



March 2016

# RARE DISEASES

## Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program

# GAO Highlights

Highlights of [GAO-16-319](#), a report to congressional committees

## Why GAO Did This Study

Almost 7,000 rare diseases, most of which are serious or life-threatening, affect more than 25 million Americans. About half of all rare diseases affect children, and few of these diseases have viable treatments. To encourage the development of drugs to treat or prevent rare pediatric diseases, the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 authorized FDA to award a priority review voucher to a drug sponsor upon approval of that sponsor's drug to treat a rare pediatric disease. A drug sponsor can later redeem the voucher when submitting another new drug application to treat any disease or condition in adults or children, or sell or transfer the voucher to another sponsor. A voucher entitles a sponsor to a 6-month priority review by FDA rather than the 10-month standard review.

FDASIA included a provision for GAO to study the pediatric voucher program. GAO examined what is known about the effectiveness of the program in encouraging the development of drugs to prevent or treat certain rare pediatric diseases. GAO reviewed relevant laws and documentation related to the program and its management, and identified drug sponsors who were awarded vouchers, the diseases their drugs were approved to treat, and whether the vouchers were redeemed, sold, or transferred. GAO also interviewed FDA officials, drug sponsors, patient advocacy groups, and organizations representing physicians and children's hospitals, among others.

View [GAO-16-319](#). For more information, contact Marcia Crosse at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov).

March 2016

## RARE DISEASES

### Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program

#### What GAO Found

It is too early to gauge whether the Food and Drug Administration's (FDA) pediatric voucher program has stimulated the development of drugs to treat or prevent rare pediatric diseases. Given that the typical drug development process often exceeds a decade, insufficient time has elapsed to determine whether the 3 year-old program has been effective. Any drug sponsors motivated by the program to attempt to develop a drug for a rare pediatric disease may be many years from submitting new drug applications—which contain scientific and clinical data about safety and effectiveness—to FDA for review.

As of December 31, 2015, there have been 11 requests for a pediatric voucher. Of these, six have been awarded, two denied, and three remain under review. The six drugs for which vouchers were awarded were in development prior to the program's implementation and these drugs helped fulfill unmet medical needs. One drug is indicated to treat a rare pediatric cancer, and the other five drugs treat rare metabolic diseases affecting children. No other drugs had been previously approved by FDA for these conditions. Four of the six awarded pediatric vouchers have been sold to other drug sponsors for prices ranging from \$67.5 million to \$350 million. One of the six vouchers awarded has been redeemed and was used to obtain a priority review of a new drug application for a drug to treat adults with high cholesterol. FDA approved this new drug application in July 2015.

FDA officials stated that, while they strongly support the goal of incentivizing drug development for rare pediatric diseases, they have seen no evidence that the program is effective. The program's authorization, as amended, is set to terminate October 1, 2016, and FDA officials said they do not support the program's continuation. They expressed concern that the program adversely affects the agency's ability to set its public health priorities by requiring FDA to provide priority reviews of new drug applications that would not otherwise qualify if they do not treat a serious condition or provide a significant improvement in safety or effectiveness. Additionally, FDA officials said that the additional workload from the program strains the agency's resources. However, other stakeholders provided generally positive feedback on the program. For example, drug sponsors that sold these vouchers said they plan to reinvest portions of the proceeds they received into additional research on rare pediatric diseases, although there is no requirement to do so. Patient advocacy groups told GAO that the program could lead to the development of needed drugs.

We provided a draft of this report for comment to the Department of Health and Human Services (HHS). HHS provided technical comments, which we incorporated as appropriate.

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## Abbreviations

FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
HHS	Department of Health and Human Services
NIH	National Institutes of Health

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March 2, 2016

The Honorable Lamar Alexander  
Chairman  
The Honorable Patty Murray  
Ranking Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable Fred Upton  
Chairman  
The Honorable Frank Pallone, Jr.  
Ranking Member  
Committee on Energy and Commerce  
House of Representatives

Rare diseases are diseases that affect fewer than 200,000 people in the United States. However, they pose a serious health concern as approximately 7,000 rare diseases affect more than 25 million Americans, according to the National Institutes of Health (NIH).<sup>1</sup> Almost half of these diseases affect children. The onset of a rare disease can be devastating for patients and their families. Most of these diseases are serious, disabling, and life-threatening, yet little may be known about them, making it difficult to diagnose a patient correctly. Even once a patient is diagnosed, many rare diseases do not have viable treatment options. Individuals with a rare disease can experience shortened life expectancy or decreased quality of life. Finding effective treatments for these diseases is important but challenging, and developing such treatments specifically for children adds to that challenge.

Over the years, a number of laws have been enacted to improve the availability of drugs for patients with rare diseases and for children, including the Orphan Drug Act, the Pediatric Research Equity Act of

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<sup>1</sup>See National Institutes of Health, "Fact Sheet: Rare Diseases Clinical Research Network," accessed Dec. 15, 2015, <http://report.nih.gov/nihfactsheets/Pdfs/RareDiseasesClinicalResearchNetwork%28ORDER%29.pdf>.

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2003, and the Best Pharmaceuticals for Children Act.<sup>2</sup> Most recently, in 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) authorized a new program to encourage the development of new drugs for rare pediatric diseases.<sup>3</sup> Through this program, the sponsor of a new drug application that is approved by the Food and Drug Administration (FDA) may be eligible to receive a voucher entitling it to later receive a 6-month priority review for another of its new drug applications for a drug to treat any disease or condition in adults or children, rather than the typical 10-month standard review.<sup>4</sup> The voucher may also be transferred or sold to another drug sponsor, who may then redeem it.<sup>5</sup> The potential for additional revenue that comes from marketing a drug approximately 4 months sooner—or the proceeds that may come from selling the voucher to another drug sponsor—could incentivize sponsors to develop drugs that prevent or treat rare pediatric diseases.

FDASIA included a provision that we study the effectiveness of the rare pediatric disease priority review voucher program.<sup>6</sup> This report examines what is known about the effectiveness of the pediatric voucher program in

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<sup>2</sup>Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa et seq. and scattered sections of 15, 21, 26 and 42 U.S.C.). Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended at 21 U.S.C. § 355c). Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended at 21 U.S.C. §355a and scattered sections of 21 and 42 U.S.C.).

<sup>3</sup>Pub. L. No. 112-144, § 908, 126 Stat. 993, 1094 (2012) (codified as amended at 21 U.S.C. § 360ff). FDASIA included a provision providing for termination of FDA's authority to award pediatric vouchers, 1 year after the date that the third voucher was awarded. 21 U.S.C. § 360ff(b)(5). Subsequent legislation specified that this authority terminates, October 1, 2016. See Consolidated Appropriations Act 2016, Pub. L. No. 114-113, § 765, 129 Stat. 2242, 2287.

