Best Pharmaceuticals for Children Act
and
Pediatric Research Equity Act

Status Report to Congress
July 1, 2015 – June 30, 2020

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Executive Summary

Section 508 of the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, requires the Secretary of Health and Human Services to report on the implementation of sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which are commonly known as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), respectively. This report was first required to be submitted to Congress by July 9, 2016, and then every 5 years thereafter. In addition to the FDASIA requirements, the FDA Reauthorization Act of 2017 (FDARA) added more reporting requirements for HHS, including requirements related to (1) pediatric research and labeling of certain drugs[1] for the treatment of cancer, and (2) the timing for submission of pediatric studies in accordance with BPCA and PREA.

This report, submitted pursuant to FDASIA and FDARA, (1) provides an assessment of implementation of BPCA and PREA, as well as the impact of those statutes, (2) highlights additional successes stemming from these two statutes, and (3) offers suggestions for advancing pediatric drug development by ensuring that the objectives underlying BPCA and PREA are effectively and efficiently implemented.

Background

This Executive Summary will provide a brief overview of the main points included in this report regarding (1) the impact of BPCA and PREA, including pediatric studies and labeling, timeliness of pediatric drug development, drug development for special populations, including children with cancer, children with rare diseases, and neonates, and the pediatric drug testing research program at the National Institutes of Health (NIH) and (2) the additional successes stemming from BPCA and PREA, including advances in regulatory science for pediatric drug development and global harmonization of pediatric research and drug development. In addition, this Executive Summary will briefly highlight FDA's work to help ensure COVID-19 therapeutics and vaccines are appropriately developed for children and will note the importance of post-marketing safety surveillance. Finally, this Executive Summary will conclude by listing the three potential program improvements described in this report.

Pediatric Studies and Labeling

The enactment of BPCA and PREA, each permanently authorized under FDASIA, has led to significant progress in the number, timeliness, and successful completion of studies

[1] In this report, references to *drugs* and *drug products* include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

of drugs in pediatric populations. Because of these legislative initiatives which require or incentivize pharmaceutical companies to develop medicines for children, labeling for over 900 drugs now contains new pediatric use information. Further, earlier integration of pediatric study planning has now become routine in drug development, a notable shift from the era before these laws were enacted.

Timeliness of Pediatric Drug Development

The successful implementation of BPCA and PREA is due, in part, to efforts by the U.S. Food and Drug Administration's (FDA's) Pediatric Review Committee (PeRC) which works across the Agency to consistently encourage timely pediatric drug development. During PeRC's weekly meetings, pediatricians and numerous other experts in disciplines such as chemistry, ethics, neonatology, pharmacology, statistics, and toxicology provide input and recommendations on pediatric submissions received by FDA from sponsors pursuant to BPCA and PREA (e.g., initial Pediatric Study Plans (iPSPs)). The PeRC has been working diligently to ensure that FDA provides timely responses and meaningful advice to pharmaceutical industry sponsors seeking to obtain a Written Request (WR) to conduct pediatric studies under BPCA. As such, FDA has met the requirement in section 505A(d)(3) of the FD&C Act, added by FDARA, to respond to a Proposed Pediatric Study Request (PPSR) within 120 days for nearly 90 percent of submissions. Additionally, the PeRC continues to provide consultation on all pediatric study plans submitted in accordance with PREA and to review all deferral extension requests for those studies to ensure the proposed pediatric study timelines are reasonable. FDA will continue these efforts to ensure timely pediatric studies are conducted by industry, thereby helping reduce the delay between the original approval of a drug and the incorporation of pediatric use information in labeling, which currently stands at approximately 6 years.

Development of Pediatric Cancer Drugs

An important shift in the regulatory landscape for pediatric cancer drug development has occurred with the implementation of FDARA. For example, early evidence suggests that the PREA amendments under section 504 of FDARA, commonly known as the Research to Accelerate Cures and Equity (RACE) for Children Act, have had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would previously have not been required and that would historically have gone unstudied in children.

FDA has engaged with stakeholders, including academia, the pharmaceutical industry, and patient advocacy groups, to implement the requirements under FDARA and to meet the needs of children with cancer. In accordance with FDARA, FDA issued "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology

Drugs: Amendments to Sec. 505B of the FD&C Act."[2] Further, to ensure the continued success of multi-disciplinary review through the PeRC, FDA created an Oncology Subcommittee of the PeRC to manage the increasing number of submissions related to pediatric cancer drug development. This subcommittee helps facilitate not only more timely and efficient pediatric development plans but also earlier discussions with sponsors regarding the issuance of WRs for oncology products, when appropriate.

Development of Drugs for Rare Pediatric Diseases

The Rare Pediatric Disease Priority Review Voucher incentive program, which was established under section 908 of FDASIA, has also impacted the paradigm for the development of drugs to treat certain rare childhood diseases. The program specifically targets diseases that have serious or life-threatening manifestations that primarily affect children. Since the incentive program began, FDA has granted over 480 rare pediatric disease designations for over 220 unique pediatric diseases and has awarded 32 rare pediatric disease priority review vouchers. However, drug development for rare pediatric diseases remains a challenge. As described in the 2019 report to Congress titled *Pediatric Labeling of Orphan Drugs*, which was required under FDARA, there is a public health need for additional pediatric information to be included in the labeling for over one-third of approved orphan indications that are relevant to the pediatric population.[3]

Development of Drugs for Neonates

Unique challenges persist regarding the conduct of studies in neonates, but FDA continues to encourage the conduct of these studies when appropriate. Considerable strides have been made since FDA's neonatology program was developed, with steady growth of the neonatal and perinatal consultation service for FDA's reviewers. FDA has been working to foster drug development for neonates and to overcome the obstacles to advancing neonatal regulatory science, particularly through its work with the International Neonatal Consortium. Guidance development to support the conduct of studies in neonates remains a focus for FDA. In 2019, in accordance with the requirements established in FDARA, FDA issued a draft guidance document to address the clinical pharmacology considerations for any planned studies in neonatal populations.[4] However, the current paradigm for drug development under BPCA and PREA has generally not resulted in a significant increase in research addressing neonatal-specific diseases and conditions. Since the first BPCA and PREA report to Congress in 2016, the labeling for 22 drugs has been updated to include essential information for

[2] https://www.fda.gov/media/133440/download.

[3] https://www.fda.gov/media/130060/download.

[4] https://www.fda.gov/media/129532/download. When final, this guidance will represent FDA's current thinking on this topic.

neonates, of which three labeling updates resulted from studies of off-patent drugs conducted through the pediatric drug testing research program at NIH.

The NIH Pediatric Drug Testing Research Program

The NIH program, established under section 409I of the Public Health Service Act in 2002 under the Best Pharmaceuticals for Children Act, has played a critical role in obtaining information about pediatric use of off-patent drugs. FDA and the National Institute of Child Health and Human Development (NICHD), which is part of NIH, collaborate on the study of off-patent drugs in pediatric clinical trials conducted under this program. The Pediatric Trials Network, established through an NICHD-awarded contract to the Duke Clinical Research Institute in 2010, has been vital to the continued growth and success of the NIH program. Between 2002 and 2016, FDA approved the labeling for three off-patent drugs as a result of this program. In the 5 years since the 2016 report to Congress, this number has more than tripled, with FDA approving the labeling for seven additional off-patent drugs.

Advances in Regulatory Science for Pediatric Drug Development

The legislative mandates in BPCA and PREA have stimulated scientific growth and innovation in the way drugs are developed for children. FDA has hosted numerous workshops to examine ways to optimize pediatric drug development and has published many peer-reviewed manuscripts describing scientific advances. The knowledge gained from these workshops and manuscripts has extended into tangible resources, as FDA has issued multiple guidance documents specifically related to scientific considerations in pediatric drug development. In addition, as described in this report, these workshops have been helpful to address specific challenges in pediatric drug development programs and may lead to opportunities for defining a feasible path forward, particularly for historically challenging drug development areas. Advancing the regulatory science to support timely and effective pediatric drug development remains a priority for FDA.

Global Harmonization of Pediatric Research and Drug Development

As FDA's work to enhance pediatric drug development continues, particularly for pediatric cancer, rare pediatric diseases, and neonates, the importance of international collaboration remains clear. FDA has continued to engage with stakeholders internationally to help assure children around the world participate in clinical trials that are well designed to meet international regulatory standards. FDA continues to host Pediatric Cluster conference calls with international regulators which, since their inception in 2007, have facilitated discussion of 570 products proposed for pediatric studies. In addition, as described in this report, FDA has collaborated with numerous international stakeholders through working groups seeking to advance pediatric drug development and foster consensus on regulatory approaches. International collaborative efforts have helped improve the development of therapeutics globally by (1) increasing

the efficiency of clinical trial enrollment for small populations, (2) expanding information and knowledge-sharing with global experts, and (3) harmonizing clinical trial designs to meet requirements across regulatory authorities.

COVID-19 Therapeutics and Vaccines for Children

The increasing connectivity of our world and the benefits of aligning on global activities have been highlighted by the coronavirus disease 2019 (COVID-19) pandemic. FDA has been working diligently to help ensure COVID-19 therapeutics and vaccines are appropriately developed for children. For example, between January 2020 and October 2021, FDA facilitated an international discussion of COVID-19 products at 17 Pediatric Cluster conference calls and issued five Common Commentaries, which are documents that convey non-binding high-level comments from regulators to pharmaceutical industry sponsors, to align and expedite international development for COVID-19 pediatric therapeutics. Also, PeRC discussions related to COVID-19 product development have highlighted the need for the ethical inclusion of children, including neonates, in clinical trials when appropriate. Between January 2020 and October 2021, the PeRC reviewed 49 iPSPs for products relevant to COVID-19 that are subject to PREA.

Pediatric Advisory Committee and Post-Marketing Pediatric Safety Surveillance

Product development during the pandemic has underscored the importance of an efficient and effective post-marketing surveillance of the safety of products in the pediatric population. FDA continues to implement the congressionally mandated[5] post-marketing pediatric safety review process with reporting to the Pediatric Advisory Committee. Several important labeling changes, which will be highlighted in this report, have stemmed from this process and from discussions with the committee.

Program Improvements for Continued Advancement of Product Development in Children

As this report will demonstrate, BPCA and PREA have been instrumental in improving pediatric drug development and labeling. To continue advancing product development for children, FDA will conclude this report with the following three potential program improvements that may help ensure the objectives underlying the statutes are effectively and efficiently implemented: (1) removal of the orphan exemption under PREA, (2) modernize pediatric pharmacovigilance, and (3) establish a periodic review of Humanitarian Device Exemptions.

[5] See sections 505A(l) and 505B(i) of the FD&C Act.

Introduction

Pediatric drug studies and labeling are governed largely by two sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act): section 505A and section 505B. First, to incentivize sponsors to conduct pediatric studies of drugs when the U.S. Food and Drug Administration (FDA or Agency) determines the studies may produce benefits in pediatric populations, section 505A of the FD&C Act (commonly referred to as the Best Pharmaceuticals for Children Act (BPCA)), allows FDA to issue Written Requests (WRs) to pharmaceutical industry sponsors to conduct those studies. Upon completion of these studies, sponsors can qualify for 6 months of marketing exclusivity as an incentive to do so. BPCA allows FDA to request pediatric studies of drugs that cannot be required under section 505B of the FD&C Act (commonly referred to as the Pediatric Research Equity Act (PREA)) when the applications or supplements for those drugs are not subject to the requirements of PREA. Second, PREA requires that sponsors of certain new drug applications (NDAs), biologics license applications (BLAs), or supplements thereto submit, as applicable (1) assessments regarding the drug's safety, effectiveness, dosing, and administration in pediatric populations or (2) reports on the molecularly targeted pediatric cancer investigation that is designed to yield clinically meaningful pediatric study data regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.[6] Together, these statutes encourage more effective labeling of drug and biological products for use in neonates, infants, children, and adolescents.[7]

In the 2016 BPCA and PREA report to Congress,[8] FDA provided a detailed overview of the history of pediatric laws, rules, and regulations. That report highlighted FDA's efforts as early as 1994 to add pediatric use information in labeling and described the first pediatric drug development incentive legislation that was enacted as part of the Food and Drug Administration Modernization Act (FDAMA) in 1997. These early efforts paved the way for the subsequent enactment, in 2002 and 2003, of the BPCA and PREA, respectively, both of which became permanent in 2012, with modifications, under the Food and Drug Administration Safety and Innovation Act (FDASIA).[9]

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[6] Sponsors must submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation with any application (or supplement to an application) for which such assessments or reports are required by PREA, unless FDA defers or waives the requirement. See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act.

[7] There are other laws that impact pediatric studies of drugs and biologics, such as section 529 of the FD&C Act (i.e., the rare pediatric disease priority review voucher program) and sections 526 and 527 of the FD&C Act (which authorize orphan drug designation and orphan exclusivity). A further discussion of these laws is included, when relevant, in this report.

[8] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

[9] FDASIA (Pub. L. 112-144). 126 Stat. 993 (July 9, 2012).

BPCA and PREA have been amended several times over the years,[10] most recently in 2017 under the Food and Drug Administration Reauthorization Act of 2017 (FDARA). FDARA amended sections 505A of the FD&C Act and 505B of the FD&C Act as follows:

- Amended section 505A to require FDA (1) to review and act on a Proposed Pediatric Study Request (PPSR) or proposed amendment to a WR within 120 days of submission and (2) to submit to the Pediatric Review Committee (PeRC) any response to a PPSR.

- Amended section 505B(e)(2)(C) to require FDA, upon request, to meet with the sponsor of an application for a drug intended to treat a serious or life-threatening disease or condition to discuss preparation of the initial Pediatric Study Plan (iPSP) no later than the end-of-Phase 1 meeting or within 30 calendar days of request receipt, whichever is later.[11]

- Amended section 505B to require the sponsor of an original application for a new active ingredient, including a drug for an indication for which orphan designation has been granted, to submit with the application reports on the molecularly targeted pediatric cancer investigation if the drug or biological product that is the subject of the application is intended to treat an adult cancer and is directed at a molecular target that FDA determines is "substantially relevant to the growth or progression of a pediatric cancer."

- Amended section 505B(d) to require FDA to inform the Pediatric Advisory Committee (PAC) of correspondence about noncompliance with certain PREA requirements.

Section 508 of FDASIA requires the Secretary of Health and Human Services to report by July 9, 2016, and every 5 years thereafter, on various activities resulting from the implementation of sections 505A (BPCA) and 505B (PREA) of the FD&C Act. The 2016 BPCA and PREA status report to Congress, which was the initial such report, highlighted the progress made in the study of drugs in the pediatric population with a focus on the impact of the pediatric-specific provisions under FDASIA.[12] The current report provides an assessment of the implementation and impact of the pediatric statutes

[10] Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85). 121 Stat. 823 (September 27, 2007); Patient Protection and Affordable Care Act (Pub. L. 111-148). 124 Stat. 119 (March 23, 2010); FDASIA(July 9, 2012); FDARA (Pub. L. 115-52). 131 Stat. 1005 (August 18, 2017).

