

March 2007

# PEDIATRIC DRUG RESEARCH

## Studies Conducted under Best Pharmaceuticals for Children Act





Highlights of [GAO-07-557](#), a report to congressional committees

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## Studies Conducted under Best Pharmaceuticals for Children Act

### Why GAO Did This Study

About two-thirds of drugs that are prescribed for children have not been studied and labeled for pediatric use, which places children at risk of being exposed to ineffective treatment or incorrect dosing. The Best Pharmaceuticals for Children Act (BPCA), enacted in 2002, encourages the manufacturers, or sponsors, of drugs that still have marketing exclusivity—that is, are on-patent—to conduct pediatric drug studies, as requested by the Food and Drug Administration (FDA). If they do so, FDA may extend for 6 months the period during which no equivalent generic drugs can be marketed. This is referred to as pediatric exclusivity.

BPCA required that GAO assess the effect of BPCA on pediatric drug studies and labeling. As discussed with the committees of jurisdiction, GAO (1) assessed the extent to which pediatric drug studies were being conducted under BPCA for on-patent drugs, including when drug sponsors declined to conduct the studies; (2) evaluated the impact of BPCA on labeling drugs for pediatric use and the process by which the labeling was changed; and (3) illustrated the range of diseases treated by the drugs studied under BPCA. GAO examined data about the drugs for which FDA requested studies under BPCA from 2002 through 2005. GAO also interviewed officials from relevant federal agencies, pharmaceutical industry representatives, and health advocates.

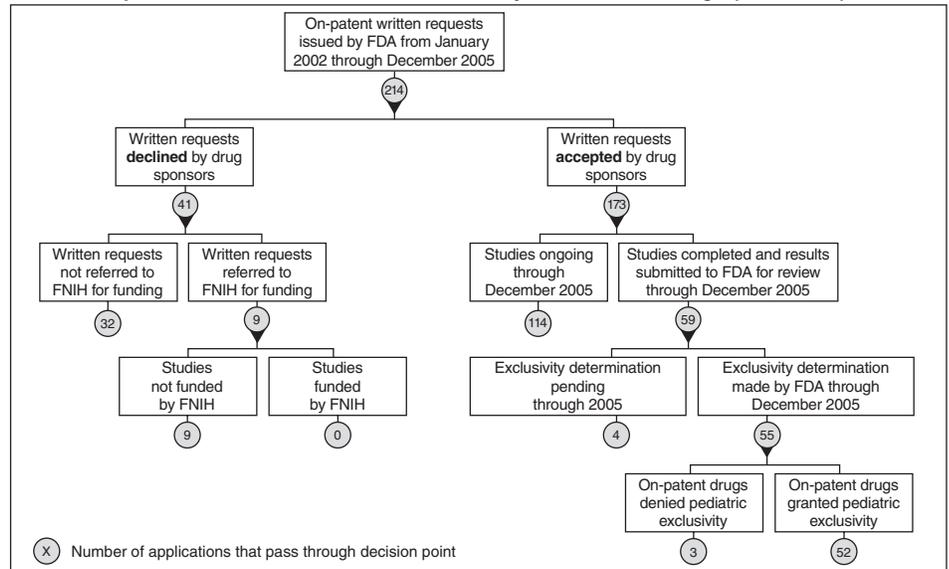
[www.gao.gov/cgi-bin/getrpt?GAO-07-557](http://www.gao.gov/cgi-bin/getrpt?GAO-07-557).

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119 or [crossem@gao.gov](mailto:crossem@gao.gov).

### What GAO Found

Drug sponsors have initiated pediatric drug studies for most of the on-patent drugs for which FDA has requested studies, but no drugs were being studied when drug sponsors declined these requests. Sponsors agreed to 173 of the 214 written requests for pediatric studies of on-patent drugs. In cases where drug sponsors decline to study the drugs, BPCA provides for FDA to refer the study of these drugs to the Foundation for the National Institutes of Health (FNIH), a nonprofit corporation. FNIH had not funded studies for any of the nine drugs that FDA referred as of December 2005.

**Written Requests Issued under BPCA for the Study of On-Patent Drugs (2002-2005)**



Source: GAO.

Most drugs (about 87 percent) granted pediatric exclusivity under BPCA had labeling changes—often because the pediatric drug studies found that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects. However the process for approving labeling changes was often lengthy. It took from 238 to 1,055 days for information to be reviewed and labeling changes to be approved for 18 drugs (about 40 percent), and 7 of those took more than 1 year. Drugs were studied under BPCA for the treatment of a wide range of diseases, including those that are common, serious, or life threatening to children. These drugs represented more than 17 broad categories of disease, such as cancer.

The Department of Health and Human Services stated that the report provides a significant amount of data and analysis and generally explains the BPCA process, but expressed concern that it did not sufficiently acknowledge the success of BPCA or clearly describe some elements of FDA’s process. GAO incorporated comments as appropriate.

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## Abbreviations

BPCA	Best Pharmaceuticals for Children Act
FDA	Food and Drug Administration
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
NDDI	Newborn Drug Development Initiative
NIH	National Institutes of Health

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United States Government Accountability Office  
Washington, DC 20548

March 22, 2007

The Honorable Edward M. Kennedy  
Chairman  
The Honorable Michael B. Enzi  
Ranking Minority Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable John D. Dingell  
Chairman  
The Honorable Joe L. Barton  
Ranking Minority Member  
Committee on Energy and Commerce  
House of Representatives

Although children suffer from many of the same diseases as adults and are often treated with the same drugs, only about one-third of the drugs that are prescribed for children have been studied and labeled for pediatric use.<sup>1</sup> This has placed children taking drugs for which there have not been adequate pediatric drug studies at risk of being exposed to ineffective treatment or receiving incorrect dosing. In order to encourage the study of more drugs for pediatric use, Congress passed the Best Pharmaceuticals for Children Act (BPCA)<sup>2</sup> in 2002 to provide marketing incentives to drug sponsors for conducting pediatric drug studies.<sup>3</sup> Drug sponsors (typically drug manufacturers) may obtain 6 months of additional market exclusivity for drugs on which they have conducted pediatric studies in accordance

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<sup>1</sup>The drug “label” refers to written, printed, or graphic material placed on the drug container, while drug “labeling” is much broader and includes all labels and other written, printed, or graphic materials on any container, wrapper, or materials accompanying the drug. 21 U.S.C. § 321(k), (m).

<sup>2</sup>Provisions regarding pediatric studies of drug are generally codified at 21 U.S.C. § 355a. Pub. L. No. 107-109, 115 Stat. 1408. The market exclusivity provisions of BPCA will sunset on October 1, 2007. 21 U.S.C. § 355a(n).

<sup>3</sup>BPCA reauthorized and enhanced incentives for conducting pediatric drug studies that were first established in the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296.

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with pertinent law and regulations.<sup>4</sup> This market exclusivity is known as pediatric exclusivity. When a drug has market exclusivity, it is protected from competition for a limited period, for example by prohibition on Food and Drug Administration (FDA)<sup>5</sup> approval of a generic copy for marketing.<sup>6</sup> Generally, pediatric exclusivity can only be granted to those drugs that are on-patent—that is, those that still have market exclusivity<sup>7</sup>—and for which FDA has issued a written request for pediatric drug studies.<sup>8</sup> Once a drug’s patent or market exclusivity has expired, however, FDA can still request pediatric drug studies for off-patent drugs. BPCA also included provisions designed to provide for the study of both on-patent and off-patent drugs that drug sponsors have declined to study.

When FDA determines that a drug may provide health benefits to children, it may issue a written request to the drug sponsor to conduct pediatric drug studies. Under BPCA, drug sponsors of on-patent drugs must accept or decline a written request. Drug sponsors of off-patent drugs are not required to respond to a written request. However, if FDA does not receive a response within 30 days, the written request is assumed to be declined. When a drug sponsor accepts a written request for an on-patent drug and subsequently submits a study report in response, FDA generally has 90 days to complete its review of the reports to determine whether to grant pediatric exclusivity to the drug. If FDA is satisfied that the studies have been conducted and the report submitted as required, the drug in

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<sup>4</sup>The value of 6 months additional marketing exclusivity is difficult to assess and depends on a number of factors for which data are not available. However, a recent study estimated that for some drugs the benefit of 6 months of marketing exclusivity was quite large, while for others the return the drug sponsor received for pediatric exclusivity was less than the cost of the studies. See Jennifer S. Li, et al., “Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program,” *JAMA*, vol. 297, no. 5 (2007).

<sup>5</sup>FDA is an agency within the Department of Health and Human Services.

<sup>6</sup>Drug sponsors can obtain market exclusivity for drugs protected by patents, as well as for drugs designed to treat rare diseases, drugs consisting of new chemical entities, and already-marketed drugs approved for new uses. See for example, 21 U.S.C. §§ 355(j)(5)(F)(ii), (iii); 21 C.F.R. § 314.108 (2006). Pediatric exclusivity under BPCA attaches to an existing listed patent or any existing market exclusivity held by the drug sponsor.

<sup>7</sup>For purposes of this report, we refer to drugs 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 drug under BPCA.

<sup>8</sup>FDA is responsible for issuing written requests for pediatric studies, determining whether a drug merits pediatric exclusivity as a result of those studies, and all steps in between.

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question may receive additional market exclusivity. FDA also reviews these pediatric drug study reports to see if the drug requires labeling changes. The agency refers to this review as its scientific review, which it has a goal of completing within 180 days.

BPCA provides for pediatric drug studies even if the drug sponsor declined the written request. First, if a drug sponsor declines a written request by FDA to study an on-patent drug, BPCA provides for FDA to refer the drug to the Foundation for the National Institutes of Health (FNIH), which can fund the study if funds are available.<sup>9</sup> When a sponsor declines a written request for an on-patent drug, the sponsor cannot receive pediatric exclusivity in response to that written request. Second, BPCA provides for the funding of the study of off-patent drugs by the Department of Health and Human Services' (HHS) National Institutes of Health (NIH).

BPCA required that we assess, among other things, the effect of provisions regarding pediatric drug studies on the study and proper labeling of drugs for pediatric use. As discussed with the committees of jurisdiction, we (1) assessed the extent to which pediatric drug studies were being conducted under BPCA for on-patent drugs, including when drug sponsors declined to conduct the studies; (2) evaluated the impact of BPCA on labeling of drugs for pediatric use and the process by which the labeling was changed; and (3) illustrated the range of diseases treated by the drugs studied under BPCA.

To assess the extent to which pediatric drug studies were being conducted under BPCA for on-patent drugs, including when drug sponsors declined to do the studies, we examined data about the drugs for which FDA issued written requests from January 2002 through December 2005. Our work focused on actions regarding these drugs prior to 2006. Specifically, we examined data on the numbers of written requests, drugs studied, written requests that were declined, and drugs granted pediatric exclusivity during this 4-year period. We reviewed data from FNIH on the funding status of on-patent drugs that drug sponsors declined to study. To evaluate the impact of BPCA on the labeling of drugs for pediatric use and the process by which labeling was changed, we reviewed summaries of the labeling changes for drugs studied from the enactment of BPCA through 2005. We

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<sup>9</sup>FNIH is an independent, nonprofit corporation. The majority of funds that FNIH receives are from the private sector. Only a portion of these funds are available for FNIH to award to researchers to conduct studies related to BPCA.

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reviewed the dates the labeling changes were agreed to and the reasons why some drugs did not have labeling changes. To illustrate the range of diseases treated by the drugs studied under BPCA, we identified the diseases the drugs were studied to treat, as well as the therapeutic areas addressed by the drugs. We also examined data from national surveys on the extent to which these drugs are prescribed for children. In addition, to assist with our review in general, we interviewed officials from FDA, NIH, and FNIH as well as representatives of the pharmaceutical industry and health advocates—such as the American Academy of Pediatrics, the Pharmaceutical Research and Manufacturers of America, the Generic Pharmaceutical Association, the National Organization for Rare Disorders, Public Citizen, the Elizabeth Glaser Pediatric AIDS Foundation, and the Tufts Center for the Study of Drug Development. (See app. I for a detailed description of our methodology.)

We conducted our work from September 2005 through March 2007 in accordance with generally accepted government auditing standards.