<sup>4</sup>Typically, a drug may be eligible for priority review if it is for a serious condition and, if approved, would provide significant improvement in safety and effectiveness—the goal is to complete the priority review in 6 months. In this case, a pediatric voucher gives a sponsor the opportunity to obtain a priority review for a new drug application when it would otherwise be reviewed through FDA's standard review process, which takes approximately 10 months. A new drug application contains scientific and clinical data about a drug's safety and effectiveness. A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

<sup>5</sup>21 U.S.C. §360ff(b)(2).

<sup>6</sup>For the purposes of this report, we use the term "pediatric voucher program" to refer to the rare pediatric disease priority review voucher program.

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encouraging the development of drugs to prevent or treat certain rare pediatric diseases.

To perform our work, we examined relevant laws, policies, FDA guidance, and other documentation related to the pediatric voucher program and its management, including FDASIA's provisions, FDA's draft guidance for industry on pediatric vouchers, and FDA's report on developing drugs for rare pediatric diseases and its strategic plan for accelerating drug development for them.<sup>7</sup> Additionally, we obtained information from FDA about the number of requests FDA has received for pediatric vouchers and related requests for rare pediatric disease designations, which are usually a precursor to receiving a voucher and which a drug sponsor may request any time during the drug development process. In addition, we reviewed information from FDA related to the new drug applications for which vouchers were awarded. We identified drug sponsors that were awarded these vouchers and the diseases their drugs were approved to treat, as well as the status of the vouchers once awarded—that is, whether they had been sold, transferred, or redeemed. We reviewed the medical literature and information from NIH, patient advocacy groups, and physicians to learn about the rare pediatric diseases for which these drugs had been developed, including how patients with these diseases are currently treated.

We interviewed FDA officials to supplement our understanding of the pediatric voucher program, and FDA and NIH officials to supplement our understanding of the diseases for which vouchers were awarded. We also spoke with 9 of the 10 drug sponsors that were awarded, purchased, or otherwise received or redeemed a voucher.<sup>8</sup> Among other things, we discussed their perspectives on the program, including the extent to which they believed the program acted as an incentive for drug sponsors to encourage the development of drugs for rare pediatric diseases. Additionally, we spoke with six patient advocacy groups associated with the rare pediatric diseases for which a voucher was awarded, and with

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<sup>7</sup>See FDA, *Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry, Draft Guidance* (Silver Spring, Md.: Nov. 17, 2014), and *Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Disease* (Silver Spring, Md.: July 2014).

<sup>8</sup>One of the drug sponsors who purchased a pediatric voucher, AbbVie, declined to speak with us.

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several organizations representing the pharmaceutical industry, the insurance industry, and other interested organizations and individuals.<sup>9</sup> (See app. I for a complete list of those we interviewed.)

We conducted this performance audit from July 2015 to March 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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## Background

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### Rare Pediatric Diseases and Drug Development Challenges

A rare pediatric disease, as defined by statute, is one that primarily affects children 18 years and younger and generally affects fewer than 200,000 individuals in the United States.<sup>10</sup> Some diseases affect less than a handful of children, while others affect many more. In many cases, no FDA-approved therapy exists for the treatment of the disease.

Drug development is inherently challenging, and developing drugs to treat rare pediatric diseases adds layers of complexity. The drug development process in general is time-consuming and costly for drug sponsors. The drug industry estimates that, on average, a sponsor spends over a decade developing a drug at an average cost of \$2.6 billion.<sup>11</sup> The industry also reports that the percentage of drugs that enter clinical trials and that are eventually approved by FDA as safe and efficacious is less than 12 percent. Many more drugs will fail and prove to be either unsafe or ineffective at the earlier, preclinical stage. Developing drugs to treat rare pediatric diseases is even more challenging for several reasons. By definition, the number of patients affected by any individual rare disease is small, making it difficult to understand a disease's progression and to

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<sup>9</sup>We were unable to identify a patient advocacy group representing the rare pediatric disease, hereditary orotic aciduria.

<sup>10</sup>See 21 U.S.C. § 360ff(a)(3).

<sup>11</sup>See Pharmaceutical Research and Manufacturers of America, *2015 Biopharmaceutical Research Industry Profile* (Washington, D.C.: April 2015).



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design studies for potential new drugs. For example, FDA has pointed out that this challenge is further compounded in drug development for children, as they represent a smaller percentage of the overall population, which makes it difficult to identify and recruit sufficient numbers of patients to include in studies.<sup>12</sup> The agency further notes that conducting these studies is difficult because the manifestation and progression of the same rare disease can vary by patient. There can also be different subtypes of a single disease, which can further reduce the number of patients to study. Further, there are relatively few researchers who are knowledgeable about a particular rare disease, which makes designing studies challenging. In addition, according to drug sponsors, there may be a greater incentive for them to focus on developing drugs for large patient populations that produce higher returns on investment than drugs for smaller patient populations that may generate less revenue. As a result of these challenges and others, drug sponsors may be hesitant to attempt to develop drugs to treat rare pediatric diseases.

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## FDA and the Pediatric Voucher Program

FDA, an agency within the Department of Health and Human Services (HHS), is responsible for overseeing the safety and efficacy of drugs sold in the United States.<sup>13</sup> This responsibility includes the implementation of the pediatric voucher program, as provided for in FDASIA. FDA may award a drug sponsor a voucher upon approval of that sponsor's new drug application for a rare pediatric disease. Specifically, the drug must be for the prevention or treatment of a rare disease that primarily affects children 18 or under.<sup>14</sup> The application may include the same indication for use in adults with the same rare pediatric disease, but it cannot include a different adult indication. Other criteria must also be met in order to receive a voucher. For example, the drug must not contain an active ingredient that has been previously approved by FDA in another

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<sup>12</sup>See FDA Report: *Complex Issues in Developing Drugs*.

<sup>13</sup>Unless otherwise indicated, we use the term "drug" to refer to both chemically synthesized drugs and therapeutic biological products in this report. Biological products—which include vaccines, blood products, and proteins—are derived from living sources such as humans, animals, and microorganisms, while drugs are chemically synthesized. We use the term "new drug application" to refer to both new drug applications and biologics license applications submitted to FDA for review.

<sup>14</sup>To date, the drugs for which vouchers have been awarded are indicated to treat rare pediatric diseases. No voucher has been awarded for a new drug application to prevent a rare pediatric disease.

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drug application, and the drug must be eligible for priority review.<sup>15</sup> New drug applications that FDA determines not to qualify for a priority review, and which therefore receive a standard review, are ineligible to receive a pediatric priority review voucher.

If a drug meets the eligibility criteria, the drug sponsor should include a request for a pediatric voucher in its new drug application, including supporting documentation demonstrating how the application meets the eligibility criteria for a pediatric voucher. Alternatively, if a drug sponsor does not submit a request for a pediatric voucher, but FDA determines that the sponsor may be eligible to receive one, FDA notifies the drug sponsor of its possible eligibility. Once FDA receives a sponsor's new drug application and pediatric voucher request, it reviews the information and considers whether it should be approved. If FDA approves the drug application, it includes its decision regarding whether to award a pediatric voucher in its approval letter. In making this decision, FDA determines whether the drug sponsor has met all of the eligibility criteria for a pediatric voucher, which includes determining that the drug is for a rare pediatric disease as well as reviewing the clinical data examining the drug's use in a pediatric population included in the drug application.

