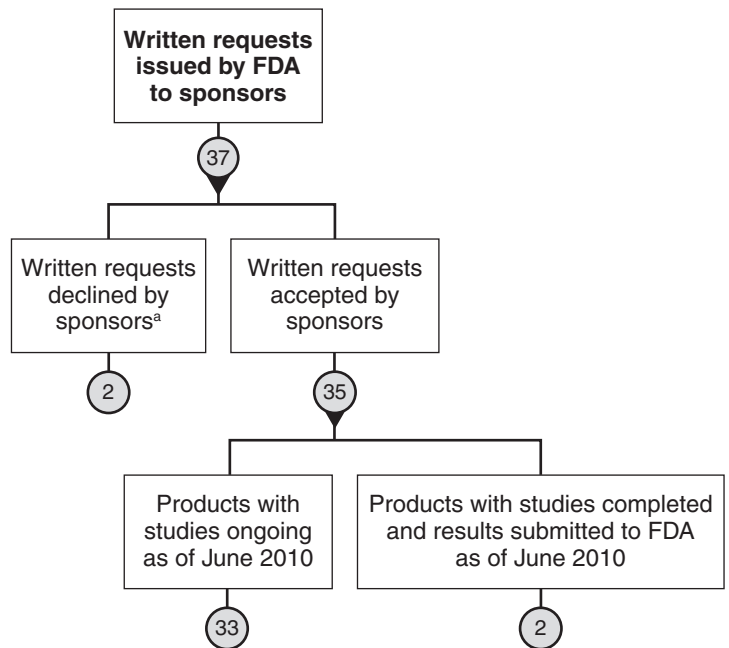
⁴⁴FDA officials explained that one product was denied pediatric exclusivity prior to the 2007 reauthorization because the sponsor did not enroll the number of participants in the study that was required by the written request. We included this product in our group of products studied since the 2007 reauthorization because FDA conducted further analysis of the product using the submitted results to try to determine the safety and effectiveness of the product's use in children. This additional information was used for a labeling change after the 2007 reauthorization.

⁴⁵According to FDA officials, sponsors have submitted 64 PPSRs to FDA since the 2007 reauthorization. Twenty-five of these PPSRs resulted in a written request. FDA officials said that some of the written requests issued after the 2007 reauthorization were issued in response to PPSRs submitted to FDA before the 2007 reauthorization. However, FDA officials noted that there was a flaw in the system that tracks PPSRs and, therefore, they could not state with certainty the exact number of PPSRs that the agency had received.

⁴⁶The two completed studies are also counted as two of the 50 products with completed and reviewed studies under BPCA. The written requests that prompted the studies were issued and the studies have been completed since the 2007 reauthorization.

request.⁴⁷ FDA officials stated that FDA is in the process of determining whether there is a continuing need for the studies described in the two declined written requests. If so, FDA will refer these studies to FNIH pending the availability of sufficient funding at FNIH. We previously reported that about 19 percent of on-patent written requests were declined from 2002 through 2005.⁴⁸ Since the 2007 reauthorization, about 5 percent of written requests have been declined.

Figure 5: Written Requests Issued for On-Patent Drug and Biological Products, September 27, 2007, through June 30, 2010



Source: GAO analysis of FDA data.

⁴⁷According to FDA officials, the timelines outlined in the written request are based on the statutory requirements outlined in BPCA.

⁴⁸See GAO, *Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act*, [GAO-07-557](#) (Washington, D.C.: March 22, 2007), p.12.

Drug and Biological Products Were Studied in a Wide Range of Therapeutic Areas

Drug and biological products were studied under PREA and BPCA for their use in the treatment of a wide range of diseases in children, including those that are common or life threatening. FDA categorized the products studied under PREA and BPCA into 16 broad categories of disease, which include endocrinology, infectious diseases, and oncology; at our request, FDA also categorized the products studied under PREA.⁴⁹ Some of the products studied were for the treatment of diseases that are common, including those for the treatment of asthma and allergies, while other products studied treat more life threatening diseases such as cancer or human immunodeficiency virus (HIV) infection. Additionally, some products studied were preventive vaccines. The largest numbers of products were studied for the treatment of neurological diseases and viral infectious diseases, with 23 products studied in each therapeutic area since the 2007 reauthorization. (See table 1.) This number includes both ongoing and completed studies that have been reviewed by FDA.

⁴⁹FDA does not generally categorize the drug and biological products studied under PREA. FDA provided the therapeutic areas for products with completed studies under PREA in response to our request.

Table 1: Products with Completed or Ongoing Pediatric Studies, Categorized by Therapeutic Area

Therapeutic areas	Examples of diseases associated with each therapeutic area	Number of products with completed or ongoing studies since the 2007 Reauthorizations of PREA and BPCA – September 27, 2007, through June 30, 2010		
		Ongoing (BPCA only)	Completed	
			PREA	BPCA
Addiction	Smoking cessation, maintenance of abstinence from alcohol in patients with alcohol dependency.	0	0	0
Analgesia/anesthesiology/anti-inflammatory	Anesthesia; pain	4	3	1
Cardiovascular disease	Congestive heart failure; hypertension	2	1	4
Dermatology	Dermatitis; skin and skin structure infections	0	6	1
Endocrinology/metabolism	Diabetes Mellitus; obesity	1	5	8
Gastroenterology	Crohn’s Disease; ulcers	1	2	6
Hematology/coagulation	Deep vein thrombosis (thromboembolism)	1	4	1
Infectious disease (viral)	Hepatitis B virus, human immunodeficiency virus (HIV) infection and/or prophylaxis of HIV infection in exposed neonates	5	7	11
Infectious disease (non viral)	Malaria; pneumonia (bacteremic)	2	4	1
Medical Imaging	Myocardial perfusion imaging; Cardiac imaging	1	1	1
Neurology	Adolescent schizophrenia; depression/major depressive disorder	5	7	11
Oncology	Brain tumors and other solid tumors; hematologic tumors	8	1	1
Ophthalmology	Conjunctivitis; intraocular pressure	1	10	0
Other therapeutic areas	Symptoms associated with common cold and influenza;	0	5	1
Pulmonary	Allergic Rhinitis; asthma	2	12	3
Preventive vaccine ^a	Vaccines	0	12	0

Source: FDA.