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## Results in Brief

Most of the on-patent drugs for which FDA requested pediatric drug studies under BPCA were being studied, but no studies resulted when the requests were declined by drug sponsors. Drug sponsors agreed to conduct studies in response to 173 of the 214 written requests for on-patent drugs (81 percent) issued by FDA from January 2002 through December 2005. Drug sponsors completed pediatric drug studies for 59 of the 173 accepted written requests—studies for the remaining 114 written requests for on-patent drugs were ongoing—and FDA made a pediatric exclusivity determination for 55 of those through December 2005. Of those 55 written requests, 52 (95 percent) resulted in FDA granting pediatric exclusivity. BPCA provides for FDA to refer the study of on-patent drugs to FNIH when drug sponsors have declined written requests. However, of the 41 written requests for on-patent drugs that drug sponsors declined to study, FDA referred 9 to FNIH, which had not funded the study of any as of December 2005.

Almost all the drugs—about 87 percent—that have been granted pediatric exclusivity under BPCA have had important labeling changes as a result of pediatric drug studies conducted under BPCA, but the process for obtaining all the necessary information, reviewing the study results, and approving these changes can be lengthy. The labeling of drugs was often changed because the pediatric drug studies revealed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects. The review and approval process,

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including time for sponsors to provide needed information, took from 238 to 1,055 days when FDA required additional information to support the proposed labeling changes.

Drugs studied under BPCA were for the treatment of a wide range of diseases, including some that are common, serious, or life threatening to children. FDA identified 17 broad categories of disease that were treated by the drugs studied under BPCA. The most frequently studied drugs were those used to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections. In addition, nearly half of the 10 drugs most frequently prescribed for children have been studied under BPCA.

In written comments on a draft of this report, HHS stated that the draft report provided a significant amount of data and analysis and generally explains the BPCA process, but expressed concern that it did not sufficiently acknowledge the success of BPCA or clearly describe some elements of its implementation. While assessing the overall success of BPCA was beyond the scope of this report, much of the information we present speaks to the impact BPCA has had on the studying and labeling of drugs for pediatric use. Further, we believe that we accurately presented the implementation of BPCA. We incorporated HHS's comments as appropriate.

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## Background

Prior to enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which first established incentives for conducting pediatric drug studies in the form of additional market exclusivity, few drugs were studied for pediatric use.<sup>10</sup> As a result, there was a lack of information on optimal dosage, possible side effects, and the effectiveness of drugs for pediatric use. For example, while physicians typically had determined drug dosing for children based on their weight, pediatric drug studies conducted under FDAMA showed that in many cases this was not the best approach. To continue to encourage pediatric drug studies,<sup>11</sup>

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<sup>10</sup>We previously described how FDAMA was responsible for an increase in pediatric drug studies. GAO, *Pediatric Drug Research: Substantial Increase in Studies of Drugs for Children, But Some Challenges Remain*, [GAO-01-705T](#) (Washington, D.C.: May 8, 2001).

<sup>11</sup>FDA generally defines the pediatric population covered under BPCA as children from birth to 16 years old, though studies have included children as old as 18. BPCA provides that neonates be included in pediatric drug studies, as appropriate. See app. II for information about federal efforts to encourage the study of drugs in neonates.

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BPCA was enacted on January 4, 2002, just after the pediatric exclusivity provisions of FDAMA expired on January 1, 2002. BPCA reauthorized and enhanced the pediatric exclusivity provisions of FDAMA. Like FDAMA, BPCA allows FDA to grant drug sponsors pediatric exclusivity—6 months of additional market exclusivity—in exchange for conducting and submitting reports on pediatric drug studies. The goal of the program is to develop additional health information on the use of such drugs in pediatric populations so they can be administered safely and effectively to children. This incentive is similar to that provided by FDAMA; however, BPCA provides additional mechanisms to provide for pediatric studies of drugs that drug sponsors decline to study.

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## BPCA Process

The process for initiating pediatric studies under BPCA formally begins when FDA issues a written request to a drug sponsor to conduct pediatric drug studies for a particular drug. FDA may issue a written request after it has reviewed a proposed pediatric study request from a drug sponsor, in which the drug sponsor describes the pediatric drug study or studies it proposes doing in return for pediatric exclusivity. In deciding whether to approve the proposed pediatric study request and issue a written request, FDA must determine if the proposed studies will produce information that may result in health benefits for children.<sup>12</sup> Alternatively, FDA may determine on its own that there is a need for more research on a drug for pediatric use and issue a written request without having received a proposed pediatric study request from the drug sponsor. A written request outlines, among other things, the nature of the pediatric drug studies that the drug sponsor must conduct in order to qualify for pediatric exclusivity and a time frame by which those studies should be completed. When a drug sponsor accepts the written request and completes the pediatric drug studies, it submits reports to FDA describing the studies and the study results. BPCA specifies that FDA generally has 90 days to review the study

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<sup>12</sup>FDA officials report that 51 of 134 proposed pediatric study requests submitted by drug sponsors from 2002 to 2005 did not result in written requests. Drug sponsors sometimes later submitted revised proposed pediatric study requests, which resulted in written requests.

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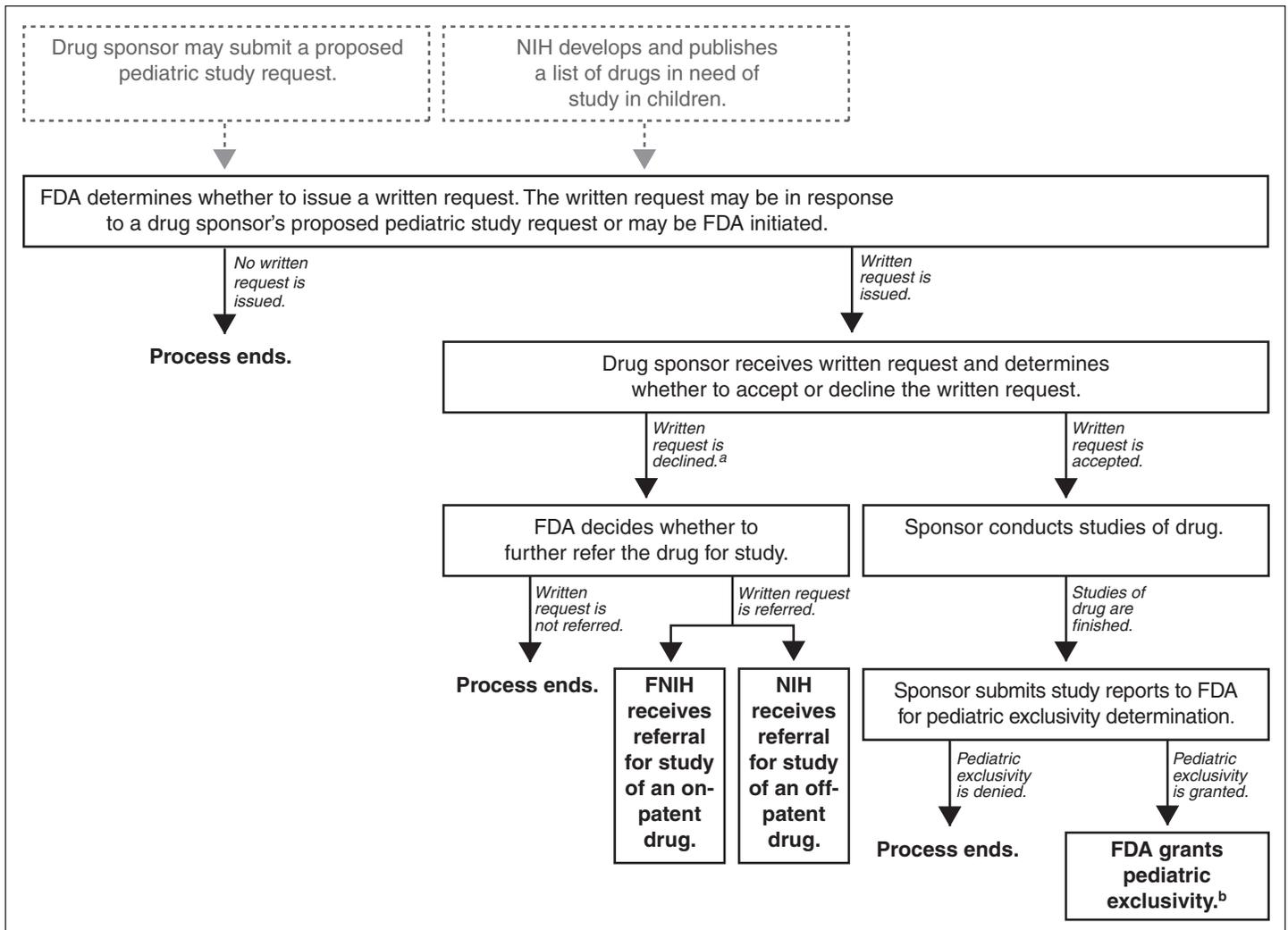
reports to determine whether the pediatric drug studies met the conditions outlined in the written request.<sup>13</sup> If FDA determines that the pediatric drug studies conducted by the drug sponsor were responsive to the written request, it will grant a drug pediatric exclusivity regardless of the study findings.<sup>14</sup> Figure 1 illustrates the process under BPCA.

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<sup>13</sup>Under certain circumstances, FDA could have only 60 days to review the study report to determine pediatric exclusivity. However, FDA officials told us that under BPCA, this has never happened. Otherwise, FDA has 90 days to determine if the studies fairly respond to the written request, were conducted in accordance with commonly accepted scientific principles and protocols, and were properly submitted.

<sup>14</sup>Pediatric exclusivity applies to all approved uses of the drug, not just those studied in children. Therefore, if the studies find that the drug is not safe for use by children, the drug will still receive pediatric exclusivity and therefore extended market exclusivity for the adult uses of the drug.

**Figure 1: BPCA Process**



Source: GAO.

<sup>a</sup>If a drug sponsor of an off-patent drug does not respond to FDA's written request within 30 days, the written request is considered declined. Pediatric exclusivity is not granted to drugs where the drug sponsor declined the written request.

<sup>b</sup>FDA has granted pediatric exclusivity in response to written requests for on-patent drugs only. Under certain circumstances FDA could grant pediatric exclusivity in response to a written request for an off-patent drug.

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## BPCA Provisions for Pediatric Drug Studies Declined by Drug Sponsors

To further the study of drugs when drug sponsors decline a written request, BPCA includes two provisions that did not exist under FDAMA. First, if a drug sponsor declines to conduct the pediatric drug studies requested by FDA for an on-patent drug, BPCA provides for FDA to refer the study of that drug to FNIH, which might then agree to fund the studies. Second, if a drug sponsor declines a request to study an off-patent drug, BPCA provides for referral of the study to NIH for funding. FDA cannot extend pediatric exclusivity in response to written requests for any drugs for which the drug sponsor declined to conduct the requested pediatric drug studies.

When drug sponsors decline written requests for studies of on-patent drugs, BPCA provides for FDA to refer the study of those drugs to FNIH for funding, when FDA believes that the pediatric drug studies are still warranted. FNIH, which was authorized by Congress to be established in 1990, is guided by a board of directors and began formal operations in 1996 to support the mission of NIH and advance research by linking private sector donors and partners to NIH programs. Although FNIH is a nonprofit corporation that is independent of NIH, FNIH and NIH collaborate to fund certain projects. FNIH has raised approximately \$300 million from the private sector over the past 10 years to support four general types of projects: (1) research partnerships; (2) educational programs and projects for fellows, interns, and postdoctoral students; (3) events, lectures, conferences, and communication initiatives; and (4) special projects. Included in these funds is \$4.13 million that FNIH raised as of December 2005 to fund pediatric drug studies under BPCA. The majority of FNIH's funds are restricted by donors for specific projects and cannot be reallocated.<sup>15</sup> In recent years, appropriations of \$500,000 were authorized to FNIH annually.<sup>16</sup>

To further the study of off-patent drugs, NIH—in consultation with FDA and other experts—develops a list of drugs, including off-patent drugs, which the agency believes are in need of study in children. NIH lists these drugs annually in the *Federal Register*. FDA may issue written requests for those drugs on the list that it determines to be most in need of study. If the

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<sup>15</sup>FNIH can certify that it has insufficient funds to fund the study of a drug and refer the funding to NIH.