Once a drug sponsor is awarded a voucher, it can later be redeemed by that sponsor with the submission of another new drug application for a drug to treat any disease or condition in adults or children, making the sponsor automatically eligible for a 6-month priority review. The original drug sponsor also has the option of selling or transferring the voucher to a new drug sponsor, who may then choose to use the voucher or similarly sell or transfer it.<sup>16</sup> The voucher may be transferred any number of times

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<sup>15</sup>Generally, FDA classifies a drug application eligible for priority review if it treats a serious condition and, when compared to the products that are already on the market, the drug would provide relatively significant improvements in safety or effectiveness. Examples of significant improvements include increased effectiveness in the treatment of a disease or evidence of safety and effectiveness in a new subpopulation. Applications for those drugs with little or no additional therapeutic benefits compared to existing products are classified by FDA as standard. FDA's goal is to complete the review of a priority application within 6 months and a standard application within 10 months.

<sup>16</sup>However, FDA may revoke any pediatric voucher if the rare pediatric disease drug for which the pediatric voucher was awarded is not marketed in the United States within 1 year following the date of approval. 21 U.S.C. § 360ff(e)(1).

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before it is used.<sup>17</sup> When the sponsor who possesses the voucher ultimately decides to redeem it, the sponsor must notify FDA at least 90 days in advance of submitting the new drug application.<sup>18</sup> The sponsor redeeming the voucher must also pay any other required user fees.<sup>19</sup> Figure 1 provides a general overview of the pediatric voucher program.

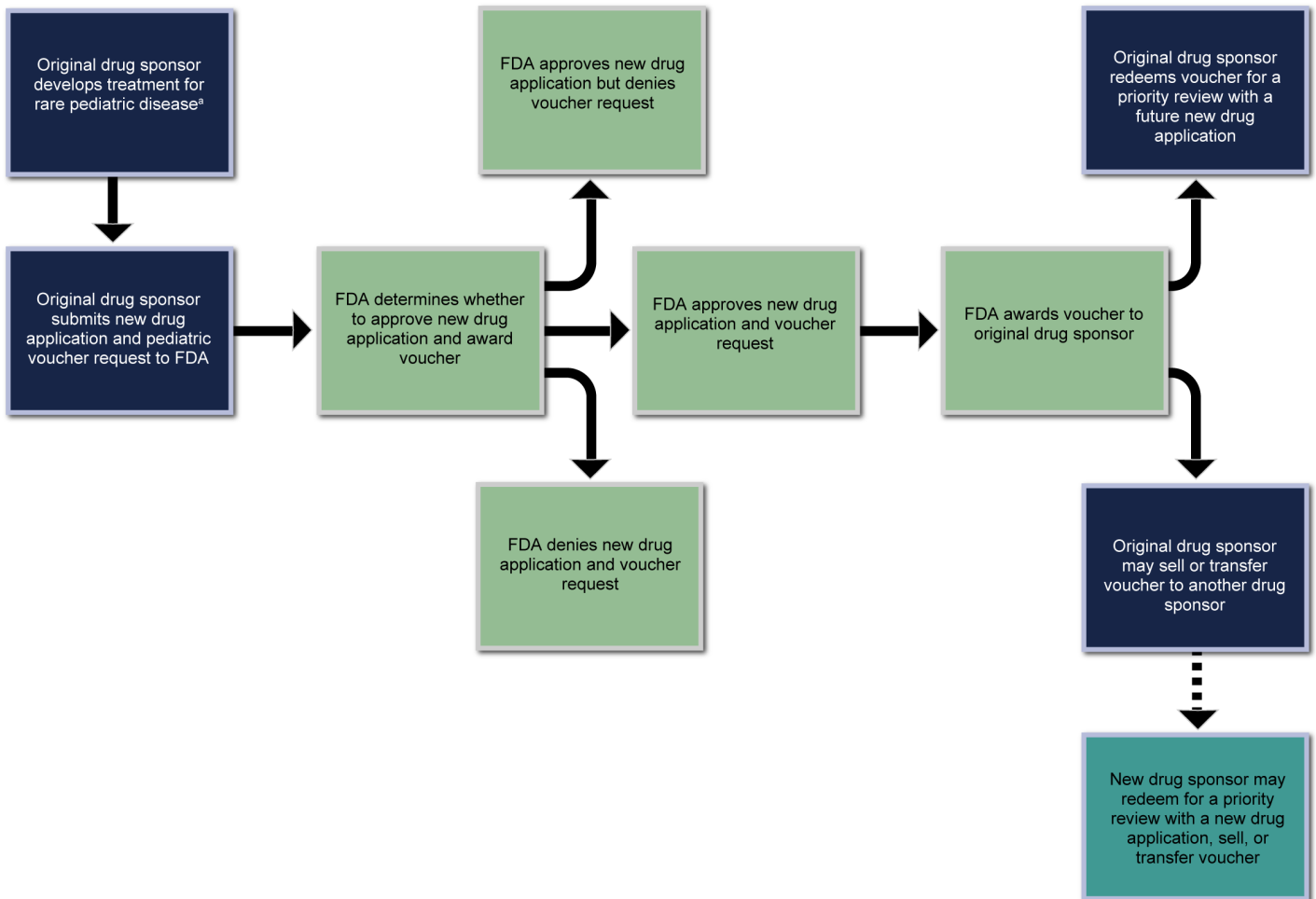
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<sup>17</sup>Each person to whom a voucher is transferred must notify FDA of the change of voucher ownership within 30 days. 21 U.S.C. § 360ff(b)(2)(B).

<sup>18</sup>21 U.S.C. § 360ff(b)(4)(A).

<sup>19</sup>FDA is authorized to collect user fees to provide additional resources for FDA to support the process of reviewing applications for new drugs. 21 U.S.C. § 379h. Additionally, priority review user fees are collected from drug sponsors redeeming one of two types of priority review vouchers—for a rare pediatric disease or a tropical disease—to cover FDA's additional costs incurred from reviewing drug applications submitted with these vouchers. 21 U.S.C. §§ 360ff(c) 360n(c). For fiscal year 2016, the rare pediatric disease priority review fee is approximately \$2.7 million.

**Figure 1: General Overview of the Rare Pediatric Disease Priority Review Voucher Program, as of December 2015**



- Original drug sponsor
- FDA
- New drug sponsor

Source: GAO analysis of FDA information. | GAO-16-319

Note: Among other things, a new drug application submitted by a sponsor seeking a pediatric priority review voucher must itself be deemed eligible by FDA for a priority review. New drug applications that FDA determines not to qualify for a priority review, and which therefore receive a standard review, are ineligible to receive a pediatric priority review voucher.