Note: A product may be used to treat more than one therapeutic area. For the purposes of this table, a product is counted once for each therapeutic area it is used to treat. Therefore, the number of products with completed or ongoing studies by therapeutic area is greater than the total number of products with completed or ongoing studies.

^aPreventive vaccines are not considered by FDA to be therapeutic products but rather, are considered to be vaccines to prevent disease caused by specific bacteria or viruses. We included them for the purpose of providing a full outline of the types of products studied under PREA.

Few Drugs Have Been Studied When Sponsors Have Declined Written Requests

Since the 2007 reauthorization, none of the on-patent products for which written requests were declined or not completed by sponsors have been funded for study by FNIH. A provision under BPCA allows FDA to refer declined written requests for on-patent products to FNIH pending the availability of sufficient funding. However, according to FNIH representatives, FNIH does not have sufficient funding because it is no longer raising funds for the study of on-patent drugs under BPCA. Since the 2007 reauthorization, FNIH has partially funded the study of two on-patent drugs for which written requests were declined by sponsors or not completed, but NIH initiated and also partially funded those studies prior to the 2007 reauthorization. FDA has not referred any on-patent drugs to FNIH since the 2007 reauthorization of BPCA.

Since the 2007 reauthorization of BPCA, FDA has referred written requests for the study of two off-patent drugs that have been declined or not responded to by sponsors to NIH for funding. As of June 30, 2010, NIH initiated funding for the study of one of these two products, but NIH has not submitted any study results for this product to FDA. NIH has also funded 12 studies that are not product specific since the 2007 reauthorization of BPCA.

Prior to the reauthorization of BPCA, FDA referred 15 written requests for the study of off-patent drugs that were declined, or not responded to, by sponsors to NIH for funding. Of these 15 drugs, NIH funded the study of 10 of these drugs. As of June 30, 2010, NIH has submitted study results for two of these off-patent drugs to FDA; however, NIH has not yet completely satisfied the requirements of any written request for the study of an off-patent drug under BPCA.

NIH does not receive appropriations specifically to fund studies for products under BPCA. NIH officials said that NIH institutes and centers spend a total of \$25 million annually on BPCA activities, which are coordinated by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. NIH officials have said that when FDA refers a written request for the study of a product under BPCA to NIH, NIH must determine if it is feasible to initiate funding for the product's studies. This determination depends on the availability of funding and the feasibility of conducting the necessary pediatric studies.⁵⁰ NIH officials

⁵⁰When determining the feasibility of conducting the necessary pediatric studies, NIH considers the frequency and severity of the condition, the availability of a patient population, and the capability of researchers to conduct the studies.

stated that funding a clinical trial with approximately 200 patients costs an average of almost \$10 million over 5 years. In addition, NIH annually spends \$4.5 million of this \$25 million it spends on BPCA activities on the contract for NIH's BPCA data coordinating center.

All Products with Completed Pediatric Studies Had Labeling Changes, and FDA's Goals Often Differ from the PREA Requirement for Reaching Agreement on Labeling Changes

All of the drug and biological products with pediatric studies completed and applications reviewed since the 2007 reauthorization had labeling changes that included important pediatric information. FDA's goals for the time it takes to review applications often differ from the requirement in PREA for reaching agreement on labeling changes with the sponsor.

All Products with Completed Pediatric Studies Since the 2007 Reauthorization Had Labeling Changes That Included Important Pediatric Information

All of the 130 drug and biological products with studies completed and applications reviewed by FDA since the 2007 reauthorization had labeling changes.⁵¹ As a point of comparison, in the 9 years prior to the 2007 reauthorization, 256 products had pediatric study-related labeling changes agreed upon by FDA and the product's sponsor. (See table 2.) In addition, we previously reported that not all products studied under BPCA had labeling changes.⁵² According to FDA officials, instances in which there were no labeling changes for products studied prior to the 2007 reauthorization were generally due to study results that did not establish that the products were safe and/or effective in children. The 2007 reauthorizations of PREA and BPCA provided FDA with authority to make labeling changes on its own initiative when a product has been studied in children, including when a study does not determine that the product is safe or effective in pediatric populations.

⁵¹PREA requires that if a product is granted a waiver due to strong evidence that the product would be ineffective and/or unsafe in children, such information must be included in the labeling. 21 U.S.C. § 355c(a)(4)(D). Since the 2007 reauthorization, an additional 17 products received waivers that resulted in a labeling change on this basis.

⁵²See [GAO-07-557](#).

Table 2: Number of Drug and Biological Products That Had Pediatric Labeling Changes as a Result of Studies Conducted under PREA or BPCA

	PREA labeling changes		BPCA labeling changes		Pediatric Rule labeling changes ^a		Total
	Drugs	Biological products	Drugs	Biological products ^b	Drugs	Biological products	
Pre 2007 Reauthorization (Oct. 1998 – Sept. 26, 2007)	72	0	136	0	48	0	256
Post 2007 Reauthorization (Sept. 27, 2007 – June 30, 2010)	59	21	50	0	0	0	130
Total							386

Source: GAO analysis of FDA data.

^aThe Pediatric Rule went into effect in 1999, but a federal court declared the Pediatric Rule invalid in October 2002. In 2003 Congress codified much of the Pediatric Rule in PREA.

^bBPCA did not apply to biological products until the Patient Protection and Affordable Care Act extended pediatric exclusivity to biological products.

The labeling changes for drug and biological products studied under PREA and BPCA reflected important pediatric information. FDA categorizes labeling changes into one or more of nine categories, and each drug or biological product can have more than one category of labeling change. These categories illustrate the important pediatric information provided in labeling changes, ranging from providing new or enhanced safety information to inserting a boxed warning for pediatric populations. Since the 2007 reauthorization, the most commonly implemented labeling change expanded the pediatric age groups for which a product was indicated. There were 99 instances of this type of labeling change. (See table 3.) For example, a labeling change for a drug treating gastroesophageal reflux disease extended the approved indication from adults only to pediatric patients 5 years of age and older. In addition, 28 labeling changes indicated that, though a study was conducted, safety and effectiveness had not been established in pediatric populations. For example, pediatric studies on a drug meant to treat osteogenesis imperfecta, a genetic disorder commonly known as brittle bone disease, did not show a reduction in the risk of bone fracture in children. Therefore, the drug’s labeling was changed to describe the study conducted and indicate that safety and effectiveness were not established in pediatric populations.