[11] The law continues the requirement for applications for other drugs that FDA meet as soon as practicable, but within 90 calendar days of the receipt of the iPSP, unless FDA determines that a written response to the iPSP is sufficient to communicate comments on the iPSP and that no meeting is necessary. See section 505B(e)(2)(C) of the FD&C Act. FDA is also required to meet with applicants to discuss the bases for deferrals or waivers in accordance with section 505B(e)(2)(C)(i)(III) of the FD&C Act.

[12] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

on specific measures in accordance with requirements established under FDASIA, as well as the additional reporting requirements created under FDARA.[13] The report also highlights additional successes stemming from BPCA and PREA and offers suggestions for advancing pediatric drug development by ensuring that the objectives underlying the statutes are effectively and efficiently implemented.

Implementation and Impact of Pediatric Statutes: Mandated Reporting Elements and Other Requirements Under the Law

In accordance with the reporting requirements specified under FDASIA and FDARA, this section provides an assessment of the implementation and impact of BPCA and PREA in improving pediatric use information in labeling; describes FDA's implementation of the requirements under FDARA not only to achieve earlier submissions by sponsors of pediatric studies under BPCA but also to improve pediatric research and the labeling of drugs for pediatric cancer; describes successes and limitations to studying drugs for rare pediatric diseases; provides an overview of the progress and challenges in developing drugs for neonates; and describes achievements of the program under section 409I of the Public Health Service Act (409I program) at the National Institutes of Health (NIH). This section also highlights FDA's continued progress in the congressionally mandated[14] post-marketing pediatric safety review process with reporting to the PAC.

1.1 Pediatric Labeling and Timeliness of Pediatric Drug Development

1.1.1 Progress in Improving Pediatric Use Information in Labeling

Enactment of BPCA and PREA has led to significant progress in the number, timeliness, and successful completion of studies of drugs in pediatric populations. Over 900 drugs now contain new pediatric labeling information, largely resulting from the successful implementation of both BPCA and PREA.

Since the 2016 BPCA and PREA report to Congress, labeling for 281 products (211 drugs and 70 biologics) has been updated with pediatric use information. The labeling

[13] Unless otherwise noted, the data provided in this report extend 5 years from the end of the reporting period for the 2016 report to Congress (i.e., from July 1, 2015, through June 30, 2020). The additional reporting requirements under FDARA are reported from July 1, 2017, through June 30, 2020. However, to facilitate an assessment of the early impact of FDARA on pediatric cancer research, the report includes information for pediatric oncology through early 2021. Finally, given that the COVID-19 pandemic is an ongoing public health emergency, data for matters related to COVID-19 are provided from January 1, 2020, through October 31, 2021.

[14] See section 505A(l) and 505B(i) of the FD&C Act.

changes have provided important information to support pediatric use for a variety of diseases or conditions, including but not limited to allergies, viral infections, asthma, cancer, neurological disorders, and rare diseases. These labeling changes support the health of children by ensuring that pediatric healthcare providers can make evidence-based decisions about treating children with these conditions. The following list provides selected examples of pediatric approvals since the 2016 report to Congress:

- **Allergenics:** Palforzia (peanut (Arachis hypogaea) allergen powder-dnfp), an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut, for patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

- **Antivirals:** Harvoni (ledipasvir/sofosbuvir) for the treatment of hepatitis C in patients aged 3 years to 11 years; Tybost (cobicistat) for the treatment of HIV-1 infection in patients weighing at least 35 kilograms; Viread (tenofovir disoproxil fumarate) for the treatment of chronic hepatitis B in patients aged 2 years and older; and Intelence (etravirine) for the treatment of HIV-1 in patients aged 2 years to 6 years.

- **Asthma:** Nucala (mepolizumab), an add-on maintenance treatment of patients with severe asthma aged 6 years to 11 years; Dulera (mometasone furoate and formoterol fumarate dihydrate) for the treatment of asthma in patients 5 years to 11 years; Dupixent (dupilumab) as an add-on treatment in moderate to severe asthma in patients aged 12 years and older; and Arnuity Ellipta (fluticasone furoate) for the maintenance of asthma in patients aged 5 years to 11 years.

- **Cancer:** Blincyto (blinatumomab) for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in pediatric patients; Kymriah (tisaegenlecleucel; CAR T cell) for the treatment of acute lymphoblastic leukemia in patients aged 3 years and older; Opdivo (nivolumab) for treatment of microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer in patients aged 12 years and older; Rozlytrek (entrectinib) for treatment of solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy, in patients aged 12 years and older; and Sprycel (dasatinib) for Philadelphia chromosome-positive acute lymphoblastic leukemia in patients aged 1 year and older.

- **Neurological Disorders:** Gilenya (fingolimod) for the treatment of pediatric patients aged 10 years and older with relapsing-remitting multiple sclerosis; Lyrica (pregabalin) for treatment of partial-onset seizures in patients aged 1 month to 4 years; and Fycompa (perampanel) for the treatment of partial onset seizures in patients aged 4 years and older.

- **Rare Diseases:** Koselugo (selumetinib) for the treatment of patients aged 2 years and older with neurofibromatosis type 1; Lampit (nifurtimox) for the treatment of Chagas disease in patients aged birth to less than 18 years; and Luxturna (voretigene neparvovec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy in pediatric patients.

See Appendix 1 for a complete list of labeling changes under BPCA and PREA.

1.1.2 Timeliness of Pediatric Study Planning and Conduct Under BPCA and PREA

Earlier integration of pediatric study planning has now become routine in drug development, a notable shift from the era before BPCA and PREA were enacted. Successful implementation of these laws is due, in part, to FDA's efforts to consistently encourage, across the Agency through weekly meetings of the PeRC, the timely development of pediatric drugs. Although it remains difficult to assess the impact of earlier study planning under these laws on the timeliness of completing pediatric studies, FDA has implemented the strategies described below that have improved this timeliness. See section 1.1.2.5 of this report for more information.

1.1.2.1 *Encouraging Earlier Submission of Studies Under BPCA and PREA*

Section 505(c) of FDARA required FDA, acting through the PeRC, to develop and implement a plan no later than 1 year after enactment to achieve, when appropriate, a sponsor's earlier submission of pediatric studies under BPCA. This plan was to include recommendations to achieve (1) an earlier discussion of PPSRs and WRs between FDA and sponsors and, if appropriate, a discussion of such requests at the meetings required under section 505B(e)(2)(C) of the FD&C Act; (2) an earlier issuance of WRs for pediatric studies under BPCA, including for investigational new drugs prior to the submission of an application; and (3) shorter timelines, when appropriate, for completion of studies pursuant to a WR.

FDA's efforts to date have primarily focused on the pediatric oncology program and meetings of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), but FDA has also taken steps in non-oncology programs, recognizing that a single approach may not fit all areas of pediatric drug product development. The PeRC has successfully implemented the following:

- Established an Oncology Subcommittee of the PeRC to specifically address FDA's implementation of the pediatric oncology-related provisions of FDARA. This subcommittee works to assure a consistent clinical and scientific expertise in FDA's review of proposed studies under these FDARA provisions. The review of these studies may allow for earlier and more efficient discussions of PPSRs to accelerate pediatric drug development through the earlier issuance of WRs for oncology products.

- Increased the duration of the weekly PeRC meetings not only to provide more time to address WRs, amended WRs, and inadequate PPSR letters but also to allow for more discussion on the feasibility, timing, and types of studies to request in a WR, with the goal of helping FDA provide improved advice to sponsors that could lead to the earlier issuance of WRs for non-oncology products.

In addition, FDA created Early Advice (Type F) meetings in accordance with FDARA to allow for discussions with sponsors, early in the drug development process, regarding the sponsors' development plans for pediatric patients. These meetings are intended to provide an opportunity to discuss the Agency's current thinking about a product development program and FDA's expectations for early assessment in the pediatric population unless the sponsor can provide a justification for a waiver or deferral. The availability of such early advice meetings may also allow for discussions of the appropriateness and timing of a submission of a PPSR.

The plan that was implemented under section 505(c) of FDARA to achieve an earlier submission of studies requested under BPCA appears to have been effective to the extent that there has been an increase in the combined number of WRs and amended WRs[15] issued by FDA for both oncology and non-oncology products in recent years. An analysis of the last 8 years was conducted to evaluate any effect from the 2017 changes in BPCA and PREA on FDA's issuance of WRs and amended WRs. The data were divided into two roughly equal 4-year cohorts for comparison: (1) WRs and amended WRs issued August 2012 to June 2016 and (2) those issued between August 2016 and June 2020. Between August 2012 and June 2016, FDA issued 37 original or amended WRs for oncology products. Between August 2016 and June 2020, FDA issued 56 original or amended WRs, which was a 51 percent increase. For non-oncology drugs, a similar but less dramatic trend was observed. Between August 2012 and June 2016, FDA issued 112 original or amended WRs. During the current review period (between August 2016 and June 2020), FDA issued 125 original or amended WRs, which was a 12 percent increase.

Whether the increase in the number of original and amended WRs will lead to an earlier completion of studies by industry is not yet clear. Importantly, in certain cases, delaying the issuance of an original or amended WR is not only reasonable but appropriate. For example, when studies are considered to be infeasible because of a need to identify appropriate endpoints, populations, or study designs, the issuance of a WR earlier would likely not lead to an earlier completion of studies. Similarly, the need to further evaluate safety concerns in adults that may be relevant to the pediatric population may appropriately lead to delays in the issuance of a WR. Additionally, the earlier issuance of WRs would not in all cases lead to an earlier completion of studies because the completion of pediatric studies under a WR remains voluntary. The obligation to complete studies pertains only to pediatric studies conducted under PREA. Finally,

[15] FDA believes that there is often a need to amend a WR in order to incorporate important changes in drug development approaches over time.

whether shorter timelines can be achieved is dependent on things other than just the earlier establishment of a WR or the mandatory requirements under PREA.

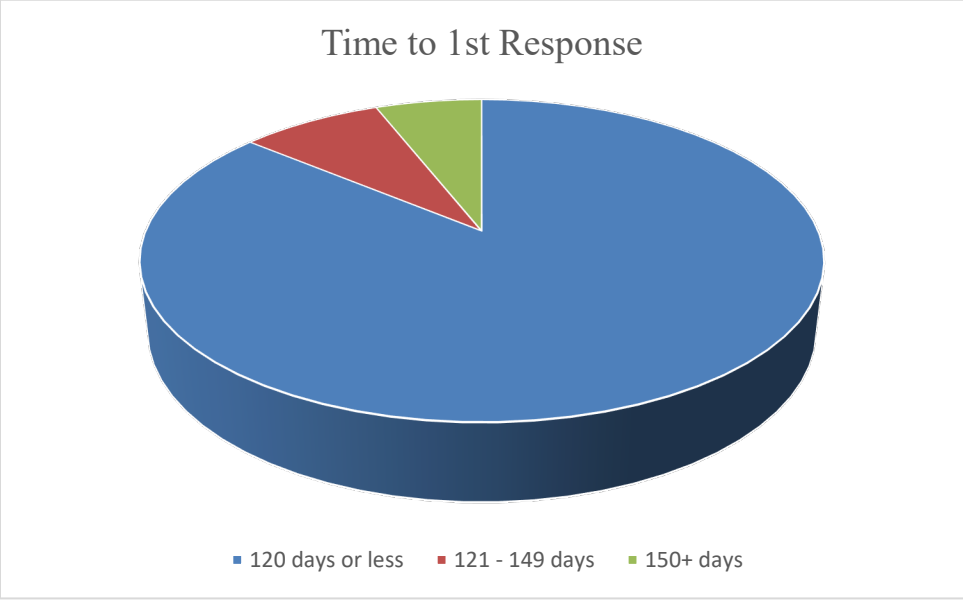
In addition to encouraging earlier discussions, shorter timelines for FDA to receive pediatric submissions for many pediatric drug development programs will likely involve an improvement in the efficiency of clinical trial operations, the availability of efficient clinical trial networks, and the use of innovative trial designs. Such discussions have been ongoing in many areas of pediatric therapeutics development. See section 1.6 of this report for more information.

1.1.2.2 *FDA's Responses to PPSRs*

FDARA amended section 505A of the FD&C Act by, among other things, adding section 505A(d)(3), which requires FDA to respond to all PPSRs within 120 days of receipt, and by adding section 505A(f)(7), which requires FDA to provide to the PeRC any response issued to a PPSR, including all letters informing sponsors that a PPSR was inadequate to receive a WR.

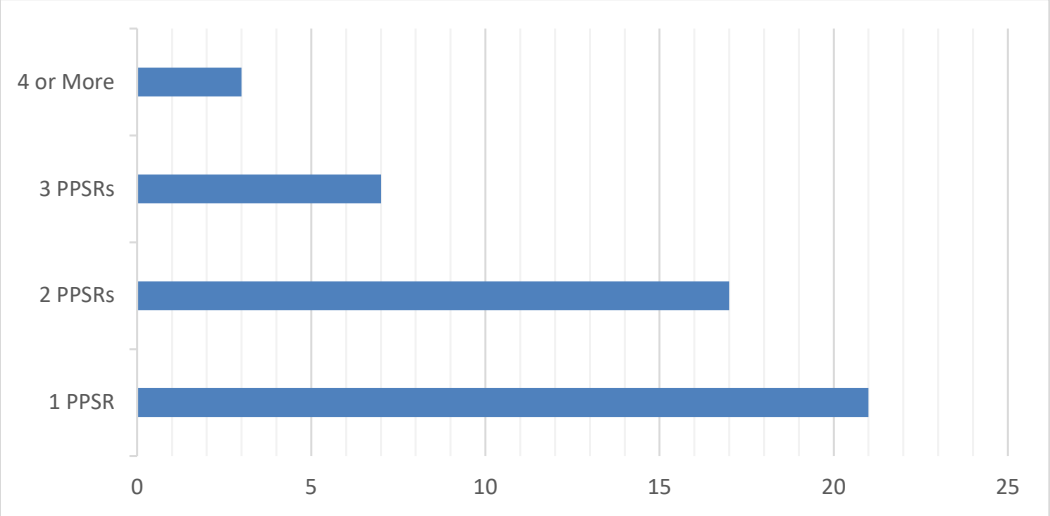
Since the implementation of FDARA, FDA has received 170 PPSRs. The mean time from receipt of a PPSR to an initial response (either a WR or an inadequate PPSR letter) was 110 days (range 17-375 days). FDA responded to 86 percent (147/170) of the PPSRs within 120 days as required under FDARA. See Figure 1. FDA's response was delayed by more than 30 days in only 6 percent (10/170) of the PPSRs. During the same time frame (i.e., from July 1, 2017, to June 30, 2020), FDA issued 48 WRs. Of the WRs issued, 44 percent (21/48) were issued in response to the first PPSR. These data demonstrate that FDA is responding to PPSRs in a timely manner and that submission of a single PPSR often leads to FDA's issuance of a WR.