<sup>a</sup>Prior to submitting a new drug application, a drug sponsor may request a rare pediatric disease designation. To receive such designation, the sponsor must provide information supporting why it concludes that the disease is rare and primarily affects children. FDA encourages drug sponsors to request this designation to ensure, for example, that the agency has the necessary information to later evaluate a drug's pediatric voucher eligibility. In the absence of a sponsor designation request, FDA may request and review supporting documentation from the sponsor in order to verify that a disease qualifies as rare and pediatric.

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Before submitting a new drug application, a sponsor may also request a rare pediatric disease designation for a drug that is still in development. This designation was established as part of the pediatric voucher program in 2012.<sup>20</sup> In its designation request, a sponsor is to include information about, among other things, the drug and the rare pediatric disease for which the drug is being investigated, and the basis for concluding that the disease is rare and primarily affects children. FDA reviews the provided information and generally informs a drug sponsor of its designation decision within 60 days of receiving the request. FDA encourages drug sponsors to request such a designation in order for the agency to have the necessary information to evaluate a drug's pediatric voucher eligibility and to ensure that drug sponsors have an adequate opportunity to provide this information before requesting a voucher. However, requesting such designation is not required in order to receive a rare pediatric disease voucher. If a rare pediatric disease designation is not requested prior to a drug sponsor submitting its new drug application, FDA officials may determine through their reviews of a new drug application and discussions with a drug sponsor that a certain drug may be eligible for a voucher. FDA officials will ask the drug sponsor to submit the necessary information to demonstrate that the drug is for a rare pediatric disease as, according to FDA, that information is generally not included in a new drug application.

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## Too Early to Gauge if Pediatric Voucher Program Stimulates Drug Development

Drugs for Which Vouchers Were Awarded Were in Development Prior to the Program's Implementation, though They Helped Fulfill Unmet Medical Need

Given that the typical drug development process often exceeds a decade, insufficient time has elapsed to gauge whether the 3-year-old pediatric voucher program has been effective at encouraging the development of drugs for rare pediatric diseases. We found that each of the drugs awarded pediatric vouchers were in development prior to the voucher program's implementation. Any sponsors motivated by this relatively new

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<sup>20</sup>21 U.S.C. § 360ff(d).

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program to attempt to develop drugs for such diseases would likely be years away from submitting their new drug applications to FDA.

Although it is too early to gauge whether the program stimulates drug development, a potential indication of sponsor interest in the program may be reflected by the number of requests that have been submitted for a pediatric voucher or a rare pediatric disease designation. We examined how many requests for pediatric vouchers and rare pediatric disease designation were submitted to FDA and how many of these vouchers were awarded and designations were granted. As of December 31, 2015, there have been 11 requests for a pediatric voucher. Of these, 6 have been awarded, 2 denied, and 3 are still under review.<sup>21</sup> The fact that the sponsors of these drugs took the steps to request vouchers and demonstrate their eligibility—either on their own initiative or in response to FDA's suggestion—suggests interest in the program. Similarly, taking steps to demonstrate that their drugs are intended to treat rare pediatric diseases and requesting such designations also indicates that these sponsors are considering applying for a pediatric voucher. Since the pediatric voucher program and designation were established, through December 31, 2015, there have been 52 rare pediatric disease designations requested and 29 granted.<sup>22</sup> Because requests for a rare pediatric disease designation can be submitted at any time in the drug development process prior to submitting a new drug application, these designations could be for drugs that, for example, are in early stages of development and were pursued specifically in response to the program. Alternatively, these designations could be for drugs that were being studied before FDASIA was enacted and thus are farther along in the development process. According to FDA, the agency does not track which stage of development a drug is in when a request for this designation is submitted.

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<sup>21</sup>Two pediatric voucher requests were denied because the diseases for which the drugs were under development to treat did not satisfy the definition of a rare pediatric disease.

<sup>22</sup>The rare pediatric disease designation was established as part of the pediatric voucher program in 2012. Therefore all of these designations have been granted since the program began. Of the remaining 23 requests for rare pediatric disease designations, 3 have been denied, 5 are pending review, and 15 are pending responses from the sponsors to provide additional information to enable FDA to make a final determination. In addition, there have been 5 other instances in which FDA requested information for a rare pediatric disease determination for a drug with a new drug application under review but without a designation request from a sponsor. Three of these were determined to meet the definition of a rare pediatric disease, while 1 has been denied and 1 is pending review.

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The six drugs for which pediatric vouchers were awarded helped fulfill an unmet medical need. Specifically, these six drugs were the first drugs approved by FDA to treat the seven rare pediatric diseases for which they are indicated. No other drugs had been previously approved for these diseases.

- Vimizim, sponsored by BioMarin Pharmaceutical, treats children with Mucopolysaccharidosis Type IVA, a rare inherited metabolic disorder resulting from an enzyme deficiency. According to FDA and NIH, the drug significantly improves patients' ability to walk.
- Unituxin, sponsored by United Therapeutics, is intended to help patients with high-risk neuroblastoma, a rare pediatric cancer, and, according to FDA, improves the overall survival rates of affected children.
- Cholbam, sponsored by Asklepiion Pharmaceuticals, is considered by relevant patient advocacy groups to be an effective and important therapy for children with some bile acid synthesis disorders and some peroxisomal disorders, both of which are metabolic disorders.
- Xuriden, sponsored by Wellstat Therapeutics, allows certain children with hereditary orotic aciduria—an extremely rare, genetic metabolic disorder—to live life unimpeded by the disease as long as they continue treatment, according to FDA.
- Strensiq, sponsored by Alexion Pharmaceuticals, is for use by children suffering from hypophosphatasia, a genetic, rare metabolic disorder. FDA and physicians reported that the drug increased survival rates and alleviated symptoms among children in clinical trials.
- Kanuma, also sponsored by Alexion Pharmaceuticals, is for use by patients with lysosomal acid lipase deficiency, a rare, genetic, progressive metabolic disorder. According to FDA, the drug demonstrated increased life expectancy in a clinical trial among children who were diagnosed as infants.

Officials from both NIH and FDA agree that these drugs are meaningful for patients with the rare pediatric diseases as the drugs may, for example, increase life expectancy, alleviate certain symptoms, or otherwise improve quality of life. Similarly, patient advocacy groups and physicians said that these drugs provide important new treatment for patients and improve survival rates and symptoms. (See app. II for a

summary about each of these diseases based on information available from NIH, patient advocacy groups, and physicians familiar with these diseases.)