Table 3: Number of Labeling Changes for Drug or Biological Products by Category of Change, September 27, 2007, through June 30, 2010

Categories of labeling changes for drug or biological products ^a	PREA		BPCA		Total
	Drugs	Biological products	Drugs	Biological products ^b	
Expanded pediatric age groups approved in the label, including the addition of new pediatric indications	50	19	30	0	99
Provided new or enhanced pediatric safety information	10	4	8	0	22
Determined that safety and effectiveness was not established in pediatric populations and added a description of the study conducted	3	2	23	0	28
Provided information on a specific change or adjustment to the pediatric dosing	3	0	2	0	5
Provided label for a new pediatric formulation of an existing drug or biological product	2	0	6	0	8
Provided original labeling, including pediatric information, for a new active ingredient that was never before marketed in the United States	3	0	0	0	3
Inserted a boxed warning for pediatric populations	0	0	1	0	1
Provided pharmacists with detailed step-by-step instructions on how to prepare formulations for pediatric populations	0	0	4	0	4
Provided details on dosing differences between pediatric and adult populations due to pharmacokinetic differences	0	0	1	0	1

Source: GAO analysis of FDA data.

^aEach labeling change can be categorized as more than one category of change.

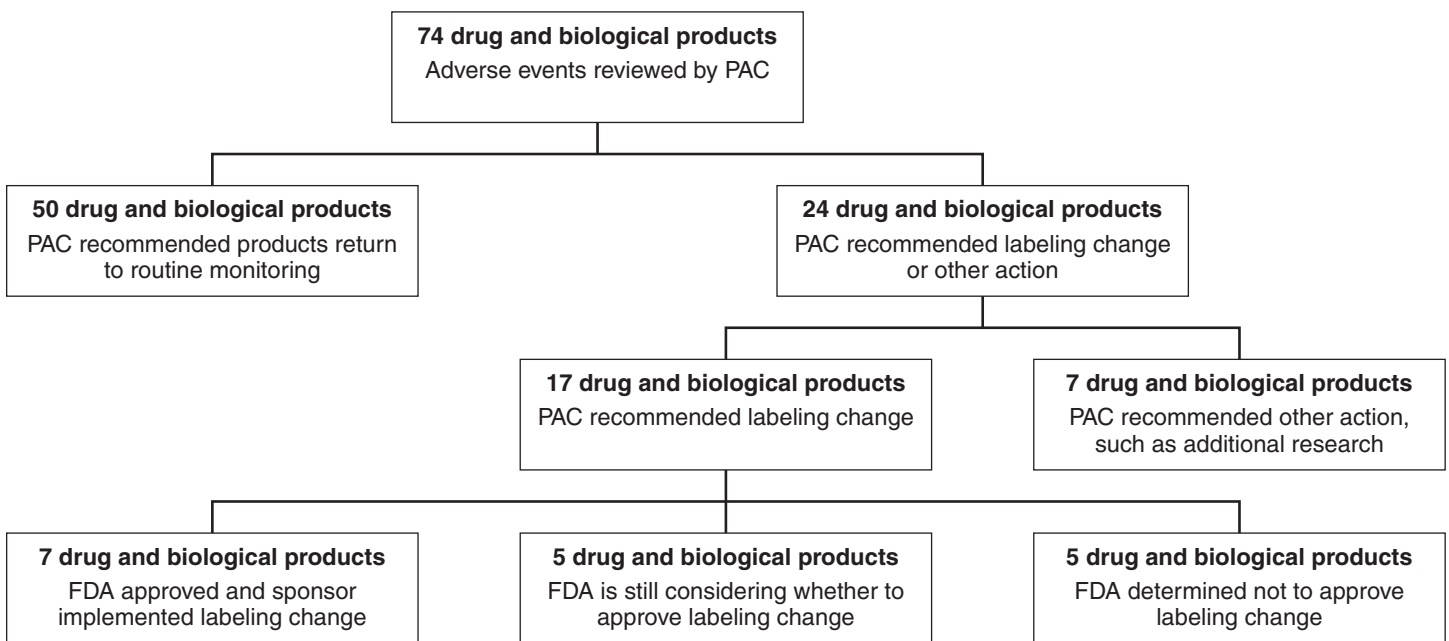
^bBPCA did not apply to biological products until the Patient Protection and Affordable Care Act extended pediatric exclusivity to biological products.

Since the 2007 reauthorization, the PAC reviewed the adverse events reported for 74 drug and biological products and recommended additional labeling changes for 17 of those 74 products.⁵³ (See fig. 6.) As of June, 30, 2010, FDA reported that it had approved 7 of the 17 PAC-recommended labeling changes. Of the remaining 10 PAC-recommended labeling changes, FDA was still considering whether to approve 5 labeling changes and had decided not to approve 5 labeling changes. According to FDA, these five PAC-recommended labeling changes were not approved because, after further review of the adverse events, FDA determined that labeling changes were not necessary. Reasons underlying these determinations include an insufficient link between the reported adverse

⁵³PREA and BPCA require that one year after a product's labeling change is implemented, the PAC review any adverse events reported for that product. In subsequent years, FDA will determine whether to refer any additional pediatric adverse events reported for that product to the PAC for review.

events and the product and the presence of confounding factors, such as other preexisting conditions that may have contributed to the adverse event.

Figure 6: Pediatric Advisory Committee (PAC) Recommendations for Drug and Biological Product Adverse Events, September 27, 2007, through June 30, 2010



Source: GAO analysis of FDA data.

FDA's Goals Often Differ from the PREA Requirement for Reaching Agreement on Labeling Changes

FDA's performance goal for the time it takes for FDA to review most PREA applications often differs from PREA's requirement for the time FDA is to take to reach agreement with the sponsor on labeling changes.⁵⁴ According to FDA officials, the agency cannot adequately consider and agree upon a labeling change until it completes its review of an application. FDA is required by both PREA and BPCA to negotiate and reach agreement with the sponsor on labeling changes based on pediatric study results within 180 days of submission of the application. If FDA is unable to reach agreement with the sponsor, it is required to enter the labeling change dispute resolution process. FDA's review of suggested

⁵⁴An application includes, among other things, suggested labeling changes based on study findings.

labeling changes is part of a broader review—FDA’s review to determine whether or not to approve the application—for which it has specific performance goals that include time periods within which it seeks to review applications.⁵⁵ Under these performance goals, applications are classified as either priority or standard, depending on the characteristics of the application, and FDA has committed to completing its review of 90 percent of priority applications within 180 days of submission and 90 percent of standard applications within 300 days of submission. BPCA requires that applications submitted under BPCA that propose a labeling change, which are all BPCA applications, receive priority status. Therefore, all BPCA applications have been subject to 180-day review. However, according to FDA officials, only a subset of applications subject to PREA requirements—those that provide major advances in therapy or new therapies—receive priority status. All other applications submitted under PREA are to be reviewed within the standard 300 days of submission.