Figure 1: Time (Days) From Submission of a PPSR to FDA's Response (n=170)



Additionally, there is often a need for the sponsor to negotiate with FDA the details of a WR (including the appropriate conditions/indications and types of studies needed) prior to FDA's issuance of a WR. When this need arises, sponsors may receive an inadequate PPSR letter. If a sponsor intends to pursue a WR after receipt of an inadequate PPSR letter, then the sponsor may respond by submitting another PPSR. Seventeen sponsors submitted two PPSRs before receiving a WR; seven sponsors submitted three PPSRs before receiving a WR; and three sponsors submitted four or more PPSRs before receiving a WR. See Figure 2. The mean time from submission of the first PPSR to issuance of a WR was 261 days (median 137 days; range 17-851 days).

Figure 2: Number of PPSRs Submitted Before Issuance of a WR (n=48)



These data demonstrate that often, there is a need for a sponsor to negotiate with FDA the details of a WR prior to FDA's issuance of a WR. Notably, there is a difference in the number of PPSRs reviewed (170) compared to the number of WR issued (48) during this reporting period (i.e., from July 1, 2017, to June 30, 2020); this difference, in part, is explained because some sponsors choose not to pursue a WR after FDA has issued an inadequate letter.

Of the 48 WRs issued, 16 (33 percent) have been amended at least one time (range 1-3 amendments). (The average time from the sponsor's request for an amendment to an amended WR was 98 days (range 39-132 days).) Ten (21 percent) of the 48 WRs were issued prior to FDA's approval of an original NDA or BLA for an adult indication. Together, these data demonstrate that FDA is willing to amend WRs when appropriate, and in some cases, multiple amendments have been agreed upon by FDA and sponsors.

Finally, these data confirm that, in the vast majority of cases, FDA is meeting timelines established for the review of PPSRs as required under FDARA. In addition, these data suggest that many PPSRs do not lead to the issuance of a WR. Although the specific reasons for this finding were not evaluated, sponsors often choose not to pursue a WR

after receiving FDA's feedback because the conduct of studies under a WR is voluntary. A WR may include requests for studies for one or more indications that may benefit children and may include indications that are not being pursued in adult populations. These data also suggest, however, that when a WR is issued, only a single PPSR was needed nearly 50 percent of the time.

1.1.2.3 *WRs Issued Under BPCA and Sponsor Responses*

Section 508 of FDASIA requires that FDA report on the number of WRs issued, accepted, and declined and provide a listing of any important gaps in pediatric information as a result of such declined requests.[16] From July 1, 2015, through June 30, 2020, FDA issued 96 WRs under BPCA. For the 96 WRs, 92 sponsors agreed to conduct the studies and four sponsors declined. These data demonstrate that sponsors rarely decline WRs after they are issued and suggest that FDA issues WRs for studies that sponsors are willing to conduct.

The sponsors who declined the WR cited the following reasons: (1) non-agreement with the types and designs of the studies in the WR; (2) non-agreement with the additional studies requested in the WR that were not required under PREA; (3) there was an insufficient amount of time remaining for the studies to be completed before the remaining exclusivity expired; and (4) an inability to conclude that the studies requested in the WR were feasible.

1.1.2.4 *Pediatric Study Planning Under PREA*

Section 508 of FDASIA requires that FDA provide an assessment of the timeliness and effectiveness of pediatric study planning under PREA. This provision requires that FDA report on the number of required studies that have not met the initial deadline, including the number of deferrals and deferral extensions[17] granted and the reasons such extensions were granted; the number of waivers granted;[18] and the number of noncompliance letters issued.[19]

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[16] For the current reporting period (i.e., from July 1, 2015, to June 30, 2020), FDA has not referred any pediatric studies pursuant to section 505A(n) of the FD&C Act.

[17] Section 505 of FDASIA amended PREA to ensure the completion of pediatric studies and authorized FDA to grant an extension of assessments deferred under PREA.

[18] See https://www.fda.gov/science-research/pediatrics/pediatric-tracking-requirements-under-fdaaa.

[19] Section 505 of FDASIA requires FDA to issue, and publicly post, noncompliance letters for failure to comply with certain PREA requirements, including the failure to submit required pediatric assessments under PREA.

iPSPs

The total number of iPSPs reviewed by FDA and agreed[20] by calendar year from January 1, 2015, to June 30, 2020) is presented in Table 1.

Table 1: iPSPs Submitted to FDA*

Calendar Year	*iPSPs*	*Agreed iPSPs*	*Amended Agreed iPSPs*	*Non-Agreed iPSPs*
2015	256	229	0	14
2016	265	226	6	18
2017	250	190	8	15
2018	280	199	13	8
2019	359	245	8	19
2020	167	153	18	11
Totals	**1577**	**1242**	**53**	**85**

* The data collected are by calendar year. The numbers provided for 2015 include the entire calendar year; in the last BPCA and PREA report to Congress, only the first 6 months of 2015 were reported. Similarly, because the numbers in the table reflect FDA's reviews through June 2020, the 2020 numbers reflect only the first 6 months of the year. Due to the timeline described in section 505B(e) of the FD&C Act, the number of agreed and non-agreed iPSPs may not equal the number of iPSPs each year because iPSPs submitted later in the calendar year may be acted upon in the following year.

The data on the number of iPSPs submitted to FDA clearly demonstrate an increase since 2018, which is largely due to the implementation of the pediatric oncology-related provisions of FDARA. See section 1.2.1 of this report. Despite the increase in the number of iPSP submissions, there has not been an apparent increase in the number of non-agreed iPSPs issued by FDA, suggesting that FDA and sponsors are agreeing on iPSPs in the vast majority of cases, including iPSPs submitted for oncology products.

Deferral Extensions

The total number of deferral extension (DE) requests that were received, granted, and denied by FDA from January 1, 2015, to June 30, 2020 by calendar year and by FDA's Centers is presented in Table 2.

[20] After a sponsor submits an iPSP, the FDA has 90 days to review the iPSP and provide a written response to the iPSP, or meet with the sponsor to discuss the iPSP, as appropriate. This review process includes consultation with the PeRC. The sponsor then has a second 90-day period during which it may review FDA's comments and initiate any needed negotiations to discuss the iPSP. By the end of this second 90-day review period, the sponsor must submit an agreed iPSP. FDA then has 30 days after receipt of the agreed iPSP to review and issue correspondence confirming agreement or issue correspondence stating disagreement. If the FDA does not agree, the iPSP is considered a non-agreed iPSP. See section 505B(e) of the FD&C Act.

Table 2: DE Requests Received, Granted, and Denied by CDER (CBER)^ by Calendar Year*

Calendar Year	*DE Requests Granted*	*DE Requests Denied*	*DE Requests Received*
2015	37 (2)	19 (0)	71 (3)
2016	41(4)	19 (0)	76 (4)
2017	67 (2)	34 (1)	101 (1)
2018	53 (2)	19 (1)	87 (3)
2019	55 (4)	34 (0)	104 (4)
2020	31 (1)	10 (0)	60 (1)
Totals	**299**	**137**	**515**

^ CDER – Center for Drug Evaluation and Research; CBER – Center for Biologics Evaluation and Research
* The data collected are by calendar year. The numbers provided for 2015 include the entire calendar year; in the last BPCA and PREA report to Congress, only the first 6 months of 2015 were reported. Similarly, because the numbers reflect DE requests through June 2020, the 2020 numbers reflect only the first 6 months of the year. The Agency has 45 days to respond to a DE request. Therefore, the number of DE requests granted and denied may not equal the number of DE requests in a given year because a DE request that is submitted in the last 45 calendar days of a year may be acted upon in the following year.

The number of DE requests received, granted, and denied between 2015 and the first half of 2020 has remained relatively constant. Overall, approximately 70 percent of the DE request decisions resulted in FDA granting a deferral extension. However, it should be noted that the number of DE requests denied has increased since the 2016 BPCA and PREA report to Congress. Thirty-one percent (137/436) of DE requests were denied over the last 5 years compared to 14 percent in the last report. FDA reviewed the potential reasons for this increase (i.e., from 14 percent in the 2016 report to 31 percent in the current report) and has concluded that the change occurred because the 2016 report included data only from July 2012 through June 2015, which represented only the first 3 years of implementation of the DE program. During the initial phase of implementation, FDA granted a greater percentage of DE requests to allow for studies that were already delayed to be given additional time to complete these studies. Thus, there is a lower percentage of DE request denials during the first 3 years of the implementation. Since then, the percentage of denials per year has ranged from 27 percent (2018) to 37 percent (2019).

The reasons cited for sponsors requesting a DE in the current reporting period were similar to those described in the 2016 report.[21] It should be noted that the data for 2020 reflect some DE requests due to impacts of the COVID-19 pandemic on clinical trial operations. FDA granted a relatively high percentage of these DE requests in recognition of the need for sponsors to adjust study timelines due to disruptions caused by the pandemic.

[21] See "Best Pharmaceuticals for Children Act and Pediatric Research Equity Act, July 2016 Status Report to Congress" at https://www.fda.gov/media/99184/download.

NONCOMPLIANCE LETTERS

The first noncompliance letters were publicly posted on August 26, 2013, on FDA's website.[22] Between April 5, 2013, and June 30, 2020, FDA issued a total of 106 noncompliance letters to 72 sponsors. Of these 106 letters, FDA issued 63 letters (59 percent) to 52 sponsors since the 2016 BPCA and PREA report to Congress.

Under section 508(b)(13) of FDASIA, as amended by FDARA, FDA is required to report the number of sponsors who received pediatric exclusivity for studies completed and submitted after they had received a non-compliance letter. Table 3 lists the sponsors who received pediatric exclusivity for studies completed and submitted after they had received a non-compliance letter that was issued between July 1, 2017, and June 30, 2020.

Table 3: Sponsors Qualifying for Pediatric Exclusivity After Receiving a Non-Compliance Letter

Sponsor	***Product***	***Date of Non-Compliance Letter***	***Date of Submission***	***Date Qualified for Pediatric Exclusivity***
Rhodes Pharmaceuticals	Aptensio XR (methylphenidate hydrochloride extended release) capsules	7/12/2017	9/14/2018	3/15/2019
Allergan Sales, LLC	Viibryd (vilazodone hydrochloride) tablets	7/6/2018	8/1/2019	1/21/2020
Teva Pharmaceuticals	ArmonAir Respiclick (fluticasone propionate/salmeterol xinafoate inhalation powder)	1/30/20	12/21/20	6/10/2021
Teva Pharmaceuticals	AirDuo Digihaler/AirDuo Respiclick (fluticasone propionate/salmeterol xinafoate inhalation powder)	1/30/20	12/21/20	6/10/2021

Overall, these data demonstrate that qualifying for pediatric exclusivity after receiving a noncompliance letter for the completion of these studies under PREA is an uncommon occurrence. Only 11 percent (4/37) of products that qualified for pediatric exclusivity

[22] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm and https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/prea-non-compliance-letters.

between July 1, 2017, and June 30, 2020, received a non-compliance letter. FDA reviewed the circumstances under which these four products qualified for pediatric exclusivity after having received a noncompliance letter. FDA's review suggests that these rare occurrences have not identified a gap or loophole in the statutory requirements such that sponsors are qualifying for pediatric exclusivity for studies that were not conducted with due diligence.

1.1.2.5 *Time From the Application's Approval to Inclusion of Pediatric Information in the Approved Product's Labeling*

Section 504(d) of FDARA amended the reporting requirements under section 508 of FDASIA to require that FDA report on the average length of time after the approval of an application under section 505(b)(1) of the FD&C Act or section 351(a) of the Public Health Service Act (PHS Act) before studies conducted pursuant to either section 505A or 505B of the FD&C Act or section 351(m) of the PHS Act are completed, submitted, and incorporated into the labeling.

From July 1, 2017, to June 30, 2020, the average length of time between approval of an application under section 505(b)(1) of the FD&C Act or section 351(a) of the PHS Act and the inclusion of any pediatric use information in the approved product's labeling was approximately 6 years. For products regulated by CDER, the average time between original approval and the inclusion of any pediatric use information was 6.25 years (range 0.6-17.1 years). Notably, of the 96 CDER pediatric approvals identified in this analysis, only six products included any pediatric use information as part of the original approval. In addition, four products (not included in this analysis) had studies waived because the drug was considered to be either unsafe or ineffective in pediatric patients, and this information was included in labeling at the time of the original approval. For products regulated by CBER, the average time between original approval and the inclusion of any pediatric use information was 4.8 years (range 1-10.1 years). Notably, 86 percent (12/14) of original CBER applications approved during this period included pediatric-specific use information for all or part of the intended pediatric age range.

These data suggest that there remains a substantial lag between the original approval of a drug and the inclusion of specific pediatric-use information in the drug's labeling. FDA believes that measures to decrease this lag, such as the requirement in section 505B(e)(2) of the FD&C Act to submit iPSPs no later than 60 days after an end-of-Phase 2 meeting, unless another time is agreed upon between FDA and the applicant, will have a positive effect, but this effect is difficult to assess at this time because many of the sponsors for drugs with pediatric labeling changes identified for this analysis had an end-of-Phase 2 meeting that pre-dated the requirement. Notably, there appears to be some improvement in the inclusion of pediatric use information at the time of original approval for CBER-regulated products.

1.1.2.6 *Summary of the Timeliness of Pediatric Study Planning and Conduct Under BPCA and PREA*

Overall, FDA believes that the programs directed toward the timely completion of pediatric assessments under BPCA and PREA have been successful. FDA's review of iPSPs, DE requests, PPSRs, and WRs have met required timelines in the vast majority of cases. For example, FDA has met the requirement enacted under FDARA to respond to a PPSR within 120 days for nearly 90 percent of PPSR submissions. Additionally, the PeRC continues to provide consultation on all pediatric study plans submitted in accordance with PREA and to review all DE requests for PREA studies, with both actions aimed at ensuring the proposed pediatric study timelines are reasonable. Additionally, the issuance of noncompliance letters has called attention to sponsors who have not completed studies according to agreed-upon timelines required under PREA.

The consistency in the data over the last 5 years has been due, in large part, to the work of the PeRC and the Oncology Subcommittee of the PeRC. In addition to reviewing iPSPs, DE requests, PPSRs, and WRs, the experts on the PeRC provide important scientific and regulatory advice to aid FDA's review divisions in achieving efficient and feasible pediatric product development plans across CDER and CBER. FDA will continue these efforts to encourage the submission of timely pediatric studies by sponsors to help reduce the delay between the original approval of a drug and the incorporation of pediatric use information in the drug's labeling, which currently stands at approximately 6 years.

1.2 Special Populations: Children with Cancer, Children with Rare Diseases, and Neonates

1.2.1 Pediatric Cancer: Advances in Research and Labeling of Cancer Drugs

Section 504 of FDARA, commonly known as the Research to Accelerate Cures and Equity (RACE) for Children Act, amended PREA by requiring sponsors to submit reports to FDA on pediatric investigations for certain new drugs directed at a molecular target determined to be substantially relevant to the growth or progression of one or more pediatric cancers regardless of whether that drug is for an indication for which orphan designation has been granted.