As of December 31, 2015, four of the six pediatric vouchers—for Vimizim, Unituxin, Cholbam, and Xuriden—have been sold or transferred to other drug sponsors. Sale prices of the pediatric vouchers have ranged from \$67.5 million to \$350 million.<sup>23</sup> The other two awarded vouchers—for Strensiq and Kanuma—remain held by the original sponsor. Only the voucher awarded for Vimizim has been redeemed. It was used to expedite the review of Praluent, a new drug to treat adults with high cholesterol. See table 1 for more detailed information about the status of these vouchers.

**Table 1: Status of the Rare Pediatric Disease Priority Review Vouchers Awarded to Drug Sponsors by FDA as of December 31, 2015**

Drug	Date voucher awarded and drug sponsor	Status of voucher	Sale price of voucher	Details on voucher redemption
Vimizim (elosulfase alfa), to treat Mucopolysaccharidosis Type IVA (Morquio A syndrome)	February 14, 2014; BioMarin Pharmaceutical	Sold to Regeneron Pharmaceuticals; transferred to Sanofi <sup>a</sup>	\$67.5 million	Redeemed November 24, 2014, for Praluent (a new cholesterol drug) approved by FDA July 24, 2015 <sup>b</sup>
Unituxin (dinutuximab), to treat patients with high-risk neuroblastoma	March 10, 2015; United Therapeutics	Sold to AbbVie	\$350 million	N/A
Cholbam (cholic acid), to treat (1) bile acid synthesis disorders due to single enzyme defects, and (2) peroxisomal disorders (including Zellweger spectrum disorders)	March 17, 2015; Asklepiion Pharmaceuticals	Transferred to Retrophin as part of a purchasing agreement; <sup>c</sup> later sold to Sanofi	Unable to quantify price of first transfer; then sold for \$245 million	N/A
Xuriden (uridine triacetate), to treat hereditary orotic aciduria	September 4, 2015; Wellstat Therapeutics	Sold to AstraZeneca	Financial terms of the voucher sale are unavailable	N/A
Strensiq (asfotase alfa), to treat hypophosphatasia	October 23, 2015; Alexion Pharmaceuticals	Unsold	N/A	N/A

<sup>23</sup>The financial terms for one of the voucher sales were unavailable at the time of our review.



Drug	Date voucher awarded and drug sponsor	Status of voucher	Sale price of voucher	Details on voucher redemption
Kanuma (sebelipase alfa), to treat lysosomal acid lipase deficiency	December 8, 2015; Alexion Pharmaceuticals	Unsold	N/A	N/A

Source: GAO summary of FDA and drug sponsor information. | GAO-16-319

<sup>a</sup>Regeneron purchased the voucher from BioMarin. Regeneron and another drug sponsor, Sanofi, collaborated to develop Praluent. According to these two drug sponsors, they shared the purchase price of the voucher equally. Regeneron transferred the voucher to Sanofi, who redeemed it with FDA for Praluent.

<sup>b</sup>Under the most recent reauthorization of the Prescription Drug User Fee Act in 2012, one of FDA's goals is to complete a priority review of a new drug application within 6 months and a standard review within 10 months of the 60-day filing date. This means a priority review can take up to 8 months, and a standard review up to 12 months. Operating under this goal, FDA achieved its goal of a priority review for Praluent.

<sup>c</sup>Retrophin purchased Cholbam and related assets, including the voucher, from Asklepiion. As a result, the voucher was transferred from Asklepiion to Retrophin under the terms of the agreement.

## FDA Does Not Believe the Pediatric Voucher Program Effectively Stimulates Drug Development and Opposes Its Reauthorization

FDA officials expressed concern about the pediatric voucher program, and do not support its continuation after its current authorization expires October 1, 2016. In written responses to our questions, FDA officials reported that they have seen no evidence that the program has encouraged increased development of drugs for rare pediatric diseases. The agency also indicated that while it strongly supports the goal of the program—incentivizing the development of drugs for rare pediatric diseases—it has not seen evidence that the program has yet been effective in achieving this goal. Instead, the agency suggested that companies may consider that other incentives, such as provision of an additional period of “market exclusivity,” may be more effective at incentivizing drug development than the priority review vouchers.<sup>24</sup> FDA specifically cited its authority to provide an additional 6 months of market exclusivity for FDA requested pediatric studies in products that may produce health benefits in the pediatric population—known as pediatric exclusivity—as providing an effective incentive to drug sponsors.<sup>25</sup>

In addition to sharing its views regarding the program's effectiveness in incentivizing drug development, FDA cited concerns about what it considers to be the significant adverse impact of the program on the

<sup>24</sup>Market exclusivity generally delays marketing of generic forms of an approved product, thereby protecting its sponsor from competition for a limited period. See for example, 21 C.F.R. § 314.108 (2015).

<sup>25</sup>See 21 U.S.C. § 355a(b).

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agency's ability to determine its public health priorities. According to FDA, the program interferes with its ability to set priorities on the basis of public health needs by requiring FDA to provide priority reviews of new drug applications that would not otherwise qualify, based on the merits of those applications. The agency noted that an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. However, FDA anticipates that sponsors will seek to redeem their vouchers for new drug applications that would otherwise receive a standard 10-month review for more prevalent conditions that already have available treatments. Such applications may be for drugs to treat diseases or conditions such as elevated blood pressure, high cholesterol, obesity, or diabetes and other drugs with substantial market potential. FDA explained that, in effect, the program allows sponsors to "purchase" a priority review at the expense of other important public health work in FDA's portfolio, which undermines FDA's public health mission and the morale of its professional review staff.

According to FDA, the pediatric voucher program also places a substantial strain on its workload. First, the agency explained that performing a priority review on a drug that would otherwise merit a standard review requires the agency to conduct significant work in a compressed timeframe. FDA pointed out that, while patients and providers are willing to accept a greater risk for a drug that fulfills an unmet medical need, there is a different benefit risk balance that must be considered when assessing drugs for more prevalent conditions that may be used in millions of patients. A new drug application qualifying for a standard review is typically accompanied by very large data sets, reflective of the study of thousands of patients to support substantial evidence of the drug's effectiveness and to provide the safety data required to demonstrate that its benefits outweigh its risks. As a result, 6-month priority reviews of applications that would otherwise receive a 10-month standard review require FDA to conduct work in 4 months less time. FDA noted that, in order to meet the required shortened timeframe for review, staff must divert attention from other important work or management must assign more reviewers to review an application. FDA noted that it confronted this challenge and had to curtail or defer other important work with the first redemption of a pediatric voucher for Praluent.