For priority applications, FDA’s goal to complete its review of the application within 180 days is consistent with the labeling change requirements of PREA and BPCA since the two review periods—the application review goal and the labeling change review period—are both 180 days. However, for PREA applications subject to standard review, which includes most PREA applications, the goal and required review period are different. FDA’s goal to complete its review of the application within 300 days differs from PREA’s requirement to reach agreement on labeling changes within 180 days. FDA officials acknowledged that the agency has generally not agreed upon labeling changes within the required 180 days for PREA applications subject to standard review. However, as noted previously, FDA could not account for 381 applications submitted to the agency under PREA, making it difficult for FDA to determine whether it is meeting either the requirements of PREA or the agency’s goals for these applications. FDA has never initiated the labeling change dispute resolution process. According to FDA officials, the agency has been able

⁵⁵Under the 2007 reauthorization of the prescription drug user fee program as part of FDAAA, FDA committed to performance goals related to the review of drug applications and biologics license applications, including time frames within which it seeks to review applications. See Pub. L. No. 110-85, § 101(c), 121 Stat. 823, 825 (2007). The performance goals are identified in letters sent by the Secretary of Health and Human Services to the Chairman of the Senate Committee on Health, Education, Labor, and Pensions and the Chairman of the House Committee on Energy and Commerce and are published on FDA’s website. Each fiscal year FDA is required to submit a report on its progress in achieving those goals and future plans for meeting them. See 21 U.S.C. § 379h-2(a).

to reach agreement with sponsors on labeling changes without needing to initiate this process.

Stakeholders Identified Agency Guidance, Uncertainty Associated with Reauthorization, and Lack of Economic Incentives as Potential Challenges to Conducting Pediatric Studies

Stakeholders whom we interviewed described several challenges to conducting pediatric studies. One challenge stakeholders, including sponsors, identified was confusion about how to comply with PREA and BPCA due to a lack of current guidance from FDA. FDA officials acknowledged that the most recent PREA guidance is draft guidance from 2005 and that the most recent BPCA guidance was revised in 1999. FDA has not provided guidance for changes to the laws from the 2007 reauthorization for PREA or BPCA. FDA officials stated that they plan to publish updated guidance on PREA and BPCA. However, they have no timeline for when they plan to do so. FDA explained that officials can discuss study timelines and questions or concerns sponsors may have regarding their study submissions throughout the process.

Stakeholders said another challenge is that reauthorizations of PREA and BPCA have led to uncertainty given the time required to conduct studies. They said that since PREA and BPCA are subject to reauthorization every 5 years, some of the statutory requirements for studies could change while studies are under way or as they are being planned; therefore, there is uncertainty as to the requirements that will apply when they conduct studies.⁵⁶ Two sponsors stated this uncertainty makes it difficult to know what will be involved in developing products for use in children over the long term, which makes it difficult to plan studies. For the 50 drugs for which FDA has completed its review since the 2007 reauthorization of BPCA, the average amount of time from when FDA issued a written request through when it completed its review of a drug's study results was 6 years. Based on this experience, PREA and BPCA would be reauthorized during the course of a drug or biological product study, possibly changing the requirements with which the sponsors must comply. For example, the 2007 BPCA reauthorization added the requirement that sponsors submit

⁵⁶However, the 2007 reauthorization of PREA and BPCA provides that certain studies pending before the date of the 2007 reauthorization are subject to prior versions of PREA and BPCA. See Pub. L. No. 110-85, §§ 402(b), 502(a)(2), 121 Stat. 823, 875, 885 (2007).

applications at least 9 months before the end of the product's market exclusivity.⁵⁷

Another challenge identified by stakeholders is complying simultaneously with the U.S. laws, PREA and BPCA, and the European Union's (EU) Paediatric Regulation.⁵⁸ (See app. III for a description of the Paediatric Regulation.) Stakeholders stated that it is common for a sponsor to seek approval of a drug or biological product in both the EU and the United States simultaneously, making it necessary for the study to comply with PREA or BPCA and the Paediatric Regulation if the sponsor wants to market the drug in the United States and in the EU. For example, in the EU, the sponsor submits a plan for the study of a product in pediatric populations that must be approved by the European Medicines Agency before studies are conducted. Stakeholders stated, in the United States, sponsors do not have formal contact with FDA regarding their pediatric study design for studies submitted under PREA until they submit completed study results to FDA. Therefore, sponsors cannot be certain that studies done to comply with the Paediatric Regulation will meet FDA requirements.

Finally, stakeholders told us that the lack of economic incentives presents a challenge to sponsors' willingness to conduct pediatric studies voluntarily, as under BPCA. Stakeholders, including industry representatives, told us that sponsors are reluctant to conduct studies for drug and biological products that are nearing the end of their market exclusivity or are off-patent because there is no economic benefit associated with conducting these studies. Once a drug or biological product is off-patent, the sponsor cannot receive pediatric exclusivity for conducting pediatric studies. Stakeholders told us that these drug and biological products are among the least likely to be studied in pediatric populations. Given the lack of economic incentive, a provision in BPCA gives NIH the responsibility of awarding funds to entities that have the expertise and ability to conduct studies of off-patent drug and biological

⁵⁷BPCA requires that FDA make the determination that the sponsor has met the study requirements outlined in the written request 9 months prior to the end of the drug or biological product's market exclusivity. 21 U.S.C. § 355a(b)(2), (c)(2). FDA officials explained that because BPCA provides the agency with 180 days to review the study results, FDA recommends that the sponsor submit its results a minimum of 15 months prior to the end of its market exclusivity. See 21 U.S.C. § 355a(d)(3).

⁵⁸The Paediatric Regulation is a single law that both requires sponsors to conduct studies as well as provides a 6-month exclusivity extension.

products. However, stakeholders reported that NIH's ability to conduct these studies is limited due to a lack of resources devoted to this type of research.