FDA, with the National Cancer Institute (NCI), has engaged with stakeholders, including the American Society of Clinical Oncology, the American Association for Cancer Research, Biotechnology Innovation Organization (BIO), Pharmaceutical Research and Manufacturers of America (PhRMA), Drug Information Association (DIA), Friends of Cancer Research, the American Academy of Pediatrics (AAP), the American Society of Pediatric Hematology-Oncology, the International Society of Pediatric Oncology, and numerous patient advocacy organizations, as part of its implementation of the

amendments to the FD&C Act under section 504 of FDARA to meet the needs of children with cancer.

FDA convened a public meeting of the Pediatric Oncology Subcommittee of the ODAC in collaboration with NCI on April 20, 2018, for numerous reasons, including (1) to solicit feedback from physicians and researchers on FDA's development of a guidance document and the molecular target lists and (2) to discuss additional scientific and operational challenges related to pediatric cancer drug development in accordance with the requirements added by FDARA. In May 2021, FDA issued a final guidance document titled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act."[23] This guidance document finalized the draft guidance document entitled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs" that was issued in December 2019 and finalized certain recommendations related to FDA's implementation of FDARA that were included in the January 2020 draft guidance document entitled "Pediatric Study Plans for Oncology Drugs: Questions and Answers." Additionally, the "Relevant Molecular Target List" and the "Non-Relevant Molecular Target Leading to Waiver List" are available on FDA's website and updated quarterly.[24]

As mentioned earlier, Type F meetings provide an opportunity for sponsors to discuss their pediatric development plans early in their drug development process. Specifically, Type F meetings related to oncology have provided an opportunity for sponsors to discuss the Agency's current thinking about the relevance of a specific molecular target and FDA's expectations for early investigation in the pediatric population unless the sponsor can provide justification for a waiver or deferral. Between August 2019 and June 2020, 16 Type F meetings were requested to discuss 16 distinct new drugs directed at a molecular target. All meetings were conducted by the Pediatric Oncology Program in FDA's Oncology Center of Excellence, in collaboration with the appropriate oncology review division or office in CDER or CBER and members of the Oncology Subcommittee of the PeRC, within the 30-day timeline.

1.2.1.1 *Impact of FDARA on Sponsors' Conduct of Pediatric Cancer Research*

Early evidence suggests that the RACE for Children Act has had a favorable impact on sponsors' timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would historically have gone unstudied in children. The requirement for sponsors to comply with the amended PREA provisions requiring them to submit reports on the molecularly targeted pediatric cancer investigation for certain molecularly targeted cancer drugs became effective on August 18, 2020 (which was 3 years after enactment of the legislation). Since that date, sponsors now subject to this

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec.

[24] See https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology.

requirement must include in the agreed iPSP a description of the molecularly targeted pediatric cancer investigation.

FDA analyzed the iPSPs submitted from August 18, 2019, through March 30, 2021, in advance of the related original NDA or BLA submissions. This analysis demonstrated that pediatric investigations of molecularly targeted cancer drugs were proposed by sponsors and agreed to by FDA in approximately 45 percent of cases and justifications for planned full waivers were provided by sponsors in 55 percent of agreed iPSPs. This analysis also demonstrated that justifications for age-dependent partial waivers and deferrals to obtain additional adult efficacy and safety data, as well as planned deferrals for the submission of results of pediatric studies, have been submitted to and agreed upon by FDA.

Thirty-eight agreed iPSPs associated with original NDAs or BLAs were reviewed by the Oncology Subcommittee of the PeRC during the review period cited above (i.e., between August 18, 2019, to March 30, 2021). Twenty-one of the agreed iPSPs included plans for pediatric studies, and 17 of the agreed iPSPs included justifications for a waiver of pediatric studies based on the molecular mechanism of action of the drug.

Of those 21 agreed iPSPs that included plans for pediatric studies, fourteen included age-appropriate partial waivers and planned deferrals for the sponsor's submission of the results of its pediatric studies because the associated original NDA or BLA for the adult indication of the proposed product was anticipated to occur before the completion of the pediatric studies. All approvals of products with such planned deferrals will, if the deferrals are granted, include post-marketing requirements for the sponsor's submission of data from the pediatric studies. Based on the adult indications for these products, such studies would likely have been waived under PREA if not for the revisions to PREA made by section 504 of FDARA.

For drugs approved prior to August 18, 2020, that have molecular targets that are determined to be substantially relevant to the growth or progression of a pediatric cancer and that would have been subject to PREA requirements under section 505B(a)(1)(B) of the FD&C Act if the application had been filed later, FDA has issued 10 WRs.

1.2.1.2 *Advances in Labeling Drugs for Pediatric Cancer*

Since the 2016 report to Congress, the following 16 oncology drugs have been approved and labeled for use in the pediatric population: blinatumomab, tisagenlecleucel, avelumab, ipilimumab, dasatinib, gemtuzumab ozogamicin, calaspargase pegol, tagraxofusp, larotrectinib, emapalumab, entrectinib, pembrolizumab, nivolumab, selumetinib, selpercatinib, and tazemetostat. Four of the 16 oncology drug approvals resulted from studies conducted pursuant to BPCA: blinatumomab, tisagenlecleucel, dasatinib, entrectinib. One of the 16 oncology drug approvals resulted from studies conducted pursuant to PREA: nivolumab.

Of note, tisagenlecleucel, a genetically engineered (chimeric antigen T cell (CAR-T cell)) product was initially approved for the treatment of relapsed/refractory acute lymphoblastic leukemia in the pediatric population based on the results of a clinical trial conducted as part of a WR issued under BPCA. Also of note are the simultaneous adult and pediatric approvals for tissue/histology agnostic indications of the targeted agents larotrectinib, entrectinib, and selpercatinib based on the known molecular drivers of several diverse and histologically distinct tumors that occur in adults and children.

1.2.2 Rare Pediatric Diseases: Successes and Limitations in Drug Development

Section 508 of FDASIA requires that FDA provide an assessment of the successes of and limitations to studying drugs for rare diseases under BPCA and PREA. In addition to BPCA and PREA, other laws impact the study of drugs intended to treat rare pediatric diseases, such as sections 526 and 527 of the FD&C Act (which authorize orphan drug designation and orphan exclusivity per the Orphan Drug Act[25]) and section 529 of the FD&C Act (which authorizes the rare pediatric disease (RPD) priority review voucher (PRV) program).

The Orphan Drug Act, enacted in 1983, was established to encourage the development of drugs for rare diseases. However, the provisions of the Orphan Drug Act do not require pharmaceutical industry sponsors to evaluate drugs with orphan designation in any specific populations affected by a rare disease. Section 505 of FDARA required FDA to report on the lack of pediatric use information in the labeling of drugs for indications that have received an orphan designation. As described in the 2019 report to Congress on the pediatric labeling of orphan drugs, there is a public health need for additional pediatric information in the labeling for over one-third of approved orphan indications that are relevant to the pediatric population. In some cases, there is no pediatric information at all in the labeling, and in other cases, the labeling does not address the full age range of the affected pediatric patients. As noted in that report, FDA found that studies were ongoing or that FDA had issued a WR for pediatric studies to address labeling for 29 of 127 (23 percent) of those indications not fully labeled for pediatric use.[26]

PREA does not apply to drugs for an indication for which orphan designation has been granted under section 526 of the FD&C Act, except for certain molecularly targeted cancer drugs.[27] As such, PREA does not serve to ensure the evaluation in the pediatric population of such drugs subject to this "orphan exemption." Notably, the impact of the RACE for Children Act, which requires pediatric studies of certain oncology drugs regardless of orphan drug designation, appears promising. As described above, early evidence suggests that the RACE for Children Act has had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer

[25] Public Law 97-414, as amended, codified at sections 525-528 of the FD&C Act (21 U.S.C. 360aa-360dd).

[26] See https://www.fda.gov/media/130060/download.

[27] See section 505B(k) of the FD&C Act.

drugs that would previously have not been required and that would historically have gone unstudied in children.

1.2.2.1 *Rare Pediatric Disease Priority Review Voucher Program*

The RPD PRV program, established in 2012 under FDASIA, is an additional program to encourage treatments for rare pediatric diseases.[28] Products may be designated as a "drug for a rare pediatric disease" under this program. To be a "rare pediatric disease," a disease must be (1) a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years and (2) a rare disease or condition within the meaning of section 526 of the FD&C Act.[29]

As of September 2021, FDA has granted over 480 rare pediatric disease designations for over 220 unique pediatric diseases and has awarded 32 RPD PRVs. Nearly 80 percent (25/32) of products approved under the RPD PRV program were the first approved therapy for the disease. Most products receiving RPD PRVs treat the underlying disease rather than a specific disease symptom, representing significant progress in developing disease-modifying therapies for diseases for which such therapies had not been available. Approved products receiving an RPD PRV include (1) the first ever FDA-approved gene therapy (Kymriah (tisagenlecleucel) for a form of acute lymphoblastic leukemia) and (2) the first directly administered gene therapy approved in the United States that targets a disease caused by a gene mutation (Luxturna (voretigene neparvovec-rzyl) for biallelic RPE65 mutation-associated retinal dystrophy, an eye disease that causes blindness in early childhood). Other RPD PRV products include targeted therapies for the treatment of spinal muscular atrophy and Duchenne muscular dystrophy.

1.2.3 Progress and Challenges in Developing Drugs for Neonates

Section 508 of FDASIA requires that FDA report on efforts made by the Agency to increase the number of studies conducted in the neonatal population and the results of these efforts. FDA continues to encourage and support the conduct of studies in neonates by (1) providing reviewers across the Agency with expert neonatal-perinatal consultation services, (2) encouraging inclusion of neonates, when appropriate, in drug development programs, and (3) developing guidance documents to facilitate neonatal studies. In addition, FDA has been working to overcome the obstacles to advancing neonatal regulatory science, recognizing the importance of establishing a strong scientific foundation to support drug development for neonates.

Considerable strides have been made since FDA's neonatology program was developed within the Office of Pediatric Therapeutics. This program has seen steady growth of its

[28] FDASIA, Pub. L. 112-144. 126 Stat 993 (July 9, 2012).

[29] The Consolidated Appropriations Act, 2021, extended the RPD PRV program's two-part sunset period. Under the current provisions, after September 30, 2024, FDA may award an RPD PRV only if the drug has rare pediatric disease designation and if that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any RPD PRVs.

neonatal-perinatal medicine consultation service, which provides expertise to reviewers across the Agency in the development and use of FDA-regulated products that benefit neonates. FDA's neonatology staff also remain active on the PeRC, consistent with section 505C of the FD&C Act, and are integral in fostering drug development in neonates and addressing the unique challenges of evaluating products in this population during PeRC discussions.

Guidance development to support the conduct of studies in neonates remains a focus for FDA's neonatology program. In August 2019, in accordance with FDARA, FDA issued the draft guidance document titled "General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products" to address the clinical pharmacology considerations for any planned studies in neonatal populations.[30] When final, this guidance document will represent the Agency's current thinking on this topic.

Since the 2016 report to Congress, under BPCA and PREA, the labeling for 22 drugs has been updated to include the drug's dosing, safety, and/or efficacy for neonates.[31] The labeling changes have provided important information to support neonatal use for a selection of drug products, particularly antivirals and other anti-infectives, that would historically have gone unlabeled in the neonatal population. However, the current paradigm for drug development under BPCA and PREA generally has not resulted in a significant increase in research addressing neonatal-specific diseases/conditions. Of the 22 labeling updates, only one product is indicated for a condition that solely affects the neonatal population (i.e., Cafcit (caffeine citrate) for the treatment of apnea of prematurity).

FDA considers the inclusion of neonates, when appropriate, when issuing WRs under BPCA.[32] Also, the 409I program has fostered improvements in neonatal drug labeling. However, drugs under development for adult conditions may not be relevant for addressing the unique pathophysiology of neonatal conditions, in which case studies in accordance with PREA may not be appropriate. To ensure therapeutics are available for conditions that are unique to the neonatal population, it is important that the pharmaceutical industry develop products specifically to address neonatal conditions. Currently, there are no FDA-approved drugs indicated to treat or prevent some of the major morbidities that result from preterm birth, including chronic lung disease, preterm brain injury, and necrotizing enterocolitis.

1.2.3.1 *Advancing Regulatory Science in the Conduct of Studies in Neonates*

FDA recognizes that advancing the science to support regulatory decision-making in the development of drugs to treat conditions affecting neonates is of utmost importance and

[30] https://www.fda.gov/media/129532/download.

[31] Labeling updates resulted from the 409I program (3 drugs), PREA (11 drugs), BPCA (6 drugs), and BPCA plus PREA (2 drugs).

[32] See section 505A(a) of the FD&C Act.

involves collaboration with internal and external stakeholders. FDA's neonatology program continues to support and contribute to efforts to further the science and to develop tools to streamline drug development programs. For example:

- In collaboration with CDER, FDA's neonatology program recently completed the first phase of a project re-evaluating gestational age endpoints for clinical trials of products intended to reduce preterm birth. This project involves using existing datasets to model alternative approaches to endpoint selection for these clinical trials.

- FDA collaborated in a consensus process with the International Neonatal Consortium (INC) that led to the development of a standard severity grading scale for neonatal adverse events called the neonatal adverse event severity scale. Although severity scales have been developed in other research fields, the existing scales are not applicable to neonates. Use of the neonatal severity scale will improve the quality and consistency of safety evaluations during the conduct of neonatal clinical trials.

- FDA awarded a multi-year grant to INC and the Critical Path Institute (C-Path) to advance standards and methodologies to generate real-world evidence from existing real-world data within neonatal datasets and electronic health records through a neonatal data pilot project. The INC/C-Path team has obtained electronic health records data and clinical trial data that will be used to create a disease progression model of preterm chronic lung disease to improve trial design and the development of therapies for neonates. This pilot project will also generate real-world evidence to support normal and abnormal laboratory values to guide assessments in clinical trials.

- FDA awarded a multi-year grant to Columbia University to evaluate the long-term neurodevelopmental outcomes of children with intrauterine opioid exposure. The project will use electronic health records that incorporate maternal, neonatal, and pediatric data to assess whether abnormal neurodevelopment may be associated with (1) a pharmacologic treatment for neonatal withdrawal, (2) the infant's sex, and (3) maternal/demographic characteristics. These data will help provide a better understanding of the outcomes of children with intrauterine opioid exposure and the impact of treatment during the neonatal period.