Second, FDA indicated that the pediatric voucher program hinders its ability to effectively manage its own workload. FDA pointed out that it is organized into separate review divisions with specific areas of expertise

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and that it cannot quickly train new staff. There is not a pool of review staff that can be moved from one review division to another review division on an ad hoc basis to complete priority reviews for the application based on the rare pediatric review vouchers. According to FDA, it cannot predict which review divisions will need additional staff to complete the additional priority reviews, making anticipatory hiring infeasible. Although FDA receives a special user fee from a drug sponsor when the sponsor redeems a voucher, in addition to the regular user fee that accompanies a new drug application, the agency noted that FDASIA did not authorize resources beyond the user fees—funding or staff—to administer the program, including determining rare pediatric disease designations. FDA noted that there is a disconnect in the timing of its collection of the additional user fee and the time it takes the agency to hire, orient, and train additional reviewers to assist with the additional reviews. Furthermore, the additional user fee is a one-time payment and does not provide the funding needed to sustain the longer-term employment of additional staff hired to assist with conducting the priority review. While the additional user fee is intended to compensate for FDA's increased workload related to redemption of the vouchers, FDA noted that the funding mechanism does not provide the agency the resources required to review the particular voucher priority application. FDA told us that, if the number of pediatric vouchers awarded and redeemed continues to increase, the agency's ability to meet its public health mission and other commitments will be adversely affected, including monitoring postmarket safety, engaging with patient and stakeholder groups, and advising drug sponsors on their development programs, including those focused on pediatric drugs.

Third, in a discussion with FDA, officials said that the pediatric voucher program has also significantly increased its workload due to its need to respond to requests for rare pediatric disease designations, often within 60 days, and the complexity involved in making such determinations.<sup>26</sup> Determining whether to designate a drug as one for a rare pediatric

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<sup>26</sup>FDA must respond within 60 days when a request for a rare pediatric disease designation is made at the same time as a request for designation of orphan disease status or fast-track designation is made. See 21 U.S.C. § 360ff(d)(2). An orphan disease designation provides incentives, such as tax credits, to the sponsor of a qualifying drug used in the diagnosis or treatment of certain rare diseases or disorders. The fast-track designation process is designed to facilitate the development and expedite the review of new drug applications to treat a broad range of serious conditions and fill an unmet medical need.

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disease is challenging; FDA officials told us that the vast majority of initial requests for such designation have not included adequate information to demonstrate that the disease primarily affects children 18 years and younger. As a result, FDA must work with the drug sponsor to determine what types of information are acceptable to support such an assertion.

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### Drug Sponsors, Advocacy Groups, and Other Organizations Generally Support the Pediatric Voucher Program

Feedback from stakeholders about the pediatric voucher program varied but has been generally positive, with nearly all drug sponsors and patient advocacy groups we spoke with saying that the program could potentially motivate further research in rare pediatric diseases. Drug sponsors largely favor the program; one sponsor and half of the patient advocacy groups with whom we spoke pointed to the sales of and prices for the vouchers as evidence that demand for the vouchers exists. Most sponsors also noted that each sale provides cash infusions for drug sponsors who were initially awarded—and later sold—the vouchers. Four of five sponsors that were awarded or transferred and later sold vouchers told us that they plan to reinvest a portion of the proceeds they received into additional research and development of drugs to treat other rare pediatric diseases. However, there is no requirement that sponsors must use the proceeds in this way. A few sponsors said that the program will be a factor in future business decisions and most said that it will likely encourage the development of drugs for treating rare pediatric diseases if it is reauthorized.

Patient advocacy groups also generally favor the program. For example, one group we spoke to said that the program has stimulated a transfer of cash from larger drug sponsors to smaller ones through the sales of the vouchers, and that these smaller drug sponsors may reinvest a portion of the proceeds to continue developing drugs for rare pediatric diseases. A few groups also indicated that the program could lead to the development of much-needed pediatric drugs without costing the government resources.<sup>27</sup> Most told us that they believe the program incentivizes drug development. A few groups told us that, since the creation of the program, they have spoken with several drug sponsors interested in

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<sup>27</sup>While the pediatric voucher program allows drug sponsors to buy and sell vouchers that have been awarded, the government does not incur costs associated with the sale of the vouchers. Costs associated with administering the program are intended to be covered by a user fee that drug sponsors pay FDA upon redemption of a voucher.

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discussing the extent to which their drugs in development might be able to treat the patients that these groups represent.

Although sponsors and patient advocacy groups were generally positive about the voucher program, some also expressed concerns related to the uncertain future of the program and FDA's interpretation of what diseases are considered rare pediatric diseases, concerns also expressed by organizations representing physicians and the health insurance industry. For example, some of the sponsors, patient advocacy groups, and other organizations that we contacted said that the FDASIA provision providing for termination of FDA's authority to award pediatric vouchers one year after the award of the third voucher under the program (March 2016) created ambiguity for industry that therefore diminishes the program's appeal.<sup>28</sup> Specifically, two drug sponsors told us that they are concerned about pursuing lengthy and costly drug development for rare pediatric diseases in order to obtain a voucher that may be unavailable by the time they are ready to submit new drug applications to FDA. To enhance the program's effectiveness, most drug sponsors and many patient advocacy groups said that they believe the program should be reauthorized for a longer period of time, or even permanently. Additionally, a drug sponsor and a few patient advocacy groups told us that, in their view, FDA's interpretation of the definition of a rare pediatric disease is too narrow. Some said that as a result, certain rare diseases, such as sickle cell disease and some pediatric cancers, are not eligible for a pediatric voucher because more than 50 percent of afflicted children survive to adulthood.<sup>29</sup> One patient advocacy group indicated that such an exclusion effectively penalizes all patients with these diseases because a majority of them live past 18 years, although the onset of the disease occurs during childhood. They told us that they believe such diseases should be included in FDA's definition. When asked about how the agency determined its definition of a rare pediatric disease, FDA officials pointed out that a vast majority of rare diseases are diagnosed in childhood—given this, products for all rare diseases diagnosed at that time would be eligible for a voucher. However, since children were to be the intended

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<sup>28</sup>21 U.S.C. 360ff(b)(5). This provision was subsequently amended to provide that such authority terminates effective October 1, 2016. Pub. L. No. 114-113, § 765, 129 Stat. 2242, 2287.

<sup>29</sup>See FDA, *Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry, Draft Guidance*.

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population for pediatric voucher program per FDASIA, FDA officials noted that, by law, the definition applies to those diseases that primarily affect children 18 years and younger.

Several drug sponsors and a patient advocacy group raised some concerns about the program but were uncertain about how to address them. For example, certain drug sponsors and the patient advocacy group suggested that there might be an optimal number of vouchers to be awarded to maximize their value to industry and their incentivizing effect. The patient advocacy group suggested that awarding too many vouchers would cause their value to plummet. However, most of them were uncertain about what the optimum quantity of awarded vouchers should be. In addition, similar to a concern raised by FDA, one drug sponsor told us that it was concerned that incentivizing development of drugs for rare pediatric diseases could potentially lead to unintended consequences, such as diverting attention from mass-market diseases such as diabetes.