Conclusions

At least 130 drug and biological products have been studied in pediatric populations under PREA and BPCA in a variety of therapeutic areas since the laws' 2007 reauthorization, resulting in important labeling changes. While this illustrates the laws' success in facilitating pediatric studies, we found that FDA did not have procedures in place to track and aggregate data about applications subject to PREA until the PeRC completed its review of the pediatric information included in the applications. Even though an application subject to PREA cannot be considered complete unless it contains pediatric study results or a request for a waiver or deferral, FDA has not been tracking whether these are included until information from the application is reviewed by the PeRC. According to FDA officials, the PeRC generally reviews information about pediatric studies submitted as part of the application near the end of FDA's application review process. Because of the timing of this review, FDA staff managing the review process cannot be certain how many applications that have been submitted to the agency are subject to PREA, how many of those applications include pediatric studies, or how many applications include requests for waivers or deferrals, until FDA has almost completed its review of the entire application. FDA's review of applications can last 300 days or more in some cases, depending on the specific attributes of the application.

FDA lacks an important internal control that would allow it to manage its review process to ensure that the agency and sponsors are meeting the law's requirements and that FDA is meeting its own mission, goals, and objectives during the period of its review of the application. Because several of the requirements of PREA and internal FDA goals focus on the amount of time FDA takes to conduct a review or make a decision and because some products studied under PREA may already be on the market for adult use, it is imperative that FDA have this information available to it throughout the review process. FDA's inability to track how long it has had an application or whether or not an application includes pediatric study results until after the PeRC has completed its review could delay the dissemination of important pediatric study results.

Recommendation for Executive Action

We recommend that the Commissioner of FDA move expeditiously to track applications upon their submission and throughout its review process and maintain aggregate data, including the total number of applications that are subject to PREA and whether those applications include pediatric studies.

Agency Comments and our Evaluation

We provided a draft of this report to the Secretary of HHS for comment. In its comments, HHS noted that PREA and BPCA have been very successful in generating important pediatric labeling of drugs and biological products. HHS also agreed that better tracking of pediatric labeling and other information is needed and expressed the hope that future improvements in its databases will allow the agency to easily identify all pediatric studies contained in all applications. HHS acknowledged that such improvements could permit health care providers, the public, and other stakeholders to conduct more interactive and thorough searches for pediatric studies, indications, and other information relevant to pediatric patients.

In its comments, HHS disagreed with our finding that FDA does not have a system to track data about applications under PREA. The comments note that the FDA Center for Biologics Evaluation and Research has a specific code in its Regulatory Management System for Biologics Licensing Application that allows it to track PREA-filed applications for biological products. HHS describes the FDA Center for Drug Evaluation and Research's process for tracking applications using DARRTS and suggests that DARRTS allows FDA to track the status of any application at any given time.

However, our recommendation is not based on FDA's ability to determine the status of individual applications, but rather its lack of aggregate data on applications that are subject to PREA during its review of the applications so as to be able to better manage its review process. We clarified our discussion of our findings in this area and the wording of our recommendation. As discussed in this report, FDA was unable to determine how many of the applications that had been filed with the agency since PREA's 2007 reauthorization were subject to PREA. We had initially requested this information in an effort to provide context to some of the other information that we reported about FDA's implementation of PREA. FDA was able to report that approximately 830 applications were subject to PREA, but was unable to provide a precise number. Since this was considerably more than the 449 applications that had been reviewed by the PeRC, we sought additional information about the status of these

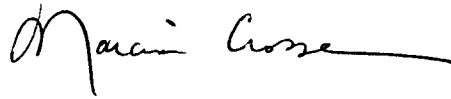
applications. In response to our request, FDA officials explained that the agency did not maintain this information and that determining the status of these applications would require that they engage in a labor intensive manual process that would require an extensive investment of FDA resources and would take months to complete. We believe that FDA's lack of aggregate data about an important program designed to enhance the safety of drug and biological products for use in children is inconsistent with sound internal controls because it does not provide FDA officials with the information they need to effectively manage the program to ensure that the review process is being implemented in accordance with statutory and other requirements until the process is almost complete.

In its comments, HHS states that in May 2011, FDA made an improvement to DARRTS that was not in place during the time of our review. HHS states that the improvement will allow FDA to better track future applications that are subject to PREA. However, the comments do not state whether the improvement will allow FDA to determine during its review process whether applications include studies or requests for waivers or deferrals. While it remains unclear what data will be readily available to FDA officials as they manage this program, FDA's efforts to improve its tracking of applications are consistent with the goal of our recommendation and should enable it to better track future applications. HHS's comments state that FDA hopes to include enhanced information about applications in DARRTS retrospectively, but notes that the agency will have to ensure that there are available resources for such a project. Therefore, DARRTS will not include this improved data for applications that are currently undergoing review.

HHS states that FDA maintains data about completed studies under PREA on its Web site. However, this data is compiled and placed on FDA's Web site after FDA's review of the applications is complete. Our finding and recommendation address the lack of data that FDA has available about PREA applications during the review process, which can last 300 days or more.

We incorporated changes to the report to address HHS's comments about FDA's ability to track applications and incorporated technical comments as appropriate. HHS's comments are reprinted in appendix IV.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix V.

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal line extending to the right.

Marcia Crosse
Director, Health Care

Appendix I: Inclusion of Neonates in Drug and Biological Product Studies

The Food and Drug Administration (FDA) Amendments Act of 2007 required that we describe the efforts made by FDA and the National Institutes of Health (NIH) to encourage that studies be conducted in children 4 weeks old or less, also known as neonates. This appendix describes the efforts of FDA and NIH to encourage studies in neonates and their efforts to ensure that those studies are safe. We also describe the number of products with completed and ongoing studies in neonates since the 2007 reauthorization of the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA).¹ In addition, we describe the challenges to increasing the inclusion of neonates in pediatric drug studies identified by physicians.