<sup>16</sup>As of fiscal year 2007, NIH is required to transfer from its appropriations at least \$500,000 but no more than \$1.25 million to FNIH annually. This requirement was established with the enactment of the NIH Reform Act of 2006 (Pub. L. No. 109-482, 120 Stat. 3675 (2007)).

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drug sponsor declines or fails to respond to the written request, NIH can contract for, and fund the conduct of, the pediatric drug studies. These pediatric drug studies could then be conducted by qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions or individuals. Drug sponsors generally decline written requests for off-patent drugs because the financial incentives are considerably limited. (See app. II for a description of federal efforts to encourage research on drugs for children less than 1 month of age and app. III for NIH efforts to support pediatric drug studies.)

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## Making Labeling Changes under BPCA for On-Patent Drugs

Pediatric drug studies often reveal new information about the safety or effectiveness of a drug, which could indicate the need for a change to its labeling. Generally, the labeling includes important information for health care providers, including proper uses of the drug, proper dosing, and possible adverse effects that could result from taking the drug. FDA may determine that the drug is not approved for use by children, which would be reflected in any labeling changes.<sup>17</sup>

According to FDA officials, in order to be considered for pediatric exclusivity, a drug sponsor typically submits results from pediatric drug studies in the form of a “supplemental new drug application.”<sup>18</sup> BPCA specifies that study results, when submitted as part of a supplemental new drug application, are subject to FDA’s performance goals for a scientific review, which in this case is 180 days.<sup>19</sup> FDA’s processes for reviewing study results submitted under BPCA for consideration of labeling changes are not unique to BPCA. These are the same processes the agency would use to review any drug study results in consideration of labeling changes. FDA’s action on the application can include approving the application, determining that the application is approvable (pending the submission of

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<sup>17</sup>The granting of pediatric exclusivity does not depend on finding that the drug is safe and effective for pediatric use.

<sup>18</sup>Most drugs studied under BPCA have previously been approved for marketing in the United States, so a supplement to the original “new drug application” is submitted. If the drug studied under BPCA was not previously approved for marketing in the United States, the application would be submitted as a new drug application. FDA has a performance goal to review non-priority new drug applications in 10 months.

<sup>19</sup>BPCA requires that supplemental new drug applications submitted by drug sponsors be treated as “priority supplements.” FDA’s goal is to take action on priority supplements within 180 days.

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additional information from the sponsor), or determining that the application is not approvable. If studies demonstrate that an approved drug is not safe or effective for pediatric use, this information would be reflected in the drug's labeling.

With a determination that the application is approvable, FDA communicates to the drug sponsor that some issues need to be resolved before the application can be approved and describes what additional work is necessary to resolve the issues. This might require that drug sponsors conduct additional analyses. However, this communication would complete the scientific review cycle. When a drug sponsor resubmits the application with the additional analyses, a new scientific review cycle begins. As a result, multiple scientific review cycles might be necessary, increasing the time between initial submission of the application, which includes the pediatric study reports, and approval of a labeling change.

If, during FDA's review of the study report submitted as part of the application, the agency determines that the application is approvable and the only unresolved issue is labeling, FDA and the drug sponsor must attempt to reach agreement on labeling changes within 180 days after the application is submitted to FDA. If FDA and the drug sponsor cannot reach agreement, FDA must refer the matter to its Pediatric Advisory Committee,<sup>20</sup> which would convene and provide recommendations to the Commissioner on the appropriate changes to the drug's labeling. The Commissioner would then consider the committee's recommendations in making the final determination on the proper labeling.

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<sup>20</sup>The Pediatric Advisory Committee is also responsible for reviewing reports of adverse effects related to drugs granted pediatric exclusivity after the period of exclusivity begins, among other things. The committee consists of 13 voting members, appointed by the Commissioner of FDA, who are knowledgeable in pediatric research, pediatric subspecialties, statistics, and biomedical ethics. The committee includes one representative from a pediatric health organization and one from a relevant patient or patient-family organization.

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## Drug Sponsors Agreed to Study the Majority of On-Patent Drugs with Written Requests under BPCA, but No Studies Were Conducted When Drug Sponsors Declined the Written Requests

Most of the on-patent drugs for which FDA requested pediatric drug studies under BPCA were being studied, but no studies resulted when the requests were declined by drug sponsors. Of the 214 on-patent drugs for which FDA requested pediatric drug studies from January 2002 through December 2005, drug sponsors agreed to study 173 (81 percent). Of the 41 on-patent drugs that drug sponsors declined to study, FDA referred 9 to FNIH for funding and the foundation had not funded any of those studies as of December 2005.

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## Drug Sponsors Agreed to Conduct Pediatric Drug Studies for Most On-Patent Drugs with Written Requests Issued under BPCA

From January 2002 through December 2005, FDA issued 214 written requests for on-patent drugs to be studied under BPCA, and drug sponsors agreed to conduct pediatric drug studies for 173 (81 percent) of those.<sup>21</sup> The remaining 41 written requests were declined.<sup>22</sup> (See app. IV for details about the study of off-patent drugs under BPCA and app. V for a detailed description of the status of all written requests issued by FDA.) Drug sponsors completed pediatric drug studies for 59 of the 173 accepted written requests—studies for the remaining 114 written requests were ongoing—and FDA made a pediatric exclusivity determination for 55 of those through December 2005.<sup>23</sup> Of those 55 written requests,

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<sup>21</sup>Some drugs have two written requests for a variety of reasons. In some cases, FDA may have requested that the drug sponsor study the effects of the drug on different diseases. In other cases, there could be two written requests for the same drug, issued to different drug sponsors for different dosage forms of the drug. In addition, FDA told us that the specified period for studies to be completed elapsed for some written requests before the completion of studies, and the agency issued new written requests. In all of these situations, we counted each of these written requests separately. Therefore, there are more written requests than there are unique drugs with written requests.

<sup>22</sup>Of the 214 written requests issued by FDA, 68 were written requests first issued under BPCA. The remaining 146 written requests were originally issued under FDAMA and reissued under BPCA because drug sponsors had not responded to the written requests or completed the requested pediatric drug studies at the time that BPCA went into effect.

<sup>23</sup>FDA had not completed its review of the study results to determine exclusivity prior to December 2005 for the remaining four drugs.

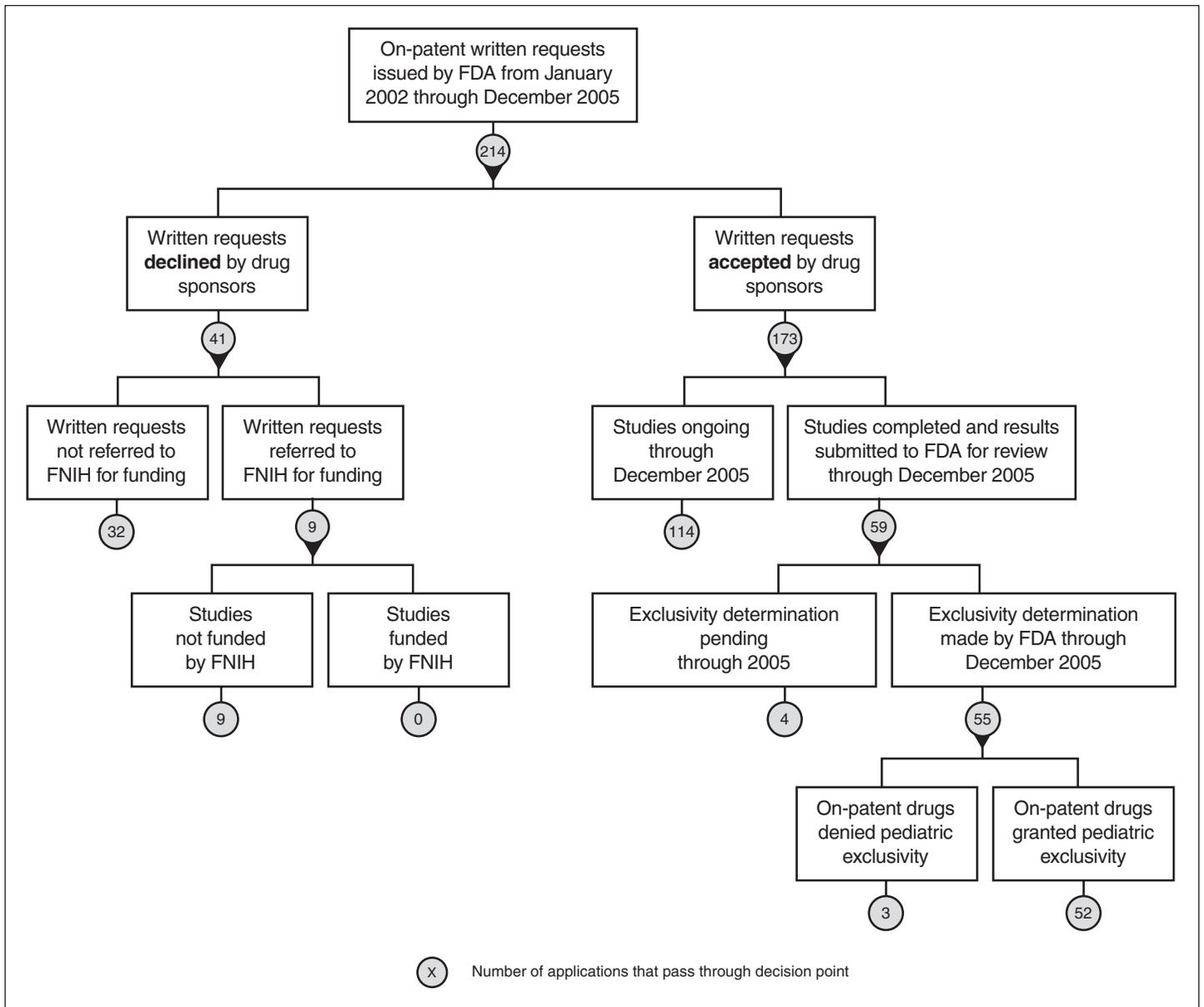
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52 (95 percent) resulted in FDA granting pediatric exclusivity.<sup>24</sup> Figure 2 shows the status of written requests issued under BPCA for the study of on-patent drugs, from January 2002 through December 2005. (See app. VI for a description of the complexity of pediatric drug studies conducted under BPCA.)

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<sup>24</sup>The other three drugs were denied pediatric exclusivity. The dates that drugs are granted exclusivity and also had labeling changes are available at <http://www.fda.gov/cder/pediatric/labelchange.htm>. The dates of exclusivity for other drugs are not available on FDA's Web site. Most of these pediatric drug studies began under FDAMA but were continued under BPCA. Most of the pediatric drug studies begun in response to written requests initially issued under BPCA have not yet been completed.

**Figure 2: Status of Written Requests Issued under BPCA for the Study of On-Patent Drugs, from January 2002 through December 2005**



Source: GAO.

Note: Written requests issued from January 2002 through December 2005 include new written requests issued under BPCA combined with written requests originally issued under FDAMA but reissued under BPCA.

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## FNIH Had Not Funded the Study of Any On-Patent Drugs in Children

Under BPCA, when a written request to study an on-patent drug is declined, the study of the drug may be referred to FNIH. However, FNIH is limited in its ability to fund drug studies by its available funds. Through December 2005, drug sponsors declined written requests issued under BPCA for 41 on-patent drugs. FDA referred 9 of these 41 written requests (22 percent) to FNIH for funding.<sup>25</sup> FNIH had not funded the study of any of these drugs.<sup>26</sup> NIH has estimated that the cost of studying the drugs that were referred to FNIH for study would exceed \$43 million (see table 1). FNIH has been raising funds for the study of drugs referred under BCPA at a rate of approximately \$1 million per year.

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<sup>25</sup>When a drug sponsor of an on-patent drug declines a written request, the agency must determine if there is a continuing need for information relating to the use of the drug in children. Reasons that FDA has concluded that there is not a continuing need include the drug was not yet approved, some part of the study was being performed by the drug sponsor or another party, the drug's patent ended, the risk-benefit assessment shifted, safe alternative therapies were already on the market even though the agency had issued the written request in hope of obtaining additional valuable information, another drug may have been approved or may soon be approved with a better safety record, or there is minimal use of the drug by children.