Finally, feedback from organizations representing physicians, health insurers, and children's hospitals about the pediatric voucher program was varied. While two of these organizations generally favored the program, all told us that there was insufficient information to judge the program's overall effectiveness or that it was simply too soon to tell. One organization shared FDA's concerns about potential unintended consequences, such as the diversion of resources from other agency priorities. Feedback from the academic community was also varied. One academic told us that the voucher program has been consistent with his expectations and echoed what a few patient advocacy groups said—that the program could be a stimulant for developing drugs for rare pediatric diseases at little cost to the federal government. In contrast, another academic said it was difficult to determine whether the program stimulated research since only a few years have elapsed since the program was implemented. He indicated, similar to FDA's concern, that the program could instead lead to unintended consequences. For example, this academic suggested that the program could strain FDA resources, commoditize its approval process, and result in the granting of a priority review to a drug that is neither novel nor fulfills an unmet medical need. He also proposed that, if the pediatric voucher program is reauthorized it could be improved by delaying the awarding of the vouchers until several years after the drugs' approval. This would allow more time to assess whether patients have actually benefitted from the drugs, and are able to access the drugs, before the voucher is awarded.

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## Agency Comments

We provided a draft of this report for comment to HHS. HHS provided technical comments, which we incorporated as appropriate.

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We are sending copies of this report to the appropriate congressional committees and the Secretary of Health and Human Services. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 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 key contributions to this report are listed in appendix III.



Marcia Crosse  
Director, Health Care

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# Appendix I: List of Organizations and Individuals Interviewed

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<b>Federal agencies</b>	<ol style="list-style-type: none"><li>1. Department of Health and Human Services, Food and Drug Administration</li><li>2. Department of Health and Human Services, National Institutes of Health</li></ol>
<b>Drug sponsors</b>	<ol style="list-style-type: none"><li>1. Alexion Pharmaceuticals Inc.</li><li>2. Asklepiion Pharmaceuticals LLC</li><li>3. AstraZeneca Pharmaceuticals LP</li><li>4. BioMarin Pharmaceutical Inc.</li><li>5. Regeneron Pharmaceuticals, Inc.</li><li>6. Retrophin, Inc.</li><li>7. Sanofi</li><li>8. United Therapeutics Corporation</li><li>9. Wellstat Therapeutics Corporation</li></ol>
<b>Drug sponsor associations</b>	<ol style="list-style-type: none"><li>1. Pharmaceutical Research and Manufacturers of America</li><li>2. Biotechnology Industry Organization</li></ol>
<b>Patient advocacy groups</b>	<ol style="list-style-type: none"><li>1. National Organization for Rare Disorders</li><li>2. EveryLife Foundation for Rare Diseases</li><li>3. Kids v Cancer</li><li>4. Children's Neuroblastoma Cancer Foundation</li><li>5. Global Foundation for Peroxisomal Disorders</li><li>6. Council for Bile Acid Deficiency Diseases</li><li>7. National MPS [mucopolysaccharidoses] Society</li><li>8. Sickle Cell Disease Association of America, Inc.</li><li>9. Soft Bones</li><li>10. LAL [lysosomal acid lipase] Solace</li></ol>
<b>Other organizations or individuals</b>	<ol style="list-style-type: none"><li>1. American Academy of Pediatrics</li><li>2. Children's Hospital Association</li><li>3. America's Health Insurance Plans</li><li>4. Jerry Vockley, MD., Ph.D. Professor of Pediatrics and Human Genetics University of Pittsburgh</li><li>5. Dr. David Ridley Duke University The Fuqua School of Business Faculty Director of the Health Sector Management Program</li></ol>



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6. Aaron S. Kesselheim, M.D., J.D., M.P.H.  
Associate Professor of Medicine, Harvard Medical School  
Director, Program On Regulation, Therapeutics, And Law  
Division of Pharmacoepidemiology and Pharmacoeconomics  
Brigham and Women's Hospital

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# Appendix II: Information about the Rare Pediatric Diseases That Can Be Treated by Newly Approved Drugs for Which Pediatric Vouchers Were Awarded

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Pediatric patients affected by seven diseases that previously had no approved treatment may now benefit from six newly-approved drugs for which pediatric vouchers were awarded. We have summarized information about each of these diseases obtained from the National Institutes of Health's Genetics Home Reference, patient advocacy groups, and physicians familiar with these conditions.<sup>1</sup>

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## Mucopolysaccharidosis Type IVA

Mucopolysaccharidosis type IVA, also known as Morquio A Syndrome, is a rare, progressive, hereditary disease that mainly affects the skeleton and can lead to paralysis and early death. Genetic mutations reduce or eliminate the activity of certain enzymes that are involved in the breakdown of large sugar molecules, resulting in the accumulation of such molecules to toxic levels in many tissues and organs, particularly in the bones, causing deformities. Affected individuals typically demonstrate signs of the disease during early childhood, including skeletal abnormalities such as knock knees, short stature, and abnormalities of the chest, hips, ribs, spine, and wrists. Other symptoms may include vision loss; hearing loss; frequent upper respiratory infections; thin tooth enamel and multiple cavities; heart valve abnormalities; and a mildly-enlarged liver. Morquio A Syndrome does not affect intelligence.

Although the exact prevalence of Morquio A Syndrome is unknown, it is estimated that the broader condition—Mucopolysaccharidosis type IV—occurs in approximately 1 in every 200,000 to 300,000 individuals. The life expectancy of individuals with Morquio A Syndrome depends on the severity of symptoms, with the most severely affected patients surviving only until late childhood or adolescence. Individuals with milder forms of the disorder may live into adulthood, although their life expectancy may be reduced.

Vimizim (elosulfase alfa), is the first FDA-approved drug for the treatment of Morquio A Syndrome. No other FDA-approved therapies exist for treatment of this disease.

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<sup>1</sup>The National Institutes of Health's Genetics Home Reference is available at <http://ghr.nlm.nih.gov/>.

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## High-Risk Neuroblastoma

Neuroblastoma, a type of pediatric cancer that occurs when immature nerve cells become abnormal and multiply uncontrollably, most often occurs in children before age 5 and rarely occurs in adults. Most commonly, a tumor forms in the adrenal gland located above each kidney and can spread to other parts of the body such as the bones, liver, or skin. Tumors also commonly grow in the nerve tissue in the abdomen, chest, neck, or pelvis. Individuals with neuroblastoma may exhibit symptoms such as fever, irritability, pain, tiredness, diarrhea, loss of appetite, and weight loss. Some symptoms may be location-specific, such as a tumor in the abdomen causing abdominal swelling; a tumor in the chest causing difficulty breathing; and a tumor metastasizing to the bone causing bone pain, bruises, and pale skin.

Neuroblastoma occurs in approximately 1 in every 100,000 children and is diagnosed in about 650 children each year in the United States. It is the most common cancer in infants younger than 1 year. Only 40 to 50 percent of children with high-risk neuroblastoma live at least 5 years after diagnosis.

Unituxin (dinutuximab) is the first FDA-approved drug for the treatment of high-risk neuroblastoma. There are currently other FDA-approved drugs for neuroblastoma (specifically, Cyclophosphamide, Vincasar PFS, and Doxorubicin Hydrochloride); however, none of these were approved specifically for the treatment of patients with high-risk neuroblastoma.