To describe the efforts of FDA and NIH to encourage studies in neonates, we interviewed FDA and NIH officials and examined FDA and NIH data to summarize the number of pediatric drug studies being conducted in neonates under PREA and BPCA. To assess the reliability of the data FDA and NIH provided, we interviewed agency officials. FDA and NIH officials described how they maintained data on pediatric studies, and the resulting labeling changes conducted under PREA and BPCA. We found the data reliable for our purposes. We also reviewed literature on studies conducted in neonates and barriers to these studies. We interviewed stakeholders including representatives from three trade groups, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization² and the Generic Pharmaceutical Association. We also interviewed health advocacy organizations, including the American Academy of Pediatrics, the National Organization for Rare Disorders, the Elizabeth Glaser Pediatric AIDS Foundation, the Tufts Center for the Study of Drug Development, the Institute for Pediatric Innovation, and the Pediatric Pharmacy Advocacy Group.

To describe the challenges to increasing the inclusion of neonates in pediatric drug studies identified by physicians, we convened two panel discussions; we were assisted in convening one of the panels by the American Association of Pediatrics and another by a director of neonatology at a large research hospital. The panelists in both instances were physicians who conducted pediatric drug studies in neonates. We also interviewed FDA and NIH officials.

¹See 21 U.S.C. §§ 355a (BPCA), 355c (PREA), 355d (PREA); 42 U.S.C. § 284m (BPCA).

²The Biotechnology Industry Organization assisted us in convening a discussion that included representatives from four of the drug sponsors.

FDA's efforts to encourage the inclusion of neonates in pediatric drug studies and its efforts to ensure that those studies are safe and effective have been focused on including neonates in its written requests. However, in some instances FDA has requested neonates' inclusion but not required it. Since the 2007 reauthorization of BPCA, FDA has issued four written requests to drug sponsors that have mentioned neonates specifically.³ FDA required the inclusion of neonates in the written request for the study of one of the four drugs. FDA's written requests for three other drugs asked for the inclusion of neonates in the study; however, the sponsors of these products had the option of not including neonates in the studies. The sponsors will inform FDA as to whether they included neonates in the studies when they submit completed study results to FDA for review.

Sponsors have submitted completed studies to FDA that have included neonates for nine products—eight drugs and one biological product—since the 2007 reauthorization; FDA has reviewed all study results and labeling changes have been made reflecting neonate information for all of the products.⁴ Seven of these studies were submitted under BPCA; two were submitted under PREA.

NIH has funded studies under BPCA for five drugs that have included neonates. These studies were initiated before the 2007 reauthorization, but are ongoing. Additionally, NIH has conducted several activities under BPCA to ensure the safety and effectiveness of drugs in neonates, including neonates that are premature. These activities include the 2009 co-funding of a large scale study of the diagnosis and treatment of hypotension in premature infants, funding of a study to determine outcome measures for chronic lung disease in premature infants, and the development of a small volume sampling technique for neonates with congenital heart disease.

FDA officials explained that a limited number of the studies conducted under PREA have included neonates because PREA only requires that pediatric studies be conducted for the indication described on the drug application, which is typically applicable to adults and older pediatric

³Since the 2007 reauthorization, FDA has issued 37 written requests for on-patent drug and biological products to sponsors under BPCA.

⁴Sponsors submitted incomplete study results to FDA for studies that included neonates for two other products. FDA has informed each sponsor that it will discontinue its review until the sponsor has completed the studies and resubmitted them.

populations that would not apply to neonates.⁵ Additionally, PREA provides sponsors with the option to request that required pediatric studies be waived by FDA when there is a valid reason. For some applications, FDA has agreed to waive studies after it has determined that including neonates in a drug study may be impossible or highly impracticable due to safety or ethical concerns.

FDA and NIH officials explained that they face challenges in increasing the inclusion of neonates in pediatric studies under BPCA. BPCA authorizes FDA to provide an incentive of an additional 6 months of market exclusivity, known as pediatric exclusivity, to product sponsors that conduct pediatric studies requested by FDA. FDA officials explained that they have been granting pediatric exclusivity for the study of products in children older than one month, so it is difficult to have manufacturers go back and do the study in neonates because it may be difficult for them to receive additional pediatric exclusivity.⁶ FDA officials told us that the neonate population has diseases that are very different from other pediatric populations and that there are limited tools that can be used to study these diseases. FDA and NIH officials told us that there are also ethical issues that arise when working with this population that create a barrier. Based on our review of the literature, we found there is an ethical issue concerning whether neonates are a vulnerable population that should not be enrolled in trials where there may be increased risk to their health.

The physicians that we spoke with as a part of our two panels explained that they encounter numerous challenges to conducting studies in neonates. One challenge the panelists described is obtaining informed consent from the parents, which is required for the neonate to be enrolled in a study. For example, one panelist stated that because the mother may be medicated from her delivery it may be difficult to obtain consent from her. One panelist stated that he encounters families for which English is their second language and he may need them to review and understand a complex 10- to 12- page study outline that is written in English. The panelist explained that while his hospital provides doctors who speak another language and may communicate in that language for families for

⁵From September 27, 2007, through June 30, 2010, sponsors have submitted completed studies to FDA that have included neonates for two products under PREA.

⁶Under very narrow circumstances specified in BPCA, a drug may be eligible for additional pediatric exclusivity for a supplemental application. See 21 U.S.C. § 355a(g)(1).

which English is a second language, they may encounter another challenge if the family is not able to read in their native language.

The panel explained that there are also scientific challenges to conducting studies in neonates. One scientific challenge is that the amount of blood in neonates is extremely limited. However, blood must be drawn to determine proper dosing of the products being tested, requiring doctors to do needle pricks to obtain blood from the neonate. These pricks are in addition to the pricks that must be done to monitor the health of the neonate and there may not be enough blood to test for both proper dosing and to monitor the neonate's health. The panel went on to explain that the outcomes of the study must be observed in the neonate between 3 to 5 years after the study. This level of monitoring is costly to the sponsor and can be an economic disincentive to conducting studies in neonates. The panel also explained that neonates are heterogeneous—there can be a significant difference in a neonate born at 23 weeks than a neonate that is 40 weeks—and any study designed to include them must account for this, making it difficult to generalize the study results.