<sup>26</sup>In April 2006, FNIH agreed to allocate all \$4.13 million it had raised for pediatric drug studies under BPCA to fund half the cost to study one on-patent drug—baclofen. Baclofen was identified by NIH and FNIH as the highest priority on-patent drug that a drug sponsor had declined to study. NIH is responsible for developing requests for proposals for the study of on-patent drugs for pediatric use. The requests for proposals outline the need for studies of specific drugs and include the specific details of the studies to be conducted. NIH requested proposals for the study of baclofen and has selected a contractor to perform the studies. NIH expects the cost of the study of baclofen to be about \$7.8 million over 3 years, and NIH agreed to cover the costs of the study that exceed the contribution from FNIH. Because FNIH has committed all of its BPCA funds to the study of baclofen, there are no resources left for FNIH to fund the study of any other drugs.

**Table 1: Estimated Costs of Funding the Study of On-Patent Drugs Referred to FNIH under BPCA**

On-patent drug	Disease or condition to be studied	Estimated cost
Baclofen	Spasticity in children with cerebral palsy	\$7.8 million
Bupropion	Depression	\$7.4 million
Dexrazoxane	Used to block the cardiac effects of the anticancer drug adriamycin	Not provided <sup>a</sup>
Eletriptan	Migraine headaches	Not provided <sup>a</sup>
Hydroxyurea <sup>b</sup>	Sickle cell disease	\$8 million to \$10 million <sup>c</sup>
Metoclopramide	Gastroesophageal reflux disease	Not provided <sup>a</sup>
Morphine	Analgesia	\$8.7 million
Sevelamer	Renal failure	\$2.7 million
Zonisamide	Refractory partial seizures	\$8.4 million
<b>Total</b>		<b>\$43 million to \$45 million<sup>d</sup></b>

Source: NIH.

<sup>a</sup>Cost estimates have not been provided by NIH.

<sup>b</sup>Hydroxyurea is available in on-patent and generic (or off-patent) formulations. According to NIH officials, after the written request was referred to FNIH for funding, NIH determined that a study funded by its National Heart, Lung, and Blood Institute would provide much of the needed information for appropriate pediatric use. In 2005, NIH's National Institute of Child Health and Human Development agreed to cofund the study.

<sup>c</sup>A formal cost estimate has not been made by NIH, but an initial estimate ranged from \$8 million to \$10 million.

<sup>d</sup>Total estimated cost is for the six drugs for which an estimated cost is available.

## Most Drugs Granted Pediatric Exclusivity under BPCA Had Labeling Changes, but the Process for Making Changes Was Sometimes Lengthy

Most drugs—about 87 percent—that have been granted pediatric exclusivity under BPCA have had labeling changes as a result of the pediatric drug studies conducted under BPCA. Pediatric drug studies conducted under BPCA showed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or side effects that were previously unknown. However, the process for reviewing study results and completing labeling changes was sometimes lengthy, particularly when FDA required additional information to support the changes.

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## Most Drugs Granted Pediatric Exclusivity Had Labeling Changes

Of the 52 drugs studied and granted pediatric exclusivity under BPCA from January 2002 through December 2005, 45 (about 87 percent) had labeling changes as a result of the pediatric drug studies. FDA officials told us that labeling changes were not made for the remaining 7 (about 13 percent) drugs granted pediatric exclusivity, generally because data provided by the pediatric drug studies did not support labeling changes. In addition, 3 other drugs had labeling changes prior to FDA making a decision on granting pediatric exclusivity.<sup>27</sup> FDA officials said these labeling changes were made prior to determining whether pediatric exclusivity should be granted because the pediatric drug studies provided important safety information that should be reflected in the labeling without waiting until the full study results were submitted or pediatric exclusivity was determined.

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## Labeling Changes for Drugs Studied under BPCA Had Important Implications for Pediatric Use

Pediatric drug studies conducted under BPCA have shown that the way that some drugs were being administered to children potentially exposed them to an ineffective therapy, ineffective dosing, overdosing, or previously unknown side effects—including some that affect growth and development. The labeling for these drugs was changed to reflect these study results. Table 2 shows some of these drugs and illustrates these types of labeling changes. FDA officials said that the agency has been working to increase the amount of information included in drug labeling, particularly when pediatric drug studies indicate that an approved drug may not be safe or effective for pediatric use.

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<sup>27</sup>These drugs had labeling changes made after the drug sponsors submitted partial results of their studies to FDA. Because some studies were ongoing, the drug sponsors had not submitted the final study results to FDA for consideration of pediatric exclusivity.

**Table 2: Examples of Labeling Changes**

Potential risks or hazards	Drug name	Disease or condition treated	Summary of new information contained in drug labeling
Unnecessary exposure to ineffective therapies	Sumatriptan	Migraines	Five studies did not establish safety and effectiveness, and postmarketing experience showed children were having serious adverse effects, such as stroke and vision loss. The product is not recommended for children under 18 years old.
	Tolterodine	Overactive bladder and urge incontinence	The drug was not shown to be effective for children and appeared to show a possible increase in aggressive, hyperactive, and abnormal behavior.
	Irinotecan	Tumors	Children had more rapid disease progression and died more quickly. The labeling states that the drug should not be used to treat children with a particular kind of tumor.
Ineffective dosing	Oxcarbazepine	Partial seizures	Dose for children aged 2 to 4 and weighing less than 44 pounds is twice the dose per body weight compared to adults.
	Methylphenidate	Attention-deficit hyperactivity disorder	Children aged 13 to 17 eliminated the drug from their bodies faster than the comparison age group. Therefore the dosing regimen may be increased to prevent ineffective dosing.
Overdosing	Leflunomide	Juvenile rheumatoid arthritis	Children weighing less than 88 pounds require a lower-than-expected dose. Overdosing leflunomide, which has significant toxicity, could make the drug's risks to children outweigh its benefits.
Previously unlabeled side effects, including effect on growth and development	Venlafaxine	Depression; generalized anxiety disorder	This drug is associated with an increased risk of suicidal thinking and behavior.
	Ciprofloxacin	Complicated urinary tract infection or kidney infection	This drug is associated with increased adverse effects to joints or surrounding tissues for children.
	Fentanyl	Chronic pain	This drug should be used only by children who are 2 years of age or older and are opioid-tolerant. Use by others can lead to life-threatening respiratory depression and death.
	Budesonide	Asthma	Budesonide can cause growth suppression.

Source: GAO analysis of FDA data.

Other drugs have had labeling changes indicating that the drug may be used safely and effectively by children in certain dosages or forms. Typically, this resulted in the drug labeling being changed to indicate that the drug was approved for use by children younger than those for whom it had previously been approved. In other cases, the changes reflected a new formulation of a drug, such as a syrup that was developed for pediatric

use, or new directions for preparing the drug for pediatric use were identified during the pediatric drug studies conducted under BPCA.<sup>28</sup> (See table 3 for examples of drugs with this new type of information.)

**Table 3: Examples of Drugs Approved for Use by Younger Children or for Which New Formulations Are Available**

Uses and formulations	Drug	Disease or condition treated or prevented	Summary of new information
New age groups	Moxifloxacin Ophthalmic	Bacterial conjunctivitis	Found to be safe and effective for children over 1 year old.
	Ondansetron	Nausea and vomiting after chemotherapy	Established dosing for surgical patients down to 1 month from 2 years of age; established dosing for cancer patients down to 6 months from 4 years of age.
New formulations or preparations	Benazepril	Hypertension	Labeled with directions for how to prepare a suspension for administering the drug to children.
	Desloratadine	Seasonal and perennial allergic rhinitis and hives	Newly available in a syrup, labeled specifically for children.

Source: GAO analysis.

<sup>28</sup>There were no off-patent drugs for which the pediatric drug studies indicated that a formulation change was necessary.

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## The Process for Reviewing Study Results and Approving Labeling Changes Was Sometimes Lengthy, Particularly When FDA Required Additional Information from Drug Sponsors

Although FDA generally completed its first scientific review of study results submitted as a supplemental new drug application—including consideration of labeling changes—within its 180-day goal, the process for completing the review, including obtaining sufficient information to support and approve labeling changes, sometimes took longer. For the 45 drugs granted pediatric exclusivity that had labeling changes, it took an average of almost 9 months after study results were first submitted to FDA for the sponsor to submit and the agency to review all of the information it required and agree with the drug sponsor to approve the labeling changes.<sup>29</sup> For 13 drugs (about 29 percent), FDA completed this scientific review process and FDA approved labeling changes within 180 days. It took from 181 to 187 days to complete the scientific review process and to approve labeling changes for 14 drugs (about 31 percent). For the remaining 18 drugs (about 40 percent), it took from 238 to 1,055 days for FDA to complete the scientific review process and approve labeling changes. For 7 of those drugs, it took more than a year to complete the scientific review process and approve labeling changes.

To determine whether and how drug labeling should be changed, FDA conducts a scientific review of the study results that are submitted to the agency by the drug sponsor. Included with the study results is the drug sponsor's proposal for how the labeling should be changed. FDA can either accept the proposed wording or propose alternative wording. For some drugs, however, the process does not end with FDA's first scientific review. While the first scientific reviews were generally completed within 180 days, for the 18 drugs that took 238 days or more, FDA determined that it needed additional information from the drug sponsors in order to be able to approve the applications. This often required that the drug sponsors conduct additional analyses or pediatric drug studies. FDA officials said they could not approve any changes to drug labeling until the drug sponsors provided this information. When FDA completed its review of the information that was originally submitted and requested additional information from the drug sponsors, the initial 180-day scientific review ended. A new 180-day scientific review began when the drug sponsors

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<sup>29</sup>These data are based on the dates on which FDA approved the labeling changes. FDA officials said that manufacturers might not immediately make approved labeling changes on the printed material associated with a marketed product. However, this information is posted on FDA's Web site, generally within 48 hours. Sponsors often update labeling on a quarterly basis or several times a year, rather than each time a labeling change is approved. FDA does not track the actual date that revised labeling enters the market. The dates that FDA agreed to these labeling changes are reported at <http://www.fda.gov/cder/pediatric/labelchange.htm>.

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submitted the additional information to FDA. Drug sponsors sometimes took as long as 1 year to gather the additional necessary data and respond to FDA's requests. This time did not count against FDA's 180-day goal to complete its scientific review and approve labeling changes because a new 180-day scientific review begins after the required information is submitted. However, we counted the total number of days between submission of study reports and approval of labeling changes. FDA considers itself in conformance with its review goals even though the entire process may take longer than 180 days.

BPCA provides a dispute resolution process to be used if FDA and the drug sponsor cannot reach agreement on labeling changes within 180 days of when FDA received the application and the only issue holding up FDA approval is the wording of the drug labeling. However, FDA officials said they have never used this process because labeling has never been the only unresolved issue for those applications whose review period exceeded 180 days. Agency officials told us that the possibility of referral to the Pediatric Advisory Committee facilitates its negotiations with drug sponsors on labeling changes because it is something that drug sponsors want to avoid. Reminding the drug sponsors that such a process exists has motivated drug sponsors to complete labeling change negotiations by reaching agreement with FDA. (See app. VII for a discussion of strengths of BPCA identified by FDA and NIH, as well as suggestions for ways to improve BPCA.)

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## Drugs Studied under BPCA Address a Wide Range of Diseases, Including Some That Are Common, Serious, or Life Threatening to Children

Drugs were studied under BPCA for their safety and effectiveness in treating children for a wide range of diseases, including some that are common, serious, or life threatening. We found that the drugs studied under BPCA represented more than 17 broad categories of disease. The category that had the most drugs studied under BPCA was cancer, with 28 drugs. In addition, there were 26 drugs studied for neurological and psychiatric disorders, 19 for endocrine and metabolic disorders, 18 related to cardiovascular disease—including drugs related to hypertension, and 17 related to viral infections. Written requests for some types of drugs were more frequently declined by the drug sponsor than others. For example, 36 percent of written requests for pulmonary drugs and 41 percent of written requests for drugs that treat nonviral infection were declined. In contrast, 19 percent of written requests were declined overall.

Some of the drugs studied under BPCA were for the treatment of diseases that are common, including those for the treatment of asthma and allergies. Analysis of two national databases shows that about half of the

10 most frequently prescribed drugs for children were studied under BPCA. Based on a survey of prescriptions written by physicians in 2004, 4 of the 10 drugs most frequently prescribed for children were studied under BPCA.<sup>30</sup> A survey of families and their medical providers in 2003 found that 5 of the 10 drugs most frequently prescribed for children were studied under BPCA.<sup>31</sup> In addition, several of the drugs studied under BPCA were for the treatment of diseases that are serious or life threatening to children, such as hypertension, cancer, HIV, and influenza. Table 4 provides information on some of the drugs studied for pediatric use and what is known about the diseases that are relevant to children.