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## Bile Acid Synthesis Disorders

Bile acid synthesis disorders are a group of rare metabolic disorders characterized by impaired production and release of a digestive fluid, called bile, from liver cells. People with bile acid synthesis disorders cannot produce bile acids, which are a component of bile that stimulate bile flow and help it absorb fats and fat-soluble vitamins, such as vitamins A, D, E, and K. Consequently, an abnormal form of bile is produced. The failure to produce normal or functional bile acids results in the accumulation of abnormal bile acids and other substances that normally would be broken down within the body, leading to deterioration of certain organ systems. Symptoms may include interruption or suppression of the flow of bile from the liver, fat-soluble vitamin malabsorption, progressive neurological disease, and liver disease.

Bile acid synthesis disorders are estimated to occur in between 1 to 9 individuals in every 1,000,000 births. If left untreated, the disorders may lead to cirrhosis of the liver and death in childhood.

Cholbam (cholic acid) is the first FDA-approved drug for the treatment of bile acid synthesis disorders due to single enzyme defects. No other FDA-approved therapies exist for these disorders.

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## Peroxisomal Disorders

Peroxisomal disorders are a group of metabolic disorders, including those in the Zellweger spectrum. These systemic diseases, which affect multiple organs and may have neurological manifestations, present as rare autosomal recessive disorders with impairment of production and release of digestive fluid, called bile, from liver cells. Bile is used during digestion to absorb fats and fat-soluble vitamins, such as vitamins A, D, E, and K. Individuals with the most severe forms of this disease develop symptoms of the condition as newborns, and experience weak muscle tone, feeding problems, hearing and vision loss, and seizures. They may also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys, and may have skeletal abnormalities. Affected individuals have distinctive facial features, including a flattened face and broad nasal bridge. Individuals with less-severe forms of the disease may not develop signs of the disease until late infancy or early childhood. They may have many of the same features as those patients with severe cases; however, their conditions typically progress more slowly. Children with these less-severe conditions often exhibit developmental delays and intellectual disability.

Zellweger spectrum disorders (a subset of peroxisomal disorders) are estimated to occur in approximately 1 in every 50,000 individuals. Peroxisomal disorders encompass a spectrum of disorders, which means the life expectancy of a patient depends on the severity of his or her disease. Patients diagnosed with the most severe form typically do not live beyond 1 year. Children with less severe forms generally live until 10 years of age, although there have been cases reported of children living longer.

Cholbam (cholic acid) is the first FDA-approved drug for the treatment of peroxisomal disorders (including Zellweger spectrum disorders). No other FDA-approved therapies exist for these disorders.

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## Hereditary Orotic Aciduria

Hereditary orotic aciduria is an extremely rare, potentially life-threatening, genetic disorder in which patients cannot produce adequate amounts of uridine, a component of ribonucleic acid that is involved in the synthesis of protein in the body. Patients with inadequate amount of uridine can suffer from blood abnormalities, failure to thrive, a range of developmental

delays, and episodes of crystal formation in the urine leading to obstruction of the ureter (a tube that carries urine from the kidneys to the bladder), causing urine to back up into the kidney, making it swell.

Hereditary orotic aciduria is extremely rare, with only four known patients with this disease in the United States, and an estimated 20 worldwide. Left untreated, the disease can contribute to early mortality.

Xuriden (uridine triacetate) is the first FDA-approved drug for the treatment of hereditary orotic aciduria. No other FDA-approved therapies exist for this disease.

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## Hypophosphatasia

Hypophosphatasia is a rare, genetic, progressive, metabolic disease in which patients experience devastating effects on multiple systems of the body, leading to severe physical disability and life-threatening complications. With a spectrum of symptoms and severity, the disease is characterized by defective bone mineralization and softening of the bones. Though forms of hypophosphatasia may appear in childhood or adulthood, the most severe forms tend to occur before birth and in early infancy. Affected newborns exhibit short limbs, an abnormally-shaped chest, and soft skull bones. Additional complications in infancy include poor feeding, a failure to gain weight, respiratory problems, and high levels of calcium in the blood that may lead to kidney problems. Early loss of primary (baby) teeth is one of the first signs of the condition in children. Affected children may have short stature with bowed legs or knock knees, enlarged wrist and ankle joints, and an abnormal skull shape. Afflicted individuals may exhibit delayed development with traditional milestones such as sitting, crawling, or walking.

Severe forms of hypophosphatasia are estimated to occur in approximately 1 in every 100,000 births. Milder cases, such as those that appear in childhood or adulthood, may occur more frequently. The life expectancy of a patient depends on which form of hypophosphatasia (perinatal, infantile, juvenile, or adult) he or she has. The life expectancy of those with the most severe form, perinatal hypophosphatasia, is measured only in days or weeks.

Strensiq (asfotase alfa) is the first FDA-approved drug for the treatment of perinatal, infantile, and juvenile-onset hypophosphatasia. No other FDA-approved therapies exist for this disease.

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## Lysosomal Acid Lipase Deficiency

Lysosomal acid lipase deficiency is an inherited spectrum condition in which affected individuals are unable to properly breakdown and use fats and cholesterol in the body. The condition ranges from the infantile-onset form (Wolman disease) to later-onset forms (known as cholesteryl ester storage disease). In affected individuals, harmful amounts of fats may accumulate in areas such as the spleen, liver, bone marrow, and small intestine. Chronic liver disease can develop, along with accumulation of fatty deposits in the arteries. The deposits may eventually block the arteries, which may increase the chance of having a heart attack or stroke. The symptoms of lysosomal acid lipase deficiency are highly variable. Individuals in which onset occurs later in life may experience mild symptoms that are undiagnosed until late adulthood, while those with early onset of the disease may have liver dysfunction in early childhood. Infants with Wolman disease may demonstrate an enlarged liver and spleen, poor weight gain, low muscle tone, jaundice, vomiting, diarrhea, developmental delay, anemia, and poor absorption of nutrients from food.

Wolman disease is estimated to occur in 1 in 350,000 newborns. Children affected by Wolman disease develop severe malnutrition and generally do not survive past early childhood. Comparatively, about 50 individuals affected by cholesteryl ester storage disease have been reported worldwide, and the lifespan of these individuals depends on the severity of the associated complications.

Kanuma (sebelipase alfa) is the first FDA-approved drug for the treatment of lysosomal acid lipase deficiency. No other FDA-approved therapies exist for this disease.

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# Appendix III: GAO Contact and Staff Acknowledgments

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## GAO Contact

Marcia Crosse, (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov)

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## Staff Acknowledgments

In addition to the contact named above, Geri Redican-Bigott, Assistant Director; George Bogart; Muriel Brown; Kaitlin Coffey; Jesse S. Elrod; and Cathleen Hamann made key contributions to this report.

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