Panelists said that another challenge to increasing the inclusion of neonates in studies involves FDA, stating that FDA sometimes seems to be creating barriers rather than working to include neonates in studies. For example, they said that FDA has required that a product be proven safe and effective for adults before it can be studied in neonates; however the panelists stated that because neonates often have illnesses that are specific to their age and condition, this requirement does not make sense. Furthermore, one panelist stated that she believed that FDA did not have enough neonatologists on staff to assist in preparing written requests. She also stated that it is important that study designs that include neonates be reviewed by neonatologists and not general pediatricians because neonatologists understand the issues that must be confronted in the neonatal intensive care unit. FDA's Pediatric Review Committee, which reviews written requests and determines whether waivers and deferrals should be granted, has about 40 members. However, FDA officials we interviewed said that there is only one neonatologist on the Committee.⁷ Additionally, the FDA officials stated that there are three neonatologists in the two FDA divisions that review pediatric studies. FDA officials said that they do not have the resources to hire additional neonatologists.

⁷Our review of the Pediatric Review Committee roster found that there are two neonatologists on the committee as of April 15, 2010.

Appendix II: Inclusion of Ethnic and Racial Minority Participants in Pediatric Drug Studies

The Food and Drug Administration Amendments Act of 2007 (FDAAA) requires that FDA consider the adequate representation of children of ethnic and racial minorities when issuing written requests to sponsors to conduct pediatric studies for a product under the Best Pharmaceuticals for Children Act (BPCA).^{1,2} It is important to include minorities in pediatric studies because proteins, metabolizing enzymes, and genetic traits can differ among races and ethnicities. We previously reported that these differences may result in a product having adverse or unexpected side effects for users depending on their race or ethnicity.³ To examine how FDA considered the representation of ethnic and racial minority participants in product studies conducted under BPCA, we reviewed the 37 written requests that FDA issued to sponsors from the time of the 2007 reauthorization of BPCA on September 27, 2007 through June 30, 2010.

FDA issued guidance in 2005 on the collection of race and ethnicity data in clinical trials recommending that sponsors use a standardized approach developed by the Office of Management and Budget to report the race and ethnicity of study participants.⁴ FDA's 2005 guidance recommends, rather than requires, that sponsors use the specified categories because participants' racial and ethnic data may not be able to be collected in some instances and because the specified categories may not be sufficient or appropriate for some studies. For example, when studies are conducted outside of the United States, the recommended categories may not adequately describe the racial and ethnic groups in foreign countries.

FDA has issued 37 written requests to sponsors for the study of on-patent products under BPCA, since the 2007 reauthorization. In these 37 written requests, FDA asked that sponsors include information on the

¹See Pub. L. No. 110-85, § 502(d)(1)(A), 121 Stat. 823, 879 (2007) (codified at 21 U.S.C. § 355a(d)(1)(A)).

²BPCA encourages sponsors to conduct pediatric studies requested by the Food and Drug Administration in drug and biological products that are new or already on the market but still under patent protection by offering the sponsors 6 months of additional market exclusivity, known as pediatric exclusivity. See 21 U.S.C. § 355a; 42 U.S.C. § 284m. In March 2010, Congress extended pediatric exclusivity and applicable BPCA provisions to biological products as part of the Patient Protection and Affordable Care Act. Pub. L. No. 111-148, § 7002(g)(1), 124 Stat. 119, 819-20 (to be codified at 42 U.S.C. § 262(m)).

³See GAO, *Pediatric Drug Research: Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children*, [GAO-03-950](#) (Washington, D.C.: Sept. 26, 2003).

⁴See FDA, *Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials* (Rockville, MD: Sept. 2005).

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representation of ethnic and racial minorities for all participants using the standardized categories specified in agency guidance when responding to written requests.⁵ In all but two of the 37 written requests, FDA also requested that if the sponsor chose to use other categories, the sponsor obtain FDA's agreement on the use of alternate categories.

⁵FDA's 2005 guidance recommends that sponsors use the United States Office of Management and Budget's categories for data on race which are: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, and White. Office of Management and Budget's categories for data on ethnicity are: Hispanic or Latino, and Not Hispanic or Latino.

Appendix III: Pediatric Drug and Biological Product Studies in the European Union and the United States

The European Union's Paediatric Regulation for the development of drug and biological products in pediatric populations was implemented in January of 2007 in order to facilitate the development of, and improve the availability of information on, products for use in children.¹ The European Union's Paediatric Regulation is similar to laws on pediatric studies in the United States, some form of which has been in existence since 1997.² To describe the European Union's Paediatric Regulation for drugs and biological products, we examined European Medicines Agency literature, the Paediatric Regulation, United States laws, and additional sources regarding United States and European Union pediatric laws and regulations. We also interviewed FDA officials.

The European Union's Paediatric Regulation

The Paediatric Regulation requires sponsors to submit a plan for the study of a product in pediatric populations, known as a paediatric investigation plan (PIP), early in the development of a new product. PIPs are required to include the sponsor's proposed timing and methods for conducting pediatric studies in all age groups. Sponsors must submit PIPs to the Paediatric Committee, which was created by the Paediatric Regulation. Sponsors submit to the Paediatric Committee through the European Medicines Agency. The Paediatric Committee reviews the PIP and determines whether to agree or refuse the study plan. The PIP is a binding agreement between the sponsor and the European Medicines Agency, but can be modified as necessary. The Paediatric Regulation allows for the agency to either defer pediatric studies until the product has been studied in adults or waive the studies altogether in certain circumstances.³ The Paediatric Committee is responsible for granting or denying deferrals and waivers. When studies are deferred, the sponsor must still submit a PIP that includes details on the pediatric studies that will be conducted and when those studies will begin, but when studies are waived, the requirement to submit a PIP is also waived.

¹Regulation (EC) 1901/2006 of 12 December 2006 on Medicinal Products for Paediatric Use, 2006 O.J. (L 378) 1; Regulation (EC) 1902/2006 of 20 December 2006 amending Regulation 1901/2006 on Medicinal Products for Paediatric Use, 2006 O.J. (L 378) 20.

²See 21 U.S.C. §§ 355a (Best Pharmaceuticals for Children Act), 355c (Pediatric Research Equity Act), 355d (Pediatric Research Equity Act); 42 U.S.C. § 284m (Best Pharmaceuticals for Children Act).

³Waivers of pediatric studies may be granted to sponsors when products: (1) are likely to be ineffective or unsafe in part or all of the pediatric population; (2) are intended for conditions that occur only in adult populations; or (3) do not represent a significant therapeutic benefit over existing treatments for pediatric patients.