- FDA used the Broad Agency Announcement process[33] (1) to study actigraphy as a potential endpoint in clinical trials involving patients with pulmonary arterial

[33] This process is a specialized contract mechanism that makes it possible for the Agency to solicit innovative ideas and approaches to developing and evaluating FDA-regulated products by tapping into external knowledge and infrastructure in areas where FDA has limited expertise or capacities. The proposals solicited from industry, academia, and other government agencies enable FDA to better understand the breath of innovative scientific and technical solutions available to solve difficult regulatory science problems.

hypertension beginning from birth and (2) to evaluate the comparative safety of feeding device types among graduates of the neonatal intensive care unit who required tube feeding.

1.3 Achievements of the 409I Program

Section 409I of the PHS Act, which was created by the Best Pharmaceuticals for Children Act in 2002, requires NIH, in consultation with FDA and experts in pediatric research, to develop and publish a priority list of needs in pediatric therapeutics. Among other things, section 409I specifically mandates NIH to (1) identify and prioritize drugs and therapeutics that need further study in pediatric populations and (2) sponsor clinical trials of prioritized drugs. Data from these trials are to be submitted to FDA, which will determine if labeling changes are appropriate.

1.3.1 Prioritizing Drugs and Therapeutics for Further Study

One of the primary responsibilities of the 409I program involves prioritizing needs in pediatric therapeutics. Based on the prioritization process, more than 220 drugs/therapeutics and 50 conditions/indications have been prioritized for further study. Due to limitations in fit and feasibility, all prioritized drugs cannot be studied under the 409I program; however, the BPCA priority list serves as a catalog of needs that remain in the pediatric population.[34]

1.3.2 Clinical Trials of Prioritized Drugs

The initial years of the program included gathering data (e.g., through systematic literature reviews); convening expert panels; and conducting or co-funding single molecule safety, efficacy, and pharmacokinetic clinical trials based on WRs that NIH received from FDA. From 2004 to 2012, NIH received approximately 22 WRs and conducted and/or co-funded 14 clinical trials in the following areas:

- Lithium for the treatment of pediatric bipolar disease (2 trials)
- Lorazepam for the treatment of status epilepticus (2 trials)
- Lorazepam for sedation
- Sodium Nitroprusside for the treatment of blood pressure (2 trials)
- Baclofen for the treatment of spasticity in cerebral palsy (2 trials)
- Meropenem for the treatment of intra-abdominal infections in neonates
- Oncology trials with the Children's Oncology Group (4 trials)

The 409I program's current success can be attributed largely to work done by the Pediatric Trials Network (PTN) at the Duke Clinical Research Institute and by the Data Coordinating Center at the Emmes Corporation. The PTN, originally funded in 2010 and

[34] See https://www.nichd.nih.gov/research/supported/bpca/prioritizing-pediatric-therapies .

funded again in 2017, has developed and implemented 40 pediatric clinical trials across more than 100 clinical sites to improve the knowledge of medicines used in children, with 21 clinical study reports submitted to FDA for label change considerations.

1.3.3 Labeling Changes Under the 409I Program

The collaborative activities of NIH and FDA that have stemmed from this program have led to 15 labeling changes, which are listed below.[35] Notably, two of these labeling changes are for devices. Of the 15 changes, 10 occurred through the process established for the 409I program.[36] Between 2002 and 2016, FDA approved labeling for three drugs through this program. Since the 2016 report to Congress, the number of drugs with approved labeling changes has more than tripled, with FDA approving the labeling for seven additional drugs. FDA approved a change to the labeling of the following products to provide details related to the product's use in pediatric patients:

- Acyclovir for the treatment of neonatal herpes simplex virus
- Ampicillin for the treatment of sepsis and/or meningitis
- Bactrim for the treatment of infections per Standard of Care
- Caffeine Citrate for the short-term treatment of apnea of prematurity
- Clindamycin for the treatment of serious infections
- Doxycycline for the treatment of life-threatening infectious diseases
- Lithium for the treatment of bipolar disorder
- Lisinopril for the treatment of hypertension in kidney transplant recipients
- Lorazepam for the treatment of status epilepticus
- Meropenem for injection for the treatment of intra-abdominal infections
- Propylthiouracil for the treatment of hyperthyroidism (the labeling was changed for safety and dosing)
- Pralidoxime for use in organophosphate poisoning
- Sodium Nitroprusside for the treatment of blood pressure in the perioperative environment
- Mercy TAPE to estimate body weight based on measurements of arm length and upper arm circumference
- Mercy BabyTAPE to estimate body weight of infants from birth to 90 days of age

1.3.4 Dissemination of Information Obtained from 409I Research

Data from NIH-funded studies pursuant to the 409I program are published in an FDA public docket for all labeling changes, in peer-reviewed journals for scientific advancements, and on the National Institute of Child Health and Human Development's (NICHD's) Data and Specimen Hub (DASH) for investigators to access the datasets publicly. To date, the 409I program and the PTN have contributed more than 100 peer-

[35] See https://www.nichd.nih.gov/research/supported/bpca/accomplishments.

[36] See https://www.fda.gov/drugs/development-resources/nih-funded-pediatric-labeling-changes-drugs-studied-under-409i-process.

reviewed publications to the scientific literature. Until recently, NIH-funded 409I findings had been accessible to pediatricians only through the FDA-issued drug labeling changes. Now, one-page study summaries are available both on the 409I website and on the DASH; in addition, the PTN website provides lay summaries geared towards families and patients and provides an overview of 409I-supported studies.[37] The summaries on the 409I website also link to FDA's drug labeling, PubMed, and NICHD's DASH.

1.3.5 NIH-Sponsored Training Programs

NIH has sponsored several programs aimed at training pediatric investigators, including the T32 Pediatric Clinical and Developmental Pharmacology Network and the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub. These two programs will be discussed in turn below.

First, the T32 Pediatric Clinical and Developmental Pharmacology Training Network was formed as a result of the requirements in section 409I of the PHS Act for NIH to consider the adequacy of the infrastructure necessary to conduct pediatric pharmacological research, including research networks and trained pediatric investigators. The training goals of the program continue to expand to foster more entry points for aspiring clinicians-scientists, cultivating their intellectual curiosity and maintain continuity promoting and sustaining their career development.

Second, the MPRINT Hub is a new initiative that is partially funded by the 409I program.[38] The goal of MPRINT will be not only to provide a bridge between translational research and clinical research but also to be a platform for improved dissemination and training in the respective pharmacology fields. The MPRINT Hub is prepared to serve as a scientific service center and science catalyst that will

- Provide a hub of knowledge and expertise in maternal and pediatric therapeutics to the scientific community
- Serve as a platform for innovative multidisciplinary research
- Synergize with other resources and networks across NIH and among various stakeholders
- Catalyze and accelerate maternal and pediatric therapeutics towards precision medicine

[37] These summaries are available at https://www.nichd.nih.gov/research/supported/bpca/resources/study-summaries, https://dash.nichd.nih.gov/, and https://pediatrictrials.org/.
[38] https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint.

1.4 PAC Activities: Evaluation of FDA's Post-Marketing Pediatric Safety Reviews and Other Matters in Pediatric Product Development and Use

FDA continues to implement the congressionally mandated pediatric-focused post-marketing safety review of drugs and biologics for the 18-month period after a pediatric labeling change pursuant to BPCA and PREA and to facilitate the sharing of these reviews with the PAC.

Since the 2016 report to Congress, FDA has reviewed 189 products (164 drugs and 25 biologics) for post-marketing pediatric safety and shared information with the PAC either through a formal presentation or posting on the web. FDA's post-market pediatric safety reviews and evaluation by the PAC have led to important labeling changes, such as the following:

- In completing the pediatric-focused safety reviews for mesalamine utilizing the FDA Adverse Event Reporting System (FAERS), FDA identified four non-fatal, serious, unlabeled adverse events. FDA presented this information to the PAC, which concurred with FDA's recommendation to add nephrogenic diabetes insipidus to the Adverse Reactions section of the labeling for all mesalamine products.

- In completing the pediatric-focused safety reviews for three stimulants indicated for the treatment of attention-deficit hyperactivity disorder (ADHD), FDA identified a potential drug-drug interaction between an ADHD stimulant and an antipsychotic agent. Upon further review, FDA identified 36 cases of acute hyperkinetic movement disorder, most involving acute dystonic reactions, in FAERS and the medical literature. FDA presented this information to the PAC, which concurred with FDA's risk mitigation plan to add this information to the Drug Interaction section of the labeling for methylphenidate products and risperidone.

As indicated above, these reviews have provided an opportunity for the detection of safety concerns in children that may not have been identified in prelicensure clinical trials. However, the legislatively mandated 18-month pediatric-focused safety reviews overlap substantially with the Agency's routine post-marketing safety surveillance. FDA previously has shown that scheduled safety assessments provide only a small, incremental benefit over ongoing FDA pharmacovigilance activities.[39] FDA is currently conducting a similar analysis for the 18-month pediatric-focused safety review process and anticipates the same trends may be observed. Using a standardized time-based approach and schedule to review the safety of drugs with new pediatric use information

[39] Sekine S, Pinnow EE, Wu E, et al. 2016. Assessment of the Impact of Scheduled Post-marketing Safety Summary Analyses on Regulatory Actions. Clinical Pharmacology & Therapeutics. 100(1): 102-108

may not be the most effective and efficient approach for safety signal detection. For example, some products may undergo multiple pediatric labeling changes, thus prompting completion of multiple 18-month pediatric safety reviews for the same product. To ensure this process is optimized to identify new or serious pediatric safety concerns, FDA is evaluating strategies to develop a more modernized approach that involves a risk-based framework for pediatric pharmacovigilance. A modernized approach that considers each product's pharmacological characteristics and clinical use to inform the time, nature, and extent of safety review strategies could result in a more efficient safety signal detection. This approach would be similar to FDA's risk-based approach to pediatric medical device surveillance for PAC review and would allow for an aligned pediatric safety surveillance approach across all medical products.

1.4.1 Strategies for Optimal Utilization of PAC Expertise

FDA has considered approaches to ensure new or serious pediatric safety concerns are prioritized for discussion during PAC meetings because of the vast and ever-expanding pediatric-focused post-marketing safety surveillance and pharmacovigilance process. In addition, FDA has sought to more effectively access valuable PAC expertise for discussion of other scientific and clinical matters surrounding pediatric product development and use.

FDA implemented a new approach in 2016 for sharing information for PAC review that involves a risk-based process in which the post-marketing safety reviews for drugs and for medical devices approved under a Humanitarian Device Exemption (HDE) with labeling for pediatric use, that have a low safety risk are posted on FDA's website for review by the PAC. The reviews for drugs and HDE devices that are not low safety risk are presented at a PAC meeting in a standard or abbreviated format. By implementing this risk-based process, FDA has been able to discuss, during PAC meetings, additional topics surrounding pediatric product development and use. For example, FDA convened a PAC meeting to discuss serious behavior and mood-related changes in children with use of montelukast, a prescription drug for asthma and allergy management. Montelukast prescribing information already included warnings about mental health side effects, including suicidal thoughts or actions; however, review of additional information and discussion at the PAC meeting led to a re-evaluation of the benefits and risks of montelukast use. This re-evaluation prompted FDA (1) to require a Boxed Warning in the prescribing information of montelukast to describe serious mental health side effects and to recommend that montelukast should be reserved to treat allergic rhinitis in patients who are not treated effectively with or cannot tolerate other allergy medicines and (2) to require that a new Medication Guide be given to patients with each montelukast prescription.

FDA has brought additional topics to the PAC for discussion as well, including drug development considerations for testosterone replacement therapy in male adolescents for conditions associated with a deficiency or absence of endogenous testosterone resulting from structural or genetic etiologies; the role of pharmacogenomics in pediatric product development; the use of prescription opioid products containing hydrocodone or codeine

for the treatment of cough in pediatric patients; and an overview of the Center for Devices and Radiological Health's perspective on the current state of pediatric medical device development and potential strategies for supporting innovators and innovation to optimize health equity and safety for pediatric populations. In addition, FDA convened a meeting of the PAC and the Pediatric Ethics Subcommittee of the PAC to discuss a referral by an Institutional Review Board under 21 CFR 50.54 for a clinical investigation involving pediatric patients with Duchenne muscular dystrophy. At the meeting, the ethical considerations regarding the placement of a totally implantable central venous access device in patients receiving placebo during the 2-year study were discussed.

1.5 Guidance Documents

FDA has issued many guidance documents since the 2016 report to Congress related to implementation of the pediatric statutes and conduct of pediatric research, including the following draft and final guidance documents that are relevant to this report:

- *Final Guidance Document — FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act (May 2021)* [40]

  This guidance document addresses early planning for the pediatric evaluation of certain molecularly targeted cancer drugs. This guidance document finalized the draft guidance entitled "FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs" that was issued in December 2019 and finalized certain recommendations related to FDA's implementation of FDARA that were included in the January 2020 draft guidance document entitled "Pediatric Study Plans for Oncology Drugs: Questions and Answers."

- *Final Guidance Document — Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020)* [41]

  This guidance document provides recommendations regarding the submission of iPSPs and amendments to an iPSP. This guidance document was required under section 505B(e)(7) of the FD&C Act, added by section 506 of FDASIA. After issuing two draft guidance documents, in July 2013 and March 2016, FDA finalized this guidance document in July 2020 after incorporating comments received on those drafts. FDA continues the process of developing a proposed rule regarding iPSPs in accordance with section 505B(e)(7) of the FD&C Act.

[40] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec.

[41] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended.

- *Draft Guidance Document — General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products (August 2019)*[42]

  This guidance document was required under section 505(d)(2) of FDARA and addresses the clinical pharmacology considerations for any planned studies in neonatal populations. When final, this guidance document will represent the Agency's current thinking on this topic.

- *Revised Draft Guidance Document — Rare Pediatric Disease Priority Review Vouchers (July 2019)*[43]

  This revised draft guidance document provides information on the implementation of the rare pediatric disease priority review voucher program. When final, this guidance document will represent the Agency's current thinking on this topic.

- *Final Guidance Document — Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (March 2019)* [44]

  This guidance document provides recommendations to help ensure that information on the use of prescription drugs in pediatric patients (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labeling so the information is clear and accessible to healthcare providers.

- *Final Guidance Document — E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)*[45]

  Pediatric drug development has evolved since the publication of the original guidance document titled "E11 Clinical Investigation of Medicinal Products in the Pediatric Population" in 2000, requiring a renewed look at regulatory and scientific advances relevant to pediatric populations. The purpose of the addendum is to complement and provide clarification and current regulatory perspectives on topics in pediatric drug development.

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[42] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance.

[43] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf.

[44] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good.

[45] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population.

Impact of Pediatric Statutes: Beyond the Mandates

The pediatric statutes have stimulated scientific growth and innovation in the way drugs are developed for children and have spurred robust international collaboration to ensure pediatric studies are well designed to meet global regulatory standards so pediatric trials are not needlessly repeated.