**Table 4: Examples of Diseases to Be Treated by Drugs Studied under BPCA**

<b>Specific disease treated by drug</b>	<b>Information about the disease</b>
Allergies	Allergies affect up to 40 percent of, or about 29 million, children in the United States.
Asthma	Asthma affects 6.2 million or 9 percent of children in the United States. Further, asthma is the most common chronic illness among children.
Cancer	Cancer is the leading cause of death by disease for children aged 1 to 14 in the United States.
HIV	About 20 percent of HIV-infected children worldwide develop serious disease before they turn 1, and most of those die before age 4. Through the end of 2002, 9,300 children under age 13 in the United States were living with HIV.
Hypertension	An estimated 3.25 million (4.5 percent ) children in the United States have high blood pressure. Untreated, high blood pressure can lead to damage to the heart, brain, kidneys, and eyes.
Influenza	Population-based studies show that 15 to 42 percent of preschool and school-aged children contract the flu. Influenza can have serious complications for children, including pneumonia and dehydration, and can lead to death. In the 2003-2004 flu season, more United States children died from the flu than chicken pox, whooping cough, and measles combined, and nearly two-thirds were under the age of 5.

Source: GAO analysis.

Note: Based on data published from 2000 through 2006.

<sup>30</sup>National Center for Health Statistics, *2004 National Ambulatory Medical Care Survey Data File* (Hyattsville, Md.: February 2004).

<sup>31</sup>Medical Expenditure Panel Survey (Agency for Health Care Policy and Research, *2003 Medical Expenditure Panel Survey Household Data File* (Rockville, Md.: November 2005)).

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Some of the drugs were studied under BPCA to treat complicating conditions in children who had other diseases, while others treated rare diseases. For example a drug was studied for the treatment of painful bladder spasms in children who have spina bifida. Other drugs were studied to treat overactive bladder symptoms in children with spina bifida and cerebral palsy, to treat children who require chronic pain management because of severe illnesses such as cancer, and to treat partial seizures and epilepsy in children who require more than one drug to control seizures. About 12 percent of the 52 drugs that were granted pediatric exclusivity under BPCA were studied for the treatment of rare diseases, including certain types of leukemia, juvenile rheumatoid arthritis, and narcolepsy.

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## Agency Comments and Our Evaluation

HHS provided written comments on a draft of this report, which we have reprinted in appendix VIII. HHS stated that the draft report provided a significant amount of data and analysis and generally explains the BPCA process. HHS also made four general comments. First, HHS commented that the report does not sufficiently acknowledge the success of BPCA. HHS noted that BPCA provides additional incentives for the study of on-patent drugs, a process for the study of off-patent drugs, a safety review of all drugs granted pediatric exclusivity, and the public dissemination of information from pediatric studies conducted. HHS concluded that BPCA has generated more clinical information for the pediatric population than any other legislative or regulatory effort to date. Second, HHS commented that the report confuses FDA's process for reviewing reports of drug studies conducted under BPCA with time frames for the labeling dispute resolution process outlined in BPCA. HHS suggested that we did not sufficiently acknowledge that some of the time it takes for FDA to approve labeling changes includes time spent by sponsors collecting and submitting additional information. Third, in commenting on our finding that few written requests included neonates, HHS pointed out that written requests for 9 drugs required the inclusion of "newborns" and written requests for 13 drugs required the inclusion of infants (children under 4 months of age). Fourth, HHS commented that we failed to mention that exclusivity attaches to patents as well as existing market exclusivity.

We believe that the draft report sent to HHS for comment accurately and adequately addressed each of the four issues upon which HHS commented. An explicit discussion of the overall success of BPCA was outside the scope of this report, as directed by the BPCA mandate and as discussed with the committees of jurisdiction. Nevertheless, the draft report extensively discussed HHS accomplishments such as the number of

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studies conducted, the number and importance of labeling changes that FDA approved, and the wide range of diseases, including some that are common, serious, or life threatening to children, for which drugs were studied.

In drafting our report we believe we clearly distinguished between FDA's goals for completing its review and approval of drug applications and the time frames mandated for using the labeling dispute resolution process as outlined in BPCA. In finding that the process for approving labeling changes is lengthy, we clearly stated that the process included time spent during FDA's initial review as well as time drug sponsors took to respond to FDA's requests for additional information, which was as long as 1 year. We also acknowledged that FDA completed its initial review of applications within its 180-day goal. We stated in the draft that FDA has never used the dispute resolution process because labeling has never been the only issue preventing FDA's approval of a label for more than 180 days. Nevertheless, we have included additional language in this report to further clarify the distinction between FDA's review process for pediatric applications and labeling dispute resolution.

Our draft clearly stated that while written requests issued under BPCA required the inclusion of neonates, the majority of those on-patent written requests—32 of 36—had been first issued under FDAMA. It is therefore not appropriate to attribute the inclusion of neonates in these written requests to BPCA. Further, we included in our count of written requests requiring the inclusion of neonates the 9 written requests that HHS referred to in its comments as requiring the inclusion of newborns. We did not specifically include in our counts the other 13 written requests mentioned in HHS's comments. According to data provided by FDA, 1 of these written requests was not issued under BPCA, and 2 others were counted among the 9 mentioned above. The remaining 10 written requests were not specifically included in our counts, because the written requests were first issued prior to BPCA and do not specifically require the inclusion of neonates. The written requests to which HHS referred in its comments required the inclusion of very young children, age 0-4 months. Our draft report had indicated that written requests requiring the inclusion of young children might produce data about neonates.

Our draft report included language that indicated the conditions under which pediatric exclusivity applies. We added language to the report to further clarify the conditions under which pediatric exclusivity can be granted.

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HHS provided technical comments which we incorporated as appropriate. HHS also stated that many of the oral comments provided by FDA were not reflected in the draft report sent to HHS for formal comment. Some of FDA's suggested revisions and comments were outside the scope of the report and in some instances we chose to use alternative wording to that suggested by FDA for readability and consistency. As we did with HHS's general and technical comments on this report, we previously incorporated FDA's oral comments as appropriate.

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We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. We will also make copies available to others upon request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>. If you have any questions about this report, please contact me at (202) 512-7119 or [crossem@gao.gov](mailto: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 IX.



Marcia Crosse  
Director, Health Care

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# Appendix I: Scope and Methodology

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In this report, we (1) assessed the extent to which pediatric drug studies were being conducted for on-patent drugs under the Best Pharmaceuticals for Children Act (BPCA), including when drug sponsors declined to conduct the studies; (2) evaluated the impact of BPCA on labeling of drugs for pediatric use and the process by which the labeling was changed; and (3) illustrated the range of diseases treated by the drugs studied under BPCA.

Our review focused primarily on those on-patent drugs for which written requests were issued or reissued by the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) from January 2002, when BPCA was enacted, through December 2005. Actions taken on these drugs after December 2005 (such as a determination of pediatric exclusivity or a labeling change) were not included in our review. In addition, we reviewed some summary data available about the number of written requests issued under the Food and Drug Administration Modernization Act of 1997 (FDAMA) from January 1998 through December 2001. We also reviewed pertinent laws, regulations, and legislative histories.

To assess the extent to which pediatric drug studies were being conducted for on-patent drugs under BPCA, including when the drug sponsors declined to conduct the studies, we identified written requests issued for on-patent drugs from January 2002 through December 2005, and determined which of those were declined by drug sponsors. We also reviewed data provided by FDA on the nature of the pediatric drug studies that were conducted in response to the written requests issued under BPCA. We also examined notices published in the *Federal Register*, identifying the drugs designated by HHS's National Institutes of Health (NIH) as most in need of study in children. We reviewed data provided to us by the Foundation for the National Institutes of Health (FNIH)—a nonprofit corporation independent of NIH—about funding for pediatric drug studies of on-patent drugs. We interviewed officials from FDA, NIH, and FNIH to understand the processes by which pediatric drug studies are prioritized by the agencies, written requests are issued, drug sponsors respond to written requests, study results are submitted to FDA, and pediatric exclusivity determinations are made. We also reviewed background material describing the role of FNIH in supporting research on children and the funding available for such research.

To evaluate the impact of BPCA on the labeling of drugs for pediatric use and the process by which the labeling was changed, we reviewed data provided to us by FDA summarizing the changes made from January 2002

through December 2005 for drugs studied under BPCA. We also used the dates that the changes were approved in order to calculate how long it took for FDA to approve labeling changes. We interviewed officials from FDA about the process by which FDA approves labeling changes as well as the reasons why some drugs did not have labeling changes.

To illustrate the range of diseases treated by the drugs studied under BPCA, we reviewed data provided by FDA about the disease each drug was proposed to treat. We also examined data from the Medical Expenditure Panel Survey—administered by the Agency for Healthcare Research and Quality—and the National Ambulatory Medical Care Survey—administered by the National Center for Health Statistics—to assess the extent to which the drugs studied under BPCA were prescribed to children.

To obtain other information that is provided in appendixes to this report, we collected and analyzed a variety of data from FDA, NIH, and FNIH about written requests and pediatric studies for both on- and off-patent drugs. To obtain a broad perspective on the many issues addressed in our report, we also interviewed representatives of the pharmaceutical industry and health advocates—such as representatives of the American Academy of Pediatrics, the Pharmaceutical Research and Manufacturers of America, the Generic Pharmaceutical Association, the National Organization of Rare Disorders, Public Citizen, the Elizabeth Glaser Pediatric AIDS Foundation, and the Tufts Center for the Study of Drug Development.

We evaluated the data used in this report and determined that they were sufficiently reliable for our purposes. We conducted our work from September 2005 through March 2007 in accordance with generally accepted government auditing standards.

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# Appendix II: FDA and NIH Efforts to Encourage the Study of Drugs in Neonates since Passage of BPCA

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FDA and NIH have engaged in efforts to increase the inclusion of neonates—children under the age of 1 month—in pediatric drug studies. As part of its encouragement of pediatric studies in general, BPCA identified neonates as a specific group to be included in studies, as appropriate. An examination of the written requests revealed that only 4 of 36 written requests for on-patent drugs first issued under BPCA required the inclusion of neonates. Further, no written requests for on-patent drugs and only two written requests for off-patent drugs have required the inclusion of neonates since FDA and NIH held a workshop that began their major initiative in this regard in 2004.

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## NIH Workshops

In 2003, NIH conducted three workshops focused on increasing the inclusion of neonates in pediatric drug studies and discussing diseases that affect neonates. In September 2003, NIH staff met to discuss drug studies in neonatology and pediatrics with special emphasis placed on ways to better apply current knowledge in future pediatric drug studies. Two months later, NIH met with a group of experts to discuss the use of the drug dobutamine—used to treat low blood pressure—in neonates. NIH ended 2003 with a 1-day seminar designed to address parental attitudes toward neonatal clinical trials.

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## NIH Initiatives

FDA and NIH have collaborated to develop the Newborn Drug Development Initiative (NDDI), a multiphase program intended to identify gaps in knowledge concerning neonatal pharmacology and pediatric drug study design and to explore novel designs for studies of drugs for use by neonates. The NDDI is intended to consist of a series of meetings that will help frame state-of-the-art approaches and research needs. After forming various discussion groups in February 2003, the agencies held a workshop in March 2004 to help frame issues and challenges associated with designing and conducting drug studies with neonates. The workshop addressed ethical issues and drug prioritization in four specialty areas: pain control, pulmonology (the study of conditions affecting the lungs and breathing), cardiology (the study of conditions affecting the heart), and neurology (the study of disorders of the brain and central nervous system). For example, participants in the pain control group reviewed data demonstrating that neonates who undergo multiple painful procedures and receive medication to treat pain may differ in their development of pain receptors compared to those who do not undergo such procedures and treatment. FDA officials said that FDA would apply the findings from the NDDI workshop to written requests for pediatric drug studies in the four specialty areas.

NIH officials said that the Pediatric Formulations Initiative is a related effort. They said that both initiatives are long-standing activities that engage in various efforts to enhance information dissemination to improve all pediatric drug studies. According to NIH officials, these initiatives have resulted in numerous publications.