Once a new product is ready to be marketed, the sponsor submits a marketing authorization application to the European Medicines Agency that must include, among other things, the results of pediatric studies conducted in accordance with the PIP or proof that a waiver or deferral of the pediatric studies was granted.⁴ If the sponsor has conducted studies in compliance with the PIP, it is entitled to a six-month extension of the product's market exclusivity. Additional information on the Paediatric Regulation can be found on the European Medicines Agency website.⁵

European Union and United States Collaboration

The European Union and the United States collaborate by exchanging information in order to ensure that pediatric studies are conducted in a scientifically rigorous and ethical manner and that pediatric patients are not exposed to duplicative studies. Stakeholders stated that it is common for a sponsor to seek approval of a drug or biological product in both the EU and the United States, making it necessary for a sponsor to comply with both the EU and United States' pediatric study processes if it wants to market the drug in both locations. In addition, the European Medicines Agency and the FDA communicate and collaborate to share information such as the status of current studies, written requests, PIPs, waivers and deferrals, study results, safety concerns, and other topics. According to FDA's Web site, from August 2007 to March 2009, the European Medicines Agency and the FDA discussed 144 products.⁶ This communication and information sharing between the European Medicines Agency and the FDA takes place through monthly teleconferences and by using a secure electronic system.

⁴The requirement also applies to applications for a new indication, new pharmaceutical form, or new route of administration.

⁵www.ema.europa.eu/

⁶This is the most recent data available from FDA's Web site. See www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm

Appendix IV: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

MAY 09 2011

Marcia Crosse, Director
Health Care
U.S. Government Accountability Office
441 G Street N.W.
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) draft report entitled: "PEDIATRIC RESEARCH: Products Studied Under PREA and BPCA, But Improved Tracking Needed by FDA" (GAO 11-457).

The Department appreciates the opportunity to review this draft report prior to publication.

Sincerely,

A handwritten signature in cursive script that reads "Jim R. Esquea".

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "PEDIATRIC RESEARCH: PRODUCTS STUDIED UNDER PREA AND BPCA, BUT IMPROVED TRACKING NEEDED BY FDA (GAO-11-457)"

The Department appreciates the opportunity to review and comment on this draft report.

Both PREA and BPCA have been very successful at generating important pediatric labeling of drugs and biological products, and we appreciate GAO's recognition of that fact. We agree that better tracking of pediatric labeling and other information is needed, and we hope that future improvements in our databases will allow us to easily identify all pediatric studies contained in all applications, and not just those required under PREA or conducted under BPCA. Such improvements could permit health care providers, the public, and other stakeholders to conduct more interactive and thorough searches for pediatric studies, indications, and other information relevant to pediatric patients.

That said, the GAO report suggests that the Food and Drug Administration (FDA) does not track applications adequately to ensure timely agency action, potentially delaying dissemination of important pediatric study results (page 35), that FDA does not maintain data on the products studied under PREA (the recommendation), and that FDA does not have adequate internal controls because it does not know whether certain applications have complied with PREA (page 21). For the following reasons, we disagree:

- First, the Center for Drug Evaluation and Research (CDER) tracks its applications through the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS). Given the requirements of various programs and the timelines they impose, DARRTS was, and is, able to track all CDER applications and identify the status of any application at any given time. DARRTS contains numerous coded fields that identify various types of information from which internal reports can be run for different purposes. What was not available in DARRTS until a recent update was a code that can be used to indicate whether or not a particular filed application triggers PREA. The Center for Biologic Evaluation and Research (CBER) uses the Regulatory Management System for Biologics Licensing Application (RMS-BLA) to track CBER applications, and RMS-BLA has a field code for PREA that CBER uses to track PREA filed applications.

For all applications moving forward, CDER will enter the PREA code into DARRTS by the time CDER files the application or within one week after filing. "Filing" is the term used by FDA to indicate the application has been accepted by FDA for review. As of May 2011, FDA will be able to use this code to run various reports that we could not run before regarding pending applications, even though the individual information for any particular pending application has always been available. Reports will more easily identify the total number of filed applications that trigger PREA as well as provide a line listing of all applications that trigger PREA. FDA will be able to generate these reports for a specific time period. We hope to eventually code applications retrospectively, but will have to ensure that there are available resources for such a project.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "PEDIATRIC RESEARCH: PRODUCTS STUDIED UNDER PREA AND BPCA, BUT IMPROVED TRACKING NEEDED BY FDA (GAO-11-457)"

Before this change to DARRTS, FDA used a number of checks and balances to help ensure that the agency identified all applications that triggered PREA and timely fulfilled our obligations under the statutory requirements. These activities will continue and will be supplemented by the new coded data to help ensure better tracking of applications subject to PREA.

- Second, FDA has tracked data on "the total number of products studied under PREA" since the Food and Drug Administration Amendments Act of 2007; indeed, these data are readily retrievable on our website. There are products such as new drug application submissions for a new strength that may have been studied in children but were not required to be studied under PREA, or were not studied under BPCA, and these data are not as easily identified and retrieved from our databases. The agency is currently involved in a project to index all labeled indications by subpopulations, which would assist in identifying all products that have labeling related to pediatrics, and may help in identifying a greater number of products for which children were studied.
- Third, although CDER and CBER determine that an application triggers PREA when, or shortly after, it is filed (and, because of the recent change, CDER will be able to track such determinations with DARRTS), under the statute FDA only makes its determination that a sponsor has or has not complied with PREA requirements when the Pediatric Review Committee (PeRC) has reviewed the application. To assess compliance, several experts in the relevant review divisions review the application, and then the PeRC reviews the data from the review divisions on these studies to ensure that all relevant experts have been consulted to determine whether the PREA requirement has been fulfilled. Simply put, under the statute, FDA will not know whether a sponsor has complied with PREA until the PeRC has conducted its review and assessment.
- Finally, it is contemplated that there will be products studied under PREA that may already be on the market. Indeed, Congress drafted PREA to apply not only to original applications but also to supplemental applications for products already on the market where the sponsor seeks approval for a new indication, new dosage form, new dosing regime, or new route of administration. The pediatric information cannot be disseminated until the application review is complete, and that review is governed by the required timelines. DARRTS, RMS-BLA and the Centers' application review SOPs have consistently provided the necessary safeguards and tracking to ensure that the PeRC review is conducted in parallel with the review of the application and in time for the agency's action on an application, and so there has never been a delay in dissemination of important pediatric study results.

Appendix V: GAO Contact and Staff Acknowledgments

GAO Contact

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