1.6 Advancing Regulatory Science for Pediatric Drug Development

FDA recognizes that encouraging the timely completion of pediatric studies involves not only the earlier review of pediatric study plans but also, increasingly, cooperation of all pediatric stakeholders involved in the drug development process. In certain areas of pediatric therapeutics development, there are difficulties in identifying a feasible path forward. FDA has created opportunities for stakeholders to meet to discuss feasible development approaches in areas of unmet need and in areas in which development has been historically difficult. Since 2015, FDA has hosted numerous workshops to examine ways to optimize pediatric drug development and has published many peer-reviewed manuscripts describing scientific advances. Workshops and publications have focused on essential areas in modern pediatric drug development programs, including the use of complex innovative trial designs, new techniques in predicting and analyzing clinical pharmacology information in children, pediatric extrapolation of adult effectiveness data, consistent data collection and sharing, and application of biomarkers and surrogate endpoints to help better understand the drug's clinical benefit in children. Table 4 provides a listing of select pediatric-focused workshops convened by FDA.

These workshops have been extremely well received by external stakeholders and have led to specific meaningful changes that have created pathways to drug approval in pediatric populations. For example, after FDA and the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) convened, in 2017, the workshop "Drug Development in Pediatric Heart Failure: Extrapolation, Clinical Trial Design, and Endpoints," FDA reviewed the data necessary to support pediatric extrapolation based on a bridging biomarker for certain drugs that may be useful in the treatment of pediatric heart failure. Based on this review, FDA agreed that a bridging biomarker could be used to support the approval of Entresto (sacubitril/valsartan). In 2019, FDA approved Entresto for the "treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older"; Entresto is only the second drug approved for the treatment of pediatric heart failure.

Table 4: Select Pediatric Workshops and Meetings Hosted by FDA (2015-2020)

Workshop Title	Date
FDA's Advancing the Development of Pediatric Therapeutics (ADEPT) Workshops	
Pediatric Clinical Trial Endpoints for Rare Diseases With a Focus on Pediatric Patient Perspectives (ADEPT 6)	November 12, 2019
Advancing Pediatric Pharmacovigilance (ADEPT 5)	September 14, 2018
Application of "Big Data" to Pediatric Safety Studies (ADEPT 4)	September 18-19, 2017
Successes and Challenges of Performing Long-Term Pediatric Safety Studies (ADEPT 3)	April 13-14, 2016
FDA and M-CERSI Co-Hosted Workshops	
Accelerating Drug Development for Polyarticular Juvenile Idiopathic Arthritis (pJIA)	October 2, 2019
Pediatric Formulations	June 18-19, 2019
Pediatric Clinical Investigator Training	February 28, 2019
Pediatric Ontogeny: Ready for Incorporation into Modeling in Pediatric Drug Development?	May 16, 2019
Pediatric Inflammatory Bowel Disease	November 16, 2018
Drug Development in Pediatric Heart Failure: Extrapolation, Clinical Trial Design, and Endpoints	October 27, 2017
Pediatric Master Protocols	September 23, 2016
Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in Pediatrics	June 1, 2016
Use of Exposure Matching and Exposure-Response for Extrapolation of Efficacy in Pediatric Product Development	January 22, 2015
FDA and Duke-Margolis Center for Health Policy Co-Hosted Meetings	
Prospect of Direct Benefit in Pediatric Clinical Trials	March 29, 2019
Advancing Endpoint Development for Preterm Neonates With Pulmonary Morbidities	October 2, 2018
Additional Workshops Co-Organized by FDA	
Institute for Advanced Clinical Trials (I-ACT) for Children Workshops	
Remote Patient Monitoring and Children in the COVID-19 Pandemic: What's the Opportunity and What's the Impact	October 16, 2020
Developing Pediatric Treatments for COVID-19	May 28, 2020
Pediatric Research Innovation Forum: Inclusion of Adolescents in Adult Clinical Trials	October 15-16, 2019

I-ACT for Children and Duke Clinical Research Institute Workshops	
Youth Tobacco Cessation: Science and Treatment Strategies	May 15, 2019
DIA Workshops	
DIA Pediatric Drug Development Workshop	October 28-29, 2019

FDA also continues to engage in various outreach activities with external stakeholders to facilitate an understanding of regulatory issues and to share updates on FDA's pediatric-focused efforts. FDA gives numerous pediatric-related presentations each year to external stakeholders and collaborates in several consortia and working groups focused on advancing pediatric research and drug development. For example, FDA participates annually in a "Pediatric Liaison" meeting with BIO. Additionally, FDA has awarded several grants to support pediatric research and development. These grants help fund activities ranging from bench research to pediatric clinical trials, including efforts toward establishing a sustainable infrastructure to support timely and efficient pediatric clinical trials.

FDA also engages in regulatory science research to address challenges in pediatric drug development, especially the development of drugs targeting rare pediatric diseases. Over the past 5 years, FDA has published numerous papers in scientific journals that have advanced the development of pediatric therapeutics. A primary focus of FDA's regulatory science research in pediatrics has involved research questions to address specific challenges encountered in the development of drugs for pediatric patients, including extrapolating efficacy, designing innovative trials, developing clinical trial endpoints, assessing safety, and selecting appropriate doses. Additionally, FDA has created a large database of clinical trial data from over 1,600 pediatric clinical trials; this database has been used to address these challenges.

In addition, pediatric research collaborations have been developed using many effective mechanisms, including research collaboration agreements, memoranda of understanding, and Broad Agency Announcements. These pediatric-focused research efforts have helped advance the development of pediatric therapies in many areas.

1.7 Global Harmonization of Pediatric Research and Drug Development

FDA continues to engage with international stakeholders to help ensure children around the world participate in clinical trials that are well designed to meet international regulatory standards. FDA's international collaborative efforts have helped improve therapeutics development globally by increasing the efficiency of clinical trial enrollment for small populations, by expanding information and knowledge-sharing with global experts, and by harmonizing clinical trial designs to help ensure pediatric clinical trials are not needlessly repeated. These efforts have helped (1) improve what is known about

therapies for pediatric populations and (2) convey this knowledge in prescribing information.

1.7.1 International Pediatric Cluster Conference Calls

FDA's Office of Pediatric Therapeutics continues to coordinate monthly Pediatric Cluster conference calls with global regulators in Europe, Japan, Canada, and Australia. From the Pediatric Cluster's inception in 2007 to June 2020, the Pediatric Cluster has discussed 570 products proposed for pediatric study. The most common clinical trial issues discussed have included the scope of pediatric drug development, safety, dosing, types of clinical trials, and trial design. In 2012, FDA and the European Medicines Agency (EMA) developed a process for sharing brief Common Commentary documents for certain topics discussed at the Pediatric Cluster. These documents convey non-binding high-level comments from regulators to pharmaceutical industry sponsors. From July 2012 to June 2020, FDA issued 45 Common Commentaries spanning most therapeutic areas.

The Pediatric Cluster has been an important forum for collaboration with international regulatory agencies regarding pediatric cancer drug development, including attempting to align decision-making and advice to sponsors, particularly since implementation of the RACE for Children Act. From August 2019 through June 2020, 14 new oncology products have been the subject of high-level scientific discussions during 16 Pediatric Cluster calls, which have attempted to provide coordinated advice to sponsors to facilitate global drug development. During this time frame, three Common Commentaries regarding three cancer drugs have been issued. In addition, in a publicly posted general topic Common Commentary, FDA and EMA jointly discussed the simultaneous submission of oncology iPSPs and Paediatric Investigation Plans (PIPs) to FDA and EMA, respectively, to further facilitate this global coordination.[46]

1.7.2 Important Efforts to Encourage International Collaboration

Highlighted below are several activities and initiatives FDA has undertaken to encourage international collaboration in pediatric drug development:

- FDA participates with EMA in the ACCELERATE Platform, an international, multi-stakeholder group focused on accelerating the development of new therapies for children with cancer. Given the rarity of cancer in children generally; in, more importantly, specific histologic types; and now in, even more significantly, genomically categorized subtypes of rare cancers, international studies and coordinated global development programs are particularly important.

- FDA serves on EMA's initiative for the European Network of Paediatric Research's working group on international cooperation, which is tasked with

[46] https://www.fda.gov/media/147197/download.

comparing the pre-market regulatory and ethical requirements for the conduct of pediatric clinical trials and for participation as a clinical trial site across the following five jurisdictions: United States, European Union, Canada, Japan, and Australia.

- FDA participates on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's E11A Expert Working Group, which is currently drafting a guideline on pediatric extrapolation.

- FDA collaborates with Japan's Pharmaceuticals and Medical Devices Agency Asia Training Center to host an annual international pediatric review workshop designed to further disseminate information on advances in scientific and technical knowledge for pediatric drug development. Over the 3 years since the joint workshop began, 81 international regulators from 21 countries have participated, as well as the World Health Organization (WHO).

- FDA is a member of the WHO Paediatric Regulatory Network, which serves as a forum for enabling dialogue and fostering development of international consensus on effective regulatory approaches for increasing the availability of pediatric medical products around the world.

- FDA serves on a working group with the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard which seeks to recommend harmonized approaches and tools to regulate and facilitate pediatric research worldwide.

Stakeholder Input

In accordance with section 508 of FDASIA, FDA held a public pediatric stakeholder meeting on November 21, 2019, to obtain input from patient groups, consumer groups, regulated industry, academia, and other interested parties on any recommendations or information relevant to this BPCA and PREA report to Congress. The meeting information, materials, and webcast are available on FDA's website.[47] In response to FDA's October 2019 *Federal Register* request for comments and announcement of a November 2019 meeting,[48] stakeholders from the pharmaceutical industry and advocacy organizations provided input on BPCA and PREA. Stakeholders generally supported the continued implementation of BPCA and PREA in the development and labeling of drugs for pediatric populations. In this section, several key themes that emerged from the stakeholder input for this meeting are described.

[47] https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/pediatric-stakeholder-meeting-public-meeting-11212019-11212019#event-information.

[48] 84 FR 57451 (Oct. 25, 2019).

1.8 Need for Issuing or Updating FDA's Guidance Documents

Stakeholders generally agreed that FDA needs to issue guidance documents on key pediatric issues as well as update and/or finalize existing guidances. One organization, BIO, noted that the draft guidance document titled "How to Comply with the Pediatric Research Equity Act," which published in 2005, had not yet been finalized.[49] BIO also asserted that the 1999 revised draft guidance document on complying with BPCA was never finalized and has since been withdrawn and replaced with a Frequently Asked Questions document, on which stakeholders never had an opportunity to comment.[50]

PhRMA expressed concern with "the delay" in publishing a final guidance document on FDA's implementation of the FDARA amendments to PREA regarding molecularly targeted cancer drugs.[51] PhRMA recommended that FDA provide "appropriate regulatory flexibility" for applications that will be submitted shortly after the FDARA implementation date.[52]

In addition, stakeholders recommended modernizing the guidance documents on BPCA and PREA to maintain a balance between the two statutes, and to provide guidance on the use of innovative approaches in pediatric drug development, the use of external data (historical clinical trial data or natural history real-world data) in single arm trials, and the use of extrapolation in pediatric programs. An early alignment on comprehensive pediatric drug development plans that encompasses studies under both PREA and BPCA was encouraged by stakeholders to allow them to initiate studies as soon as possible.

1.9 Suggestions on Policy Implementation

FDA's approach to WRs was noted, by stakeholders, as a concern. Specifically, PhRMA expressed concern with WRs for "lengthy clinical trials that cannot be completed in time to receive meaningful pediatric exclusivity"; with "overly broad" WRs, including "studies that may not be feasible or that are exploratory in nature"; and with perceived "inconsistent FDA input over time."[53] Similarly, BIO noted that "requesting numerous broad, exploratory pediatric studies in Written Requests lessens the effectiveness of

[49] BIO's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[50] Id.

[51] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[52] Id.

[53] Id.

BPCA as an incentive, because a Sponsor may be unable to complete the studies in time to earn the pediatric exclusivity incentive."[54]

PhRMA also expressed concern over the potential abandonment of the orphan-drug exemption in PREA. PhRMA stated that doing so "would undermine the incentives for innovators to pursue orphan-drug development and introduce feasibility challenges for satisfying the resulting pediatric study obligations."[55] PhRMA commented that removing the orphan-drug exemption would "disturb the balance between PREA and BPCA," suggesting that FDA can utilize the BPCA process for obtaining studies of orphan drugs.[56] PhRMA also mentioned (1) the recent changes under FDARA that narrowed the exemption in section 505B(k) so that it does not apply for certain cancer drugs and (2) FDA's issuance of a guidance document that clarified its policy on orphan designation for pediatric subpopulations.[57] PhRMA suggested that

> no new changes to PREA should be considered before the impact of the latest changes is assessed and before the Government Accountability Office (GAO) conducts a study and publishes a report on the effectiveness of requiring assessments and investigations under section 505B for the development of drugs for pediatric cancer indications.[58]

Conversely, in a presentation on behalf of the AAP, Bridgette Jones, MD, highlighted that "orphan drug approvals are increasing, and therefore, so are the number of new drugs that are exempt from pediatric study requirements" and recommended that FDA "act quickly to remove the PREA orphan exemption."[59] In addition, Katie Coester, MPP, from the Elizabeth Glaser Pediatric AIDS Foundation noted that "lack of PREA application to orphan drugs impacts numerous pediatric diseases and conditions, including common comorbidities affecting children living with HIV" and asserted that "PREA should be applied to orphan drugs."[60]

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[54] BIO's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[55] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[56] Id.

[57] See https://www.fda.gov/media/109496/download.

[58] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[59] See https://www.fda.gov/media/132831/download.

[60] See https://www.fda.gov/media/132827/download.

1.10 Importance of International Alignment on Pediatric Studies

Stakeholders urged FDA to continue to work with EMA and its international counterparts to harmonize pediatric testing requirements and provide sponsors with greater transparency on the coordination between international bodies. PhRMA, in particular, noted the significant challenges of pediatric drug development when different regulators provide inconsistent advice, which PhRMA suggests is "further complicated by the fact that discussions with EMA and FDA about pediatric drug development plans occur at different development stages."[61]

Stakeholders noted that additional discussions that are not currently addressed via the Pediatric Cluster and associated Common Commentary process are needed to better support timely pediatric access to medicines through aligned scientific advice from global health authorities. They suggested that a forum for timely and aligned pediatric testing advice from FDA and EMA would significantly facilitate efficient pediatric drug development.

1.11 Necessary Advances in Pediatric Product Development and Use

Stakeholders raised concerns regarding the challenges associated with pediatric drug development for neonates, including the lack of scientific understanding regarding endpoints and biomarkers and the lack of natural history information for diseases in the neonatal population. These stakeholders suggested that (1) FDA hold stakeholder meetings to discuss mechanisms for addressing these challenges, ensure that (2) FDA's neonatologists engage in discussion with FDA's review divisions and sponsors, and (3) FDA seek additional external expertise on the development of drugs for neonates as needed.