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### **Pediatric Drug Studies Requiring the Study of Neonates**

FDA and NIH efforts to increase the inclusion of neonates in pediatric drug studies conducted under BPCA have been limited. Through 2005, 9 of 16 (56 percent) written requests for off-patent drugs required the inclusion of neonates in the pediatric drug studies. NIH is currently funding pediatric drug studies for four of these written requests. Similarly, 36 of 214 (17 percent) written requests for the study of on-patent drugs issued from January 2002 through December 2005 included a requirement to study neonates, but only 4 of those 36 (11 percent) were first issued under BPCA. The remaining 32 (89 percent) written requests were originally issued under FDAMA, which did not place an emphasis on the inclusion of neonates in pediatric drug studies. Further, all of the written requests requiring the inclusion of neonates were issued in 2003, prior to the NDDI. Further, only two of the written requests for off-patent drugs were issued after the NDDI, and studies for neither of those have been funded. According to information provided by FDA, no written requests for on-patent drugs issued from January 2004 through December 2005 required the inclusion of neonates. FDA officials indicated, however, that they receive information about neonates in response to written requests that do not specifically target them. According to these officials, many written requests require that children from birth through 2 years of age be studied. These pediatric drug studies therefore may include neonates. In addition, inclusion of neonates in some studies may not be appropriate for medical or ethical reasons.

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# Appendix III: NIH Efforts to Support Pediatric Drug Studies

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BPCA was designed in part to increase pediatric drug studies through federal efforts. NIH has engaged in several efforts to support pediatric drug studies since the passage of BPCA.

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## NIH Funding

While NIH plays an important role in providing funding for research for children, the amount provided by NIH to support such activities has not increased significantly under BPCA. Since the enactment of BPCA, NIH funding for children's research has increased from \$3.1 billion in fiscal year 2003 to \$3.2 billion in fiscal year 2005. These figures represent about 11 percent of NIH's total budget each year from 2003 through 2005. The research funds for children were distributed by most of NIH's 28 institutes, centers, and offices.<sup>1</sup> For example, in 2005, 24 of these institutes, centers, and offices funded research on children. One institute, the National Institute of Child Health and Human Development, was responsible for about 26 percent of funding for pediatric research—the largest proportion of NIH's research funding for children. This institute organizes study design teams with FDA and other relevant NIH institutes, conducts contracting activities, and modifies drug labeling for specific ages and diseases.

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## Pediatric Pharmacology Research Units

The number of pediatric pharmacology research units—initiated by NIH—devoted to studies for children has remained the same under BPCA.<sup>2</sup> NIH provides about \$500,000 annually to each of these research units to provide the infrastructure for independent investigators to initiate and collaborate on studies and clinical trials with private industry and NIH. The number of such research units grew from 7 in 1994 to 13 in 1999 to support the infrastructure for collaborative efforts of pharmacologists to conduct clinical trials that include children. While the number has not changed since the passage of BPCA in 2002, NIH officials said that staff from these units often move on to hospitals throughout the country and enhance the pediatric research capacity nationwide. In addition, they said that an overall increase in pediatric research capacity nationwide in recent years has made it possible to conduct pediatric clinical trials at a number of other sites. They said that, on average, these pediatric pharmacology

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<sup>1</sup>NIH is made up of 28 institutes, centers, and offices that focus on different health concerns. The mission of NIH overall is to conduct and support medical research.

<sup>2</sup>Pediatric pharmacology research units are primarily located in children's hospitals and academic research centers specializing in research with children.

research units conduct more than 50 pediatric drug studies annually. Of these, as many as 20 pediatric drug studies are funded by drug sponsors. NIH officials told us that of the seven off-patent drugs being studied under BPCA with NIH funding through 2005, two were being conducted by these research units. NIH officials said that since on-patent written requests are not published, the full contribution of the research units under BPCA cannot be ascertained.

Meetings and Forums

NIH has sponsored a number of forums designed to increase the number of children included in drug studies. As shown in table 5, these forums generated advice and suggestions for NIH concerning drug testing from health experts, process improvements on drug studies and medication use with the pediatric community, and explanations of models and data related to research for children.

**Table 5: NIH-Sponsored Activities, through 2005, Related to Children in Clinical Trials**

Year(s)	Activity focus
2002, 2003, 2004, 2005	Pediatric experts offered advice to NIH concerning drugs that should be studied for use by children, leading to the published list of off-patent drugs in the <i>Federal Register</i> .
2003	Discussed ways to improve access to information on the frequency of medication use by children and improve the list development process surrounding the measurement of this frequency.
2003	Discussed ways to use current knowledge to better inform future studies of drugs in children.
2003	Discussed the use of two drugs, dobutamine and dopamine, in neonates.
2003	Discussed parent attitudes toward studies of neonates and other issues related to the consent for studies in children.
2004	Explored diverse models useful in understanding efficacy and toxicity of drugs across the course of development.
2005	Discussed the development of treatment strategies and recommendations for drugs to be studied in managing pediatric hypertension.
2005	Reviewed and analyzed databases used to describe the frequency of health conditions leading families to seek care for their children in different outpatient health care delivery settings, such as pediatric clinics and offices, and inpatient hospital settings. Those conditions leading to death were also part of the review.
2005	Reviewed and analyzed databases available to describe the frequency of use of medications by children in outpatient delivery settings.
2005	Discussed challenges from lack of appropriate pediatric formulations and improvements of pediatric therapeutics.

Source: NIH.

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NIH has also conducted meetings and entered numerous intra-agency and FDA agreements to strengthen its relationship with FDA and establish a firm commitment to study medical issues relevant to children. For example, NIH conducted a series of internal meetings in fiscal year 2004 to identify ongoing pediatric drug studies by the National Institute of Mental Health. As an outcome of these meetings, NIH identified and utilized data sets related to the study of lithium as it is used for the treatment of bipolar disorder in children. NIH will use this information to enhance its current understanding of the drug's therapeutic benefit.

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# Appendix IV: Studies of Off-Patent Drugs under BPCA

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In addition to providing a mechanism to study on-patent drugs, BPCA also contains provisions for the study of off-patent drugs. FDA initiates its process by issuing a written request to the drug sponsor to study an off-patent drug. If the sponsor declines to study the drug, FDA can refer the study of the drug to NIH for funding. NIH initiates the BPCA process for off-patent drugs by prioritizing the list of drugs that need to be studied.

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## Written Requests for Studies of Off-Patent Drugs under BPCA

BPCA includes a provision that provides for the funding of the study of off-patent drugs by NIH. BPCA requires that NIH—in consultation with FDA and other experts—publish an annual list of drugs for which additional studies are needed to assess their safety and effectiveness in children.<sup>1</sup> FDA can then issue a written request for pediatric studies of the off-patent drugs on the list. If the written request is declined by the drug sponsor, NIH can fund the studies.

Few off-patent drugs identified by NIH as in need of study for pediatric use have been studied. From 2003 through 2006, NIH has listed off-patent drugs that were recommended for study by experts in pediatric research and clinical practice.<sup>2</sup> By 2005, NIH had identified 40 off-patent drugs that it believed should be studied for pediatric use.<sup>3</sup> Through 2005, FDA issued written requests for 16 of these drugs.<sup>4</sup> All but one of these written requests were declined by drug sponsors. NIH funded pediatric drug studies for 7 of the remaining 15 written requests declined by drug sponsors through December 2005.

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<sup>1</sup>The list, published in the *Federal Register*, can include on-patent and off-patent drugs. NIH did not include on-patent drugs on this list until 2005.

<sup>2</sup>See 71 *Fed. Reg.* 23931-36 (Apr. 25, 2006), 70 *Fed. Reg.* 3937 (Jan. 27, 2005), 69 *Fed. Reg.* 7243-7244 (Feb. 13, 2004), 68 *Fed. Reg.* 48402 (Aug. 13, 2003), and 68 *Fed. Reg.* 2789-2790 (Jan. 21, 2003).

<sup>3</sup>Some drugs have two written requests; in such cases, each written request is designed to study either the effects of the drug on a different disease or dosage form, or the drug has two sponsors. In these cases, we counted each of these written requests separately. For example, Beclomethasone had written requests issued to two sponsors for different dosage forms of the drug. An additional 3 off-patent drugs were identified in 2006. From 2003 through 2006, 12 on-patent drugs have also been listed as important for study. See 71 *Fed. Reg.* 23931-23936 (2006).

<sup>4</sup>Two of these drugs changed patent status after the off-patent written request was issued because a new formulation of each drug was approved, resulting in new patents or exclusivities. They have had new written requests issued and are now considered on-patent drugs. Both drug sponsors also declined the on-patent written requests.

NIH provided several reasons why it has not pursued the study of some off-patent drugs that drug sponsors declined to study. Concerns about the incidence of the diseases that the drugs were developed to treat, the feasibility of study design, drug safety, and changes in the drugs' patent status have caused the agency to reconsider the merit of studying some of the drugs it identified as important for study in children.<sup>5</sup> For example, in one case NIH issued a request for proposals to study a drug but received no response. In other cases, NIH is awaiting consultation with pediatric experts to determine the potential for study.

Further, NIH has not received appropriations specifically for funding pediatric drug studies under BPCA. Rather, according to agency officials, NIH uses lump sum appropriations made to various institutes to fund pediatric drug studies under BPCA. In fiscal year 2005, NIH spent approximately \$25 million for these pediatric drug studies.

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### Funding for Studies of Off-Patent Drugs under BPCA

NIH anticipates spending an estimated \$52.5 million for pediatric drug studies following seven written requests to drug sponsors issued by FDA from January 2002 through December 2005.<sup>6</sup> These pediatric drug studies were designed to take from 3 to 4 years and will be completed in 2007 at the earliest. Where possible, NIH identifies another government agency or institute within NIH that might be able to meet the requirements of the written requests and conduct the pediatric drug studies. In cases where a government agency will conduct the pediatric drug studies, NIH institutes enter into intra- or interagency agreements for the studies. If those efforts fail, the agency develops and publishes requests for proposals for others to conduct the pediatric studies. NIH anticipates spending approximately \$16.0 million for the funding of pediatric drug studies of four additional off-patent drugs for which FDA did not issue written requests—and therefore are not covered by the requirements of BPCA—but three of these drugs have since been listed by NIH in the *Federal Register* as needing study in children.<sup>7</sup> (See table 6.)

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<sup>5</sup>Since its inception, no drug has been removed from the list published in the *Federal Register*, regardless of the feasibility or likelihood of being studied.

<sup>6</sup>The costs reported by NIH are estimates, which may change during the course of the studies.

<sup>7</sup>NIH determined that these drugs were a priority for study in children and certain conditions made it appropriate to initiate studies prior to FDA being able to issue a written request.

**Appendix IV: Studies of Off-Patent Drugs  
under BPCA**

**Table 6: Anticipated NIH Spending for Off-Patent Drug Studies Committed to through 2005**

<b>Drug</b>	<b>Total cost<sup>a</sup></b>	<b>Disease or condition</b>	<b>Funded agency or organization</b>	<b>Anticipated completion</b>
<b>Studies for drugs with a written request</b>				
Dactinomycin <sup>b</sup>	\$1,800,000 <sup>c</sup>	Cancer	Children's Oncology Group through the National Cancer Institute	2007
Hydroxyurea	\$7,000,000 <sup>c</sup>	Sickle cell	National Heart Lung and Blood Institute	2008
Lithium	\$17,400,000 <sup>c</sup>	Mania in bipolar disorder	Case Western University	2008
Lorazepam (two diseases/conditions)	\$15,100,000 <sup>d</sup>	Status epilepticus (seizures)	National Institutes of Health	2008
		Sedation	National Institutes of Health	2008
Sodium nitroprusside	\$9,400,000 <sup>c</sup>	Control of blood pressure	Stanford University and Duke University	2007
Vincristine <sup>b</sup>	\$1,800,000 <sup>c</sup>	Malignancies	Children's Oncology Group through the National Cancer Institute	2007
<b>Subtotal</b>	<b>\$52,500,000</b>			
<b>Studies initiated prior to a written request<sup>e</sup></b>				
Daunomycin (Daunorubicin)	\$1,400,000 <sup>c</sup>	Cancer	Children's Oncology Group through the National Cancer Institute	2008
Ketamine	\$1,000,000 <sup>d</sup>	Sedation	FDA's National Center for Toxicological Research	2008
Methotrexate	\$8,900,000 <sup>d</sup>	Cancer	Children's Oncology Group through the National Cancer Institute	2009
Methylphenidate	\$4,700,000 <sup>f</sup>	Attention deficit hyperactivity disorder	National Institute of Environmental Health Sciences	2007
<b>Subtotal</b>	<b>\$16,000,000</b>			
<b>Total</b>	<b>\$68,500,000</b>			

Source: GAO analysis of NIH data.