One stakeholder commented on the struggles with treating a range of conditions, including rare disorders, using medication and devices that lack a pediatric label or indication. This stakeholder suggested creating a National Pediatric Safety Registry and requested FDA's assistance in the collection of data that could serve to facilitate pediatric labeling while also providing patients, parents, and providers with more helpful safety data.[62]

In addition, this stakeholder expressed the need for conducting pharmacokinetic/pharmacodynamic evaluations, developing pediatric friendly drug formulations, limiting placebo control study designs, and allowing the extrapolation of

[61] PhRMA's response to FDA's *Federal Register* notice (docket FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[62] North American Society for Pediatric Gastroenterology, Hepatology and Nutrition's (NASPGHAN's) response to FDA's *Federal Register* notice (FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

efficacy from adult studies. This stakeholder also encouraged the enrollment of late adolescents in adult designed studies, the creation of pediatric-focused clinical outcome measures, and a requirement for a pediatric needs assessment early in development.[63]

Finally, another stakeholder suggested that FDA "maximize the use of biomarkers, including biomarkers for accelerated approval based on reasonable links between the proposed biomarker and the underlying condition to be treated."[64] This stakeholder suggested that "to the extent that biomarkers can be used as reasonable bases for expectation of improved clinical and welfare outcomes, they should be incorporated in the FDA structured benefit risk approach."[65]

Coronavirus Disease 2019 (COVID-19) Pandemic

FDA has been working tirelessly to address the need for therapeutic and vaccine development to address the COVID-19 pandemic, including the needs of children. A rapid global alignment on the development of pediatric therapeutics and vaccines that address the needs of children while not slowing access to adult populations has been supported by frequent and productive activities both internal and external to FDA. For example, of the 32 Pediatric Cluster conference calls hosted by FDA between January 2020 and October 2021, 17 calls included discussions related to pediatric development programs for COVID-19 therapies. These discussions resulted in the issuance of four Common Commentaries for COVID-19 products and one general Common Commentary for the submission of iPSPs and PIPs for products for the prevention and treatment of COVID-19. Early in the pandemic (May 2020), FDA co-moderated a virtual workshop held by I-ACT for Children to share information and discuss therapeutic research and innovative approaches to obtain data necessary to advance COVID-19 therapeutics for children. In June 2020, NIH announced funding for a study to evaluate drugs prescribed to children with COVID-19 through the NICHD-funded PTN.[66]

Internally at FDA, the CDER and CBER review divisions have worked with the PeRC to achieve agreed-upon iPSPs for COVID-19 therapies and vaccines. Between January 2020 and October 2021, the PeRC reviewed 49 iPSPs relevant to COVID-19 products that are subject to PREA. Importantly, Veklury (remdesivir), the first drug approved by FDA to treat COVID-19, included, as part of the original approval, pediatric patients 12 years and older who weigh at least 40 kilograms. Further, Comirnaty (an mRNA

[63] Id.

[64] Kermit Kubitz's response to FDA's *Federal Register* notice (FDA-2019-N-4560): 84 FR 57451 (Oct. 25, 2019).

[65] Id.

[66] See https://www.nichd.nih.gov/newsroom/news/061020-COVID-19-BPCA.

COVID-19 vaccine), the first FDA-approved COVID-19 vaccine, also included pediatric patients 16 years and older as part of the original approval.

In addition to moving rapidly to address the COVID-19 pandemic in children, FDA has continued work with drug developers who have experienced delays in non-COVID-19 drug development due to the pandemic. During the time period covered by this report, in recognition of the need for sponsors to adjust study timelines due to disruptions caused by the pandemic, FDA has granted a relatively high percentage of PREA deferral extension requests associated with the impacts of the COVID-19 pandemic on clinical trial operations (see Table 2).

Program Improvements for Continued Advancement of Product Development in Children

While BPCA and PREA have been instrumental in improving pediatric research, product development, and labeling, FDA continues to evaluate strategies for further improvements, which are discussed in this section.

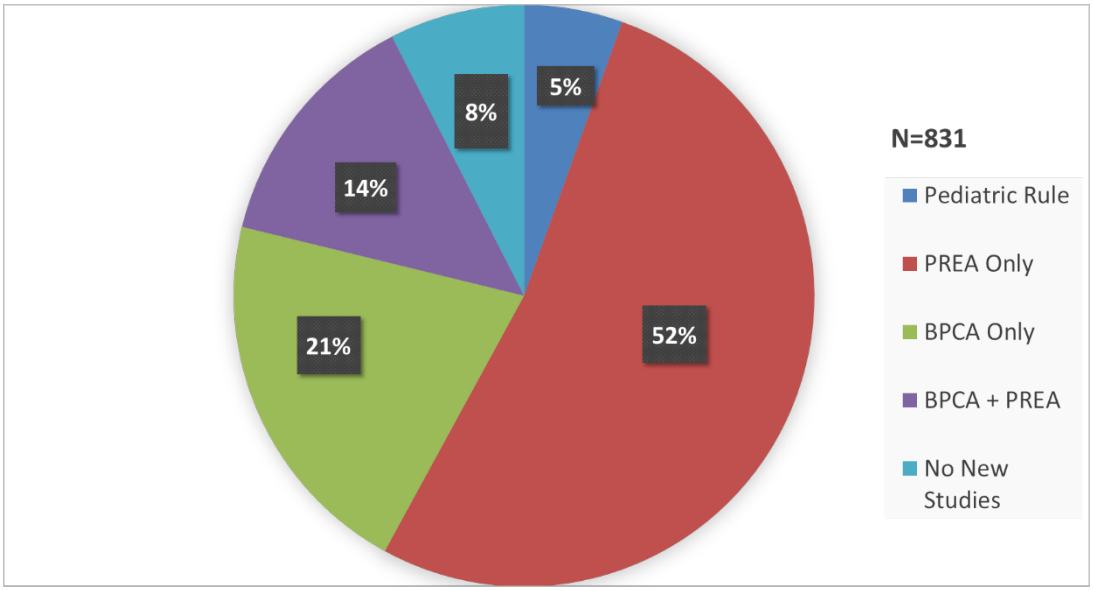
1.12 Removal of the Orphan Exemption Under PREA

As discussed in section 1.2.1, there has been some progress in the development of therapeutics to treat pediatric cancers. Some of this success can be attributed to the passage of section 504 of FDARA which, among other things, includes the removal of the orphan exemption under PREA for certain drugs that are directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer. Furthermore, as described in section 1.2.2, there is a public health need for additional pediatric information in labeling for over one-third of approved orphan indications that are relevant to the pediatric population.[67]

FDA strongly believes that requirements under PREA have driven, not impeded, the development of therapies for children. The majority of pediatric labeling changes have resulted from studies conducted under PREA, not BPCA (see Figure 3). These data suggest that removal of the orphan exemption under PREA would improve the availability of approved therapies for pediatric patients with rare diseases.

[67] See https://www.fda.gov/media/130060/download.

Figure 3: Pediatric Labeling Changes From 1998-2019



One concern expressed by industry is that the removal of the orphan exemption may change the financial calculus for the development of rare pediatric disease treatments. FDA acknowledges this concern but notes that other incentive programs are available to encourage the development of therapies to treat rare pediatric diseases that are not precluded by the elimination of the orphan exemption under PREA. Furthermore, FDA has granted waivers under PREA, as appropriate, when a rare disease that is the subject of an application does not affect children. Additionally, pediatric experts on the PeRC are able to consistently review development programs for pediatric rare diseases as presented in iPSPs and provide advice that would potentially improve the speed and efficiency of drug development in rare pediatric diseases.

FDA is concerned that the orphan exemption under PREA may be limiting the availability of evidence-based data for drugs for all relevant pediatric age groups with rare diseases and is evaluating potential strategies to address this concern.

1.13 Optimization of Post-Marketing Surveillance of Pediatric Medical Products

1.13.1 Modernize Pediatric Pharmacovigilance

Using a standardized time-based approach to review the safety of drugs with new pediatric use information may not be the most effective or efficient approach for safety signal detection. The 18-month pediatric-focused safety reviews required by sections 505A(*l*) and 505B(i) of the FD&C Act overlap substantially with the Agency's established post-marketing safety surveillance through FAERS. Risk-based approaches,

as opposed to time-based approaches, are now being implemented by FDA as part of its overall pharmacovigilance strategies.

FDA is evaluating ways to advance pediatric pharmacovigilance using similar modern risk-based approaches to help ensure pediatric pharmacovigilance is optimized to identify new or serious pediatric safety concerns.

1.13.2 Establish Periodic Review of HDEs

The Pediatric Medical Device Safety and Improvement Act of 2007 added, at section 520(m)(6)(A) of the FD&C Act, an exemption from the restriction on profit-making for certain HDE devices that are approved and labeled for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or a pediatric subpopulation. Section 520(m)(8) of the FD&C Act requires these devices to undergo an annual review by the PAC of the appropriateness of the HDE for the pediatric population for which the device was approved. This legislative requirement for an annual review by the PAC overlaps with FDA's review of annual reports required in approval orders for HDEs under 21 CFR 814.126(b).

To ensure that post-marketing HDE surveillance for these devices is optimized to focus the PAC's review on new or serious pediatric safety concerns, as well as on scientific and clinical matters surrounding pediatric product development and use, FDA is evaluating ways to align the PAC's annual review to ensure the appropriateness of the HDE for the pediatric population for which the device was approved with the currently required periodic review for adverse event reports.

Conclusion

Prior to passage of the first incentive provisions for the completion of pediatric studies under FDAMA in 1997, more than 80 percent of approved drugs had no pediatric-specific labeling information. Since then, over 900 drugs have been labeled with pediatric information because of legislative initiatives that have required or incentivized pharmaceutical industry sponsors to conduct pediatric studies. FDA now has more than 2 decades of experience implementing these legislative initiatives and reviewing data obtained from pediatric studies. The knowledge gained has affirmed the importance of obtaining information to support pediatric use. The safety, effectiveness, and dosing of drugs may differ between adults and children, and understanding these differences is essential for healthcare providers to make evidence-based decisions about treating pediatric patients.

An important shift in the regulatory landscape for pediatric cancer drug development has occurred with implementation of FDARA. Early evidence suggests that the RACE for Children Act has had a favorable impact on the timely consideration and initiation of studies of appropriate molecularly targeted cancer drugs that would previously have not

been required and that would historically have gone unstudied in children. While the pediatric statutes have led to important progress in labeling products for pediatric use, unique challenges persist regarding the conduct of studies and labeling of products for rare pediatric diseases and for neonates.

In addition to ensuring therapeutics are developed for all relevant pediatric populations, achieving shorter timelines from FDA's initial drug approval to the incorporation of pediatric use information into labeling remains a key objective for FDA. The Agency has been working diligently to ensure proposed pediatric study timelines are reasonable and to provide timely responses and meaningful advice to pharmaceutical industry sponsors regarding pediatric drug development plans. As described in this report, a delay of approximately 6 years remains between the original approval of a drug and incorporation of pediatric use information in labeling. Whether the earlier issuance of WRs and an earlier discussion of pediatric study plans will have a positive impact remains to be seen. In addition to earlier pediatric study planning, achieving shorter timelines will involve more efficient clinical trial operations and improvements in pediatric clinical trial infrastructure. Importantly, greater efficiency in pediatric drug development also involves continued progress in the regulatory science to support pediatric drug development programs. Addressing pediatric-specific study design issues, including endpoints, biomarkers, and exposure-response relationships, and incorporating into adult drug development programs assessments that help to tackle these issues is essential.

Since the last BPCA and PREA report to Congress, FDA has made substantial efforts to address scientific and regulatory issues unique to the development of therapeutics for children by hosting workshops to address pediatric drug development needs, conducting important regulatory research, issuing guidance documents related to pediatric therapeutics development, and collaborating with numerous national and international consortia and organizations to gain a consensus on approaches for pediatric therapeutics development. The Agency also continues to collaborate with international regulatory authorities to help assure pediatric trials are well designed to meet international regulatory standards.

The 409I program has played a critical role in obtaining information about pediatric use for off-patent drugs. Since the last report to Congress, the number of approved labeling changes that have occurred under this program has more than tripled. Importantly, three of the 22 drugs updated to include dosing, safety, and/or efficacy information in labeling for neonates resulted from studies conducted under the 409I program. Further, under this program, NIH continues to identify and prioritize drugs that need additional study in pediatric patients, disseminate information to researchers and the public, and serve as a source of knowledge and training for the scientific community.

FDA believes that these efforts over the past 5 years have continued to advance the important progress that has been made in increasing the availability of approved drugs for children. FDA is committed to continuing its work with all stakeholders over the next 5 years and beyond.

Appendix 1: Pediatric Labeling Changes Under BPCA and PREA Since the 2016 Report to Congress (Covering July 1, 2015, Through June 30, 2020)