<sup>a</sup>Total costs proposed for most studies are estimates and may vary over time because of modifications of initial projects, rounded to the nearest \$100,000.

<sup>b</sup>Dactinomycin and Vincristine are commonly used together and the cost to study both is \$3,600,000.

<sup>c</sup>Studies to be completed over 3 years.

<sup>d</sup>Studies to be completed over 4 years.

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<sup>a</sup>No written request was issued by FDA for the specific studies prior to being funded by NIH. Ketamine is listed in the *Federal Register* as a drug in need of study in children (69 *Fed. Reg.* 7243-44, Feb. 13, 2004). Because of data demonstrating that ketamine enhances cell death in the brain in animals, it is not possible to design an ethical study using children. Ketamine has since been listed in the *Federal Register* as having preclinical toxicology studies under way, with clinical studies awaiting their completion (71 *Fed. Reg.* 23931-36, Apr. 25, 2006). Methylphenidate was selected, though it is not included on the list published in the *Federal Register*, because of a potentially serious public health concern that arose unexpectedly. HHS officials reported that studies on ketamine and methylphenidate are not the type that typically would be requested under BPCA, nor was a written request issued for these specific studies. Daunomycin and methotrexate were selected prior to being listed in the *Federal Register* because the National Cancer Institute had access to the appropriate children for study and was developing studies that would produce data for both drugs.

<sup>1</sup>Studies to be completed over 2 years.

The drugs whose study NIH is funding without written requests were selected because of special circumstances that raised their priority for funding. NIH funded the study of daunomycin and methotrexate—both cancer drugs—before placing them on its 2006 list of drugs for study in children. NIH officials told us that the Children’s Oncology Group of the National Cancer Institute was already working with an appropriate group of patients and was at a critical stage in developing the pediatric drug studies that would produce data for both drugs, so pediatric drug studies were funded before the drugs were placed on the priority list. NIH officials also told us that ketamine is administered to more than 30,000 children for sedation each year. Studies done in animals, however, have suggested that the drug may lead to cell death in the brain. As a result, the drug cannot be ethically tested in children. NIH is therefore collaborating with FDA to conduct studies in nonhuman primates. NIH officials report that methylphenidate is used by an estimated 2.5 million school-aged children to treat attention deficit hyperactivity disorder. However, a recent study suggested some potential genetic toxicity of the drug. Because of these findings, the drug was targeted as a priority and NIH was able to fund some of the planned studies related to this drug.

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# Appendix V: Status of Pediatric Drug Studies Requested by FDA

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From January 2002 through December 2005, FDA issued 214 written requests for the study of on-patent drugs. The agency also issued 16 written requests for the study of off-patent drugs. Fewer written requests were issued and more were declined by drug sponsors under BPCA than under FDAMA.

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## Written Requests Issued under BPCA Compared to FDAMA

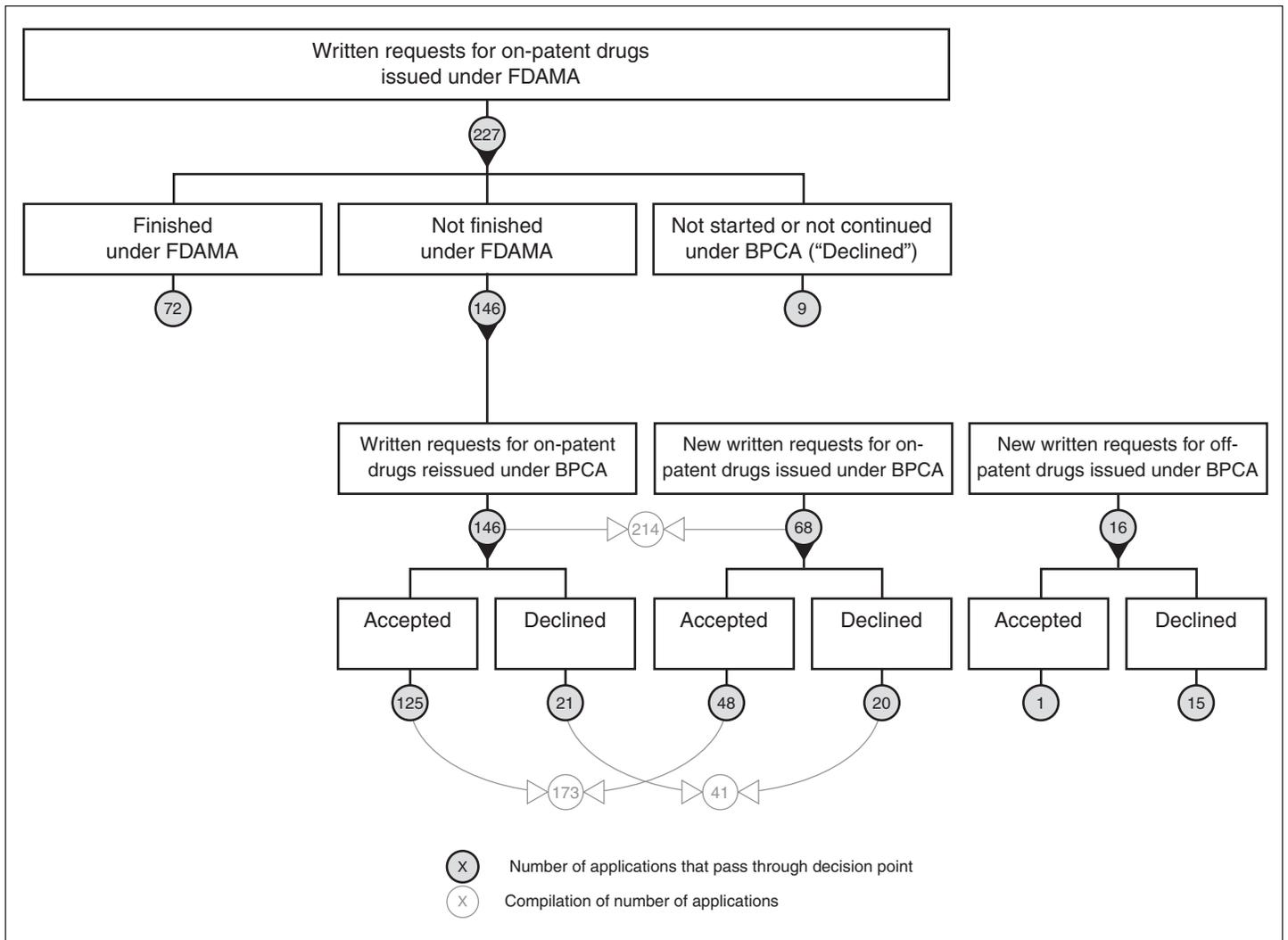
From January 2002, when BPCA was enacted, through December 2005, FDA issued or reissued 214 written requests for on-patent drugs, and drug sponsors declined 41 of those. FDA issued 68 written requests under BPCA for the study of on-patent drugs,<sup>1</sup> 20 (29 percent) of which were declined by the drug sponsors. FDA reissued 146 written requests for on-patent drugs that were originally issued under FDAMA because the pediatric drug studies had not been completed at the time BPCA went into effect. Included in the 146 were 21 (14 percent) written requests that were subsequently declined by the drug sponsors. Therefore, drug sponsors accepted 173 written requests for the study of on-patent drugs under BPCA during this period. Under FDAMA, FDA issued 227 written requests. Drug sponsors did not conduct pediatric drug studies or submit study results for 30 of the 227 (13 percent) written requests issued under FDAMA (see fig. 3).<sup>2</sup>

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<sup>1</sup>We counted all written requests individually. In some cases, FDA issued more than one written request for a drug, such as when there was more than one sponsor, when the first written request was declined by the drug sponsor and a new written request was issued when FDA became aware of new information, or when the drug was being studied for more than one disease (though these studies may also be in the same written request).

<sup>2</sup>Since FDAMA did not require that drug sponsors accept or decline a written request, as required by BPCA for on-patent drugs, we could not determine the exact number of written requests that were declined. Instead, we were able to determine the number of written requests for which study results were not submitted under FDAMA and the number of written requests declined when reissued under BPCA. This is the most conservative equivalent measure. FDA officials report that it is possible that studies were conducted under FDAMA and the drug sponsors decided not to submit them to FDA for exclusivity consideration.

Figure 3: Status of Written Requests Issued under FDAMA and BPCA through December 2005



Source: GAO.

Note: If a drug sponsor of an off-patent drug does not respond to FDA's written request within 30 days, the written request is considered declined.

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## Reasons for Decline in Written Requests Issued and Accepted under BPCA Compared to FDAMA

FDA officials offered two primary reasons why fewer written requests were issued under BPCA than under FDAMA. First, according to FDA officials, when FDAMA was enacted, FDA and some drug sponsors had already identified a large number of drugs that they believed needed to be studied for pediatric use. By the time BPCA was enacted, written requests for the study of these drugs had already been issued. Second, FDA officials said there was a surge of written requests prior to the sunset of FDAMA. Agency officials expect the same surge to occur prior to the sunset of the pediatric exclusivity provisions of BPCA in 2007.

FDA officials also offered a number of reasons that the proportion of written requests issued under BPCA that were declined was greater than that for those issued under FDAMA. While FDA does not track the reasons that drug sponsors decline specific written requests, FDA officials expect that a major reason that the written requests were declined is that the agency sometimes requests more extensive pediatric drug studies, and therefore more costly studies, than the sponsors would like to do. This may be the case even when the drug sponsors initiated the written request process. FDA officials said that upon consideration of FDA's written requests, drug sponsors may make a business decision not to conduct the requested pediatric drug studies because they may be too costly for the expected return associated with pediatric exclusivity. Agency officials reported that since the drugs studied under FDAMA were more likely to be those with the greatest expected financial return or the easiest to study, they are not surprised at the higher proportion of pediatric drug studies declined under BPCA. Further, under BPCA drug sponsors are required to pay user fees—as high as \$767,400 in fiscal year 2006—when study results are submitted for pediatric exclusivity consideration. As a result, the process of gaining pediatric exclusivity has become more expensive than it was under FDAMA when drug sponsors were exempt from such fees for pediatric drug studies.

FDA officials said they are not discouraged by the increase in the number of written requests that have been declined. In 2001, FDA reported to Congress that the agency expected drug sponsors to conduct pediatric drug studies for 80 percent of written requests. The rate at which written requests for studies of on-patent drugs were accepted under BPCA—71 percent—is close to the target of 80 percent, and it is substantially larger than the 15 to 30 percent of drugs that FDA officials have reported

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were labeled for pediatric use prior to the authorization of pediatric exclusivity under FDAMA and BPCA.<sup>3</sup>

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<sup>3</sup>Prior to FDAMA, over a 6-year period from 1991 to 1996, only 11 of 71 requested studies were completed without such an incentive.

# Appendix VI: Complexity of Completed Pediatric Drug Studies

The pediatric drug studies conducted under BPCA were complex and sizable, involving a large number of study sites and children. From July 2002 through December 2005,<sup>1</sup> drug sponsors submitted study reports to FDA in response to 59 written requests. FDA made pediatric exclusivity determinations for 55 of those written requests by December 2005, and most—51, or 93 percent—were made in 90 days or less.

For the 59 written requests for which study results were submitted to FDA, a total of 143 pediatric drug studies were conducted at 2,860 different study sites with more than 25,000 children participating (see table 7). In December 2005, FDA projected that for the drugs for which studies had not yet been submitted for review, there would be nearly 20,000 more children participating in the studies.

**Table 7: Complexity of Pediatric Drug Studies Conducted under BPCA, According to Study Reports from July 2002 through December 2005**

	Number of individual studies	Number of study sites for all studies	Number of participants in all studies
Count	143	2,860	25,397
Average	2	68	430
Median	2	48	255
Mode	2	83	192
Minimum	1	3	11
Maximum	7	232	2,517
Number of written requests data are based on	59	42	59

Source: GAO analysis of FDA data.

<sup>1</sup>For these analyses, we looked at study reports submitted after July 2002 because those submitted from January 2002 through June 2002 were in response to written requests issued under FDAMA, not BPCA.

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# Appendix VII: Strengths of and Suggested Changes for BPCA

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Officials from FDA and NIH discussed a number of important strengths of BPCA. In our interviews with industry group representatives and in a public forum, a number of suggestions have also been made for ways that BPCA could be improved.

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## Strengths of BPCA Identified by FDA and NIH Officials

FDA officials identified a number of important strengths of BCPA. Specifically, they commented on the following:

- *Economic incentives to conduct pediatric drug studies.* Because of the economic incentives in BPCA, FDA officials argue that many logistical issues inherent in conducting pediatric drug studies have been overcome. FDA may also issue a written request for pediatric drug studies for rare conditions, offering an additional incentive to develop medications for rare diseases that occur only in children.
- *Availability of summaries of pediatric drug studies.* FDA officials reported that the public dissemination of study summaries has ensured that study information is available to the health care community and has been useful to prescribers to know what has been learned about drugs' use in children.
- *Broad scope of pediatric drug studies.* BPCA allows FDA to issue written requests for pediatric drug studies for the treatment of any disease, regardless of whether the drug in question is currently indicated to treat that disease in adults. For example, FDA issued a written request for the study of a drug currently indicated to treat prostate cancer. The drug is being tested in children to see if it is effective in treating early puberty in boys.
- *Use of dispute resolution as a negotiating tool in ensuring labeling changes.* Although FDA has never invoked its authority under BPCA to use the dispute resolution process for making labeling changes, it has been an important negotiating tool. FDA officials indicated that when the agency has expressed its intention to use the process, the issues that had been raised in labeling negotiations were effectively resolved.
- *Improved safety through focused pediatric safety reviews.* BPCA's requirement that FDA conduct additional monitoring of adverse event reports for 1 year after a drug is granted pediatric exclusivity has been useful to FDA in prioritizing safety issues for children. For example, an analysis of a drug 1 year after pediatric exclusivity was granted showed that there were deaths among children as a result of overuse or misuse of

the drug. This led the agency to amend the labeling regarding the appropriate population for the drug.

NIH officials said they have found the process of developing the list of drugs important for study in children to be extremely helpful. NIH officials told us that since the inception of BPCA, they have learned a great deal about existing gaps in the drug development process for children, including a lack of data about which drugs are used by children and how frequently. To gather additional information, NIH has contracted for literature reviews to decrease the possibility that unnecessary pediatric drug studies are conducted. These officials also stated that BPCA and the development of the priority list have helped to solidify an alliance between NIH and FDA, which has led to discussions and resolutions of scientific and ethical issues relating to pediatric drug studies.

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## Suggestions for Changes to BPCA

The Institute of Medicine convened a forum on pediatric research in June 2006 where forum participants made suggestions for how BPCA could be improved.<sup>1</sup> In addition, we discussed suggestions for improving BPCA with interest group representatives. Forum participants suggested that the timing of the determination of pediatric exclusivity should parallel the scientific review of a drug application and that both should be within 180 days of FDA receiving the results from the pediatric drug studies. FDA's ability to assess the overall quality of the pediatric drug studies in the 90 days currently allotted for the review was questioned. Some forum participants also stated that a longer review period could result in different determinations in some cases. For example, FDA's scientific review of data related to the study of one drug showed that the children participating in the pediatric drug studies had not received the treatments as the drug sponsors had suggested in their description of the study results. While the agency had granted the drug sponsor pediatric exclusivity based on its 90-day review to determine pediatric exclusivity, it might not have done so based on what was learned during the longer, 180-day scientific review.

In addition, it was suggested that drug sponsors be required to submit their study results for pediatric exclusivity determination at least 1 year prior to patent expiration. This would allow the generic drug industry time

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<sup>1</sup>Forum on Drug Discovery, Development, and Translation: Addressing the Barriers to Development in Pediatrics (conference sponsored by the Institute of Medicine of the National Academies, Washington, D.C., June 2006). The program can be accessed at [www.iom.edu/CMS/3740/24155/34241.aspx](http://www.iom.edu/CMS/3740/24155/34241.aspx).

to better plan its release of drugs. We were told that sometimes generic drugs have had to be destroyed because pediatric exclusivity determinations were made after the generic version of the drug had been manufactured and the drug's expiration date would not allow the product to be sold.

Representatives from interest groups would like the written requests to be public information and would also like FDA to publicly announce when it receives study results that have been submitted in response to a written request. This would allow the generic drug industry to better schedule the introduction of generic drugs into the market.

Other suggestions for how the study of off-patent drugs could be more effectively encouraged were offered at the forum. A forum participant suggested that methods similar to those being adopted by the European Union be implemented. According to forum participants, under new legislation in Europe, companies that study off-patent drugs will be offered a variety of incentives, such as 10 years of data protection (meaning that the data generated to support the marketing of the drug cannot be used to support another drug, in an effort to delay competition), the right to use the existing brand name (to enable the drug sponsor to capitalize on existing brand recognition), and the ability to add a symbol to the drug labeling indicating the drug has been studied in children.

Another suggestion was that current fees paid by drug sponsors for review of their drug applications could be used to fund the study of off-patent drugs (as well as on-patent drugs that drug sponsors decline to study). These fees—\$767,400 for a new drug application and \$383,700 for a supplemental drug application in fiscal year 2006—are collected from drug sponsors when study results are submitted to FDA for review and consideration of pediatric exclusivity.

# Appendix VIII: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary  
for Legislation

Washington, D.C. 20201

MAR 16 2007

Ms. Marcia Crosse  
Director, Health Care  
U.S. Government Accountability Office  
Washington, DC 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "Pediatric Drug Research: Studies Conducted Under Best Pharmaceuticals for Children Act" (GAO-07-557), before its publication.

We appreciate the effort that went into the analysis of Best Pharmaceuticals for Children Act statistics and information provided by FDA to GAO. We are providing General and Technical Comments on the draft report on the primary substantive issues and factual corrections. Although we had a telephone conference call with members of the GAO team on March 7, 2007, to identify factual and technical errors in the Statement of Facts provided to FDA, many of the corrections we explained to GAO on March 7 are not reflected in the draft report. To ensure the data and analysis are not subject to misinterpretation, we identify the technical corrections that should be made to the draft report.

Sincerely,

*Rebecca Hernandez*

Vincent J. Ventimiglia  
Assistant Secretary for Legislation

for

**GENERAL COMMENTS ON THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE DRAFT REPORT ENTITLED: "PEDIATRIC DRUG RESEARCH STUDIES CONDUCTED UNDER BEST PHARMACEUTICALS FOR CHILDREN ACT (GAO-07-557)"**

The HHS Food and Drug Administration (FDA) and the National Institutes of Health (NIH) are responsible for implementation of the BPCA. FDA has the primary responsibility for the BPCA exclusivity process. Although there are no recommendations on BPCA contained in the draft report for HHS (FDA) comment, we are providing General Comments on several key substantive issues.

While the GAO draft report has provided a significant amount of data and analysis and generally explains the BPCA process, the draft report contains several statements and characterizations, which may provide a misleading impression to Congress and other readers of the final report. We believe the general comments provided below are critical to understanding the public health benefits of BPCA and the full scope of the program as currently implemented.

- **Success of BPCA.** The GAO draft report does not acknowledge that BPCA is a successful program. Although the draft report includes statistics on how many drugs have been studied in pediatric populations and how many drugs have been labeled, it fails to state that the pediatric studies were conducted and drugs were labeled as a result of the BPCA process. Approximately a quarter of the products studies resulted in either new safety or dosing labeling information or information suggesting that the product was ineffective at the dose and manner in which it was studied. In addition to the important use information now in labels, BPCA has improved the infrastructure for pediatric drug development by providing additional incentives for the study of on-patent drugs, a process for the study of off-patent drugs, a vigorous and public safety review of all products granted pediatric exclusivity, and the public dissemination of information in pediatric studies conducted. As a result, BPCA has generated more clinical information for the pediatric population than any other legislative or regulatory effort to date.

Although there have been no finished studies on certain products, such as those off-patent drugs or drugs for which the sponsor declined to conduct studies, which have gone through the NIH contracting process, these are often the most complex studies to conduct and we are confident that these efforts will show results in the next several years.

- **Label changes under BPCA.** The GAO draft report confuses FDA's review process for pediatric supplements with timeframes described in the BPCA for labeling dispute resolution. As written, the draft report states that it often takes a long time to make labeling changes. However, the time as reported in the draft report includes the review of the scientific data, requests for additional information, and the sponsor's submission of additional information that support any labeling changes. FDA was not negotiating labeling changes for the entire time period as reported in the draft report.
  - Pediatric studies submitted as supplements to a new drug application by sponsors in response to written requests must be treated as "priority supplements." FDA's performance goals are to review priority supplements in 180 days.

**GENERAL COMMENTS ON THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE DRAFT REPORT ENTITLED: "PEDIATRIC DRUG RESEARCH STUDIES CONDUCTED UNDER BEST PHARMACEUTICALS FOR CHILDREN ACT (GAO-07-557)"**

- This goal is not a BPCA mandate (although BPCA requires that pediatric supplements under BPCA receive a priority review). If FDA determines that the supplement is deficient and requests additional information from the sponsor, the first scientific review cycle is completed. A new cycle does not begin until the sponsor submits the requested information. A supplement cannot be approved and labeling negotiations generally do not begin until all of the required information from all of the review cycles is submitted and reviewed. The multiple review cycles increase the time between the initial submission and the ultimate approval of labeling change.
- If pediatric studies are submitted as a new drug application and not a supplement, then it is not required to be reviewed as a priority. FDA has a performance goal to review new drug applications in 10 months.
- If the application or supplement is otherwise ready for approval and the only outstanding issue is the need to reach agreement on labeling changes, the BPCA's dispute resolution process can be utilized. In that case, in not later than 180 days after submission of the application, the Commissioner would request that the sponsor make any labeling changes that the Commissioner deems appropriate. If the sponsor does not agree to them, the labeling issue should be referred to the Pediatric Advisory Committee. The Pediatric Advisory Committee is given 90 days after receiving such a referral to review the pediatric study reports and make a recommendation regarding appropriate labeling changes. The Commissioner then has 30 days to review the Advisory Committee recommendations and, if appropriate, make a request that the sponsor make a labeling change. If the sponsor does not agree, the Commissioner may deem the drug to be misbranded.
- ***Study of neonates under BPCA.*** The GAO draft report, in Appendix II, states that despite FDA and NIH efforts to increase inclusion of neonates, defined as children under 1 month of age, in written requests, few written requests under BPCA include neonates. BPCA requires the inclusion of neonates in pediatric studies as appropriate, but in some cases inclusion of neonates may not be appropriate for medical or ethical reasons. In addition, although no written requests have specifically required the inclusion of "neonates" as a specific group, 14 studies of 9 drugs required the inclusion of "newborns" (also defined as children under 1 month of age and which includes neonates) and 24 studies of 13 drugs required the inclusion of infants (defined as children under 4 months of age).
- ***Pediatric exclusivity attaches to an existing patent or market exclusivity.*** The GAO draft report does not mention that pediatric exclusivity under BPCA attaches to an existing listed patent or any existing marketing exclusivities held by the drug sponsor. The exclusivity is not limited to extending market exclusivity, but also attaches to existing patents even if there is no market exclusivity left on the drug in question. Like marketing exclusivity, the existence of a listed patent affects the timing of generic drug application submission and approval.

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# Appendix IX: GAO Contact and Staff Acknowledgments

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## GAO Contact

Marcia Crosse, (202) 512-7119 or [crosssem@gao.gov](mailto:crosssem@gao.gov)

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## Acknowledgments

In addition to the contact named above, Thomas Conahan, Assistant Director; Shaunessye Curry; Cathleen Hamann; Martha Kelly; Julian Klazkin; Carolyn Feis Korman; Gloria Taylor; and Suzanne Worth made key contributions to this report.

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## Public Affairs

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