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
6/26/2020	Lialda delayed-release tablets	Mesalamine	Mildly to moderately active ulcerative colitis	PREA Only
6/19/2020	Sivextro tablet	tedizolid phosphate	Acute bacterial skin and skin structure infections (ABSSSI)	PREA Only
6/12/2020	Gardasil 9	Human Papillomavirus 9-valent Vaccine, Recombinant	Prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine	PREA Only
6/12/2020	Tivicay tablets	dolutegravir	Human Immunodeficiency Virus-1 (HIV-1) infection	PREA + BPCA
6/12/2020	Tivicay PD tablets for oral suspension	dolutegravir	HIV-1 infection	PREA + BPCA
5/26/2020	Dupixent injection	dupilumab	Moderate-to-severe atopic dermatitis (AD)	PREA Only
5/26/2020	VESIcare LS oral suspension	solifenacin succinate	Neurogenic detrusor overactivity (NDO)	PREA + BPCA
5/26/2020	Zosyn injection	piperacillin/tazobactam	Nosocomial pneumonia	PREA Only
5/22/2020	Phexxi vaginal gel	lactic acid/citric acid/potassium bitartrate	Prevention of pregnancy	PREA Only
5/1/2020	Fensolvi injectable	leuprolide acetate	Central precocious puberty (CPP)	PREA Only
4/26/2020	Jublia topical solution	efinaconazole	Onychomycosis of the toenail	PREA Only
4/23/2020	MenQuadfi	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine	Prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y	PREA Only
4/20/2020	Cymbalta	duloxetine	Fibromyalgia	PREA Only
4/1/2020	Sevenfact	Coagulation factor VIIa (recombinant)-jncw	Bleeding episodes occurring in patients with hemophilia A or B with inhibitors	PREA Only
3/26/2020	Taltz injection	ixekizumab	Moderate-to-severe plaque psoriasis	PREA Only
3/23/2020	Eucrisa ointment	crisaborole	Mild to moderate atopic dermatitis	PREA + BPCA
3/19/2020	Epclusa	sofosbuvir/velpatasvir	Chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/4/2020	Cleocin Phosphate	clindamycin injection; clindamycin injection in dextrose	Clindamycin dosing and body weight	409I(BPCA)
3/4/2020	Acticlate; Acticlate Cap	doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
3/2/2020	Cafcit Injection	caffeine citrate	Apnea of prematurity	409I(BPCA)
2/12/2020	Doryx; Doryx MPC	doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
1/31/2020	Audenz	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted	Active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine	PREA Only
1/31/2020	Palforzia	Peanut (Arachis hypogaea) Allergen Powder-dnfp	Mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut	PREA Only
1/31/2020	Viibryd	vilazodone hydrochloride	Major depressive disorder (MDD)	PREA + BPCA
1/28/2020	Agriflu	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine	PREA Only
1/24/2020	Dificid	fidaxomicin	Clostridioides difficile-associated diarrhea (CDAD)	BPCA Only
12/20/2019	Vibramycin; Vibra-Tabs	doxycycline monohydrate; doxycycline hyclate; doxycycline calcium; doxycycline hyclate	Doxycycline pharmacokinetics	409I(BPCA)
12/20/2019	Mycamine	micafungin	Candidemia, acute disseminated candidiasis, Candida peritonitis and abscesses without meningoencephalitis and/or ocular dissemination	PREA Only
12/19/2019	Conjupri	levamlodipine	Hypertension	PREA Only
12/19/2019	Fiasp	insulin aspart	Diabetes mellitus	PREA Only
12/18/2019	Aralzo	tazarotene	Acne vulgaris	PREA Only
12/6/2019	Abraxane	paclitaxel	Recurrent or refractory pediatric solid tumors	BPCA Only
12/4/2019	Latuda	lurasidone hydrochloride	Growth	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
11/15/2019	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus infection in patients with severe renal impairment including patients with end stage renal disease on dialysis	PREA Only
11/13/2019	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult and pediatric patients with suboptimal echocardiograms	PREA Only
11/5/2019	Sorilux	calcipotriene	Plaque psoriasis of the scalp and body	PREA Only
10/25/2019	Opana	oxymorphone HCl	Postoperative pain	PREA Only
10/18/2019	Amzeeq	minocycline	Inflammatory lesions of non-nodular moderate to severe acne vulgaris	PREA Only
10/18/2019	Botox	onabotulinumtoxinA	Lower limb spasticity	PREA Only
10/18/2019	Ultomiris	ravulizumab-cwvz	Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA)	PREA Only
10/10/2019	Wilate	von Willebrand Factor/Coagulation Factor VIII Complex (Human)	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
10/4/2019	Aklief	trifarotene	Acne vulgaris	PREA Only
10/4/2019	Quzyttir	cetirizine hydrochloride	Acute urticaria	PREA Only
10/3/2019	Tybost	cobicistat	HIV-1 infection	PREA + BPCA
10/3/2019	Descovy	emtricitabine/tenofovir alafenamide	Pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection	PREA Only
10/1/2019	Entresto	sacubitril/valsartan	Symptomatic heart failure with systemic left ventricular systolic dysfunction	PREA + BPCA
9/26/2019	Mavyret	glecaprevir/pibrentasvir	Chronic hepatitis C virus infection (HCV)	PREA Only
9/25/2019	Dysport	abobotulinumtoxinA	Upper limb spasticity	PREA Only
9/13/2019	Teflaro Injection	ceftaroline fosamil	Acute Bacterial Skin and Skin Structure Infections (ABSSSI)	PREA Only
9/13/2019	Mydayis	mixed salts of a single-entity amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA + BPCA
9/12/2019	Nucala	mepolizumab	Severe asthma with an eosinophilic phenotype	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/10/2019	Gvoke	glucagon	Severe hypoglycemia in patients with diabetes	PREA Only
9/10/2019	Aczone Gel	dapsone	Acne vulgaris	PREA Only
8/29/2019	Riomet ER	metformin hydrochloride	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus	PREA Only
8/28/2019	Harvoni Oral Pellets	ledipasvir/sofosbuvir	Chronic hepatitis C virus	PREA + BPCA
8/28/2019	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus (HCV)	PREA + BPCA
8/28/2019	Sovaldi	sofosbuvir	Chronic hepatitis C virus	PREA + BPCA
8/22/2019	Tybost	cobicistat	HIV-1 infection	PREA + BPCA
8/15/2019	Rozlytrek	entrectinib	Solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation that are metastatic or where surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy	BPCA Only
8/12/2019	Dulera Inhalation Aerosol	formoterol fumarate/mometasone furoate	Asthma	PREA + BPCA
8/12/2019	Asmanex HFA	mometasone furoate	Asthma	PREA Only
8/8/2019	Clenpiq	sodium picosulfate/magnesium oxide/anhydrous citric acid	Cleansing of the colon as a preparation for colonoscopy	PREA Only
7/30/2019	Enstilar Foam	calcipotriene/betamethasone dipropionate	Plaque psoriasis of the scalp and body	PREA + BPCA
7/25/2019	Taclonex	calcipotriene/betamethasone dipropionate	Plaque psoriasis of the scalp and body	PREA Only
7/24/2019	Baqsimi nasal powder	glucagon	Severe hypoglycemia in patients with diabetes	PREA Only
7/8/2019	Katerzia oral suspension	amlodipine benzoate	Hypertension	PREA Only
6/20/2019	Botox	onabotulinumtoxinA	Upper limb spasticity	PREA Only
6/18/2019	Biktarvy	bictegravir/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
6/17/2019	Victoza	liraglutide	Type 2 diabetes mellitus	PREA + BPCA
6/14/2019	Aptensio XR	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/6/2019	Nucala	mepolizumab	Severe asthma	PREA Only
5/23/2019	Lyrica	pregabalin	Partial-onset seizures (POS)	PREA + BPCA
5/23/2019	Slynd	drospirenone	Prevention of pregnancy	PREA Only
5/16/2019	Gattex	teduglutide	Short Bowel Syndrome (SBS)	PREA Only
5/16/2019	Fragmin	dalteparin sodium	Symptomatic venous thromboembolism (VTE) to reduce recurrence	PREA Only
5/16/2019	Livalo	pitavastatin	Heterozygous familial hypercholesterolemia (HeFH)	PREA Only
5/7/2019	Sutent	sunitinib malate	Refractory solid tumors	BPCA Only
5/6/2019	Sorilux	calcipotriene	Plaque psoriasis of the scalp and body	PREA Only
5/1/2019	Dengvaxia	Dengue Tetravalent Vaccine, Live	Prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4	PREA Only
4/30/2019	Mavyret	glecaprevir/pibrentasvir	Chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)	PREA + BPCA
4/26/2019	Benlysta	belimumab	Active, antibody systemic lupus erythematosus (SLE)	PREA Only
4/22/2019	Corlanor Oral Solution	ivabradine	Symptomatic heart failure due to dilated cardiomyopathy (DCM)	BPCA Only
4/18/2019	Opdivo	nivolumab	Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC)	PREA Only
4/3/2019	Welchol Chewable Bar	colesevelam HCl	Heterozygous familial hypercholesterolemia	PREA Only
3/29/2019	Octaplas	Pooled Plasma (Human), Solvent/Detergent Treated	Indicated (1) as replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease or undergoing cardiac surgery and liver transplantation and (2) plasma exchange in patients with thrombotic thrombocytopenic purpura	PREA Only
3/21/2019	Doptelet	avatrombopag	Juvenile animal toxicity	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/14/2019	Avycaz	ceftazidime/avibactam	Complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI)	PREA Only
3/11/2019	Dupixent	dupilumab	Moderate-to-severe atopic dermatitis	PREA Only
3/1/2019	Flector Topical System	diclofenac epolamine	Acute pain due to minor strains, sprains, and contusions	PREA Only
2/27/2019	Adhansia XR	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
2/22/2019	Chantix	varenicline	Aid to smoking cessation	PREA + BPCA
2/19/2019	Esperoct	Antihemophilic Factor (Recombinant), GlycoPEGylated-exei	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
1/29/2019	Vfend	voriconazole	(1) Invasive aspergillosis (2) Candidemia and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds (3) Esophageal candidiasis (4) Serious infections caused by Scedosporium apiospermum and Fusarium species	PREA + BPCA
1/25/2019	Zovirax	acyclovir	Neonatal herpes virus infection (HSV)	409I(BPCA)
12/21/2018	Vaxelis	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus	PREA Only
12/21/2018	Sprycel	dasatinib	Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL)	BPCA Only
12/12/2018	Exjade; Jadenu	deferasirox	Transfusion-dependent anemia requiring chelation therapy due to iron overload	BPCA Only
12/11/2018	Viread	tenofovir disoproxil fumarate	Chronic hepatitis B (CHB)	PREA + BPCA
11/29/2018	Astagraf XL	tacrolimus	Prophylaxis of organ rejection in kidney transplant patients, in combination with other immunosuppressants	PREA Only
11/21/2018	Spy Agent Green	Indocyanine green	Visualization of vessels, blood flow and tissue perfusion before, during, and after various surgical procedures, including	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
			minimally invasive surgeries and visualization of extrahepatic biliary ducts	
11/9/2018	Oralair	Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product	PREA Only
11/7/2018	Primatene Mist	epinephrine	Mild symptoms of intermittent asthma	PREA Only
10/26/2018	Xyrem	sodium oxybate	Cataplexy or excessive daytime sleepiness in patients with narcolepsy	BPCA Only
10/24/2018	Xofluza	baloxavir marboxil	Acute uncomplicated influenza	PREA Only
10/19/2018	Dupixent	dupilumab	Moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	PREA Only
10/4/2018	Lithium	lithium	Acute manic or mixed episodes of bipolar I disorder and maintenance monotherapy of bipolar I disorder	409I(BPCA)
10/4/2018	Afluria; Afluria Quadrivalent	Influenza Vaccine	Active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
10/1/2018	Seysara	sarecycline	Inflammatory lesions of non-nodular moderate to severe acne vulgaris	PREA Only
9/28/2018	Xolair	omalizumab	Moderate to severe persistent asthma	PREA Only
9/27/2018	Promacta	eltrombopag	Chronic immune (idiopathic) thrombocytopenia (ITP)	PREA Only
9/27/2018	Fycompa	perampanel	Partial onset seizures (POS), with or without secondarily generalized seizures	PREA + BPCA
9/12/2018	Botox	onabotulinumtoxinA	Prevention of headaches in patients with chronic migraine	PREA Only
9/12/2018	Actemra	tocilizumab	Systemic juvenile idiopathic arthritis	PREA + BPCA
8/29/2018	Jivi	Antihemophilic Factor (Recombinant), PEGylated-aucl	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
8/23/2018	Altreno lotion	tretinoin	Acne vulgaris	PREA Only
8/15/2018	Prepopik for oral solution	sodium picosulfate/magnesium	Cleansing of the colon as a preparation for colonoscopy	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
		oxide/anhydrous citric acid		
8/10/2018	Annovera	segesterone acetate/ethinyl estradiol	Prevention of pregnancy	PREA Only
8/8/2018	Jornay PM	methylphenidate	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
8/3/2018	Nuvessa	metronidazole	Bacterial vaginosis	PREA Only
8/2/2018	Panzyga	Immune Globulin Intravenous, human-ifas	Primary humoral immunodeficiency (PI) and 2) chronic immune thrombocytopenic purpura (ITP)	PREA Only
7/31/2018	Granix injection	tbo-filgrastim	Severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia	PREA + BPCA
7/30/2018	Kerydin topical solution	tavaborole	Onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes	PREA + BPCA
7/20/2018	Lotemax	loteprednol etabonate ophthalmic gel	Postoperative inflammation and pain following ocular surgery	PREA + BPCA
7/16/2018	Intelence	etravirine	HIV-1 infection	PREA + BPCA
6/29/2018	Yondelis injection	trabectedin	Pediatric histotypes of sarcoma	BPCA Only
6/28/2018	Qbrexza cloth	glycopyrronium	Primary axillary hyperhidrosis	PREA Only
6/15/2018	LymePak	doxycycline hyclate	Early Lyme disease due to Borrelia burgdorferi	PREA Only
6/7/2018	Mircera	Methoxy Polyethylene Glycol-Epoetin Beta	Anemia associated with chronic kidney disease (CKD) in patients on hemodialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA	PREA Only
5/17/2018	Arnuity Ellipta	fluticasone furoate	Asthma	PREA Only
5/11/2018	Gilenya	fingolimod	Relapsing forms of multiple sclerosis	PREA + BPCA
5/11/2018	Actemra	tocilizumab	Polyarticular juvenile idiopathic arthritis (PJIA) and Systemic Juvenile Idiopathic Arthritis (SJIA)	PREA + BPCA
5/10/2018	Briviact	brivaracetam	Partial onset seizures (POS)	PREA Only
5/3/2018	Lyrica	pregabalin	Partial onset seizures (POS)	PREA + BPCA
4/30/2018	Amitiza	lubiprostone	Pediatric Functional Constipation (PFC)	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
4/3/2018	Emend Injection	fosaprepitant	Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	PREA + BPCA
3/22/2018	Symfi	efavirenz/lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
3/5/2018	Latuda	lurasidone hydrochloride	Major depressive episodes associated with bipolar I disorder	PREA Only
3/2/2018	Otiprio	ciprofloxacin	Acute otitis externa due to Pseudomonas aeruginosa and Staphylococcus aureus	PREA Only
2/28/2018	Cimduo	lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
2/20/2018	Luzu cream	luliconazole	Tinea pedis and tinea cruris	PREA Only
2/15/2018	Cialis	tadalafil	Duchenne muscular dystrophy	BPCA Only
2/15/2018	Ampicillin Injection	ampicillin	Neonatal dosing for meningitis and septicemia	409I(BPCA)
2/6/2018	Pristiq	desvenlafaxine	Major Depressive Disorder (MDD)	PREA + BPCA
2/5/2018	Symfi Lo	efavirenz/lamivudine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
1/11/2018	Fluarix Quadrivalent	Influenza Vaccine	Active immunization of persons 6 months and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
12/26/2017	Draximage DTPA	Technetium Tc99m Pentetate	Lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging in patients when administered by nebulizer for inhalation and for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate	PREA Only
12/22/2017	Lumify Ophthalmic Solution	brimonidine tartrate	Relief of redness of the eye due to minor eye irritations	PREA Only
12/22/2017	Procysbi	cysteamine bitartrate	Treatment-naïve nephropathic cystinosis	BPCA Only
12/11/2017	Xepi	ozenoxacin	Impetigo	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
12/8/2017	Omidria intraocular solution	phenylephrine/ketorolac	Prevention of intraoperative miosis and reduction of postoperative pain in patients who have undergone cataract surgery	BPCA Only
12/6/2017	Jakafi	ruxolitinib	Relapsed or refractory solid tumors, leukemias or myeloproliferative neoplasms	BPCA Only
11/22/2017	Isentress	raltegravir	HIV exposed neonates	PREA + BPCA
11/21/2017	Triumeq	abacavir sulfate/dolutegravir/lamivudine	HIV-1 infection	PREA Only
11/14/2017	Fasenra	benralizumab	Severe asthma with an eosinophilic phenotype	PREA Only
11/14/2017	Tekturna	aliskiren	Hypertension	PREA + BPCA
11/3/2017	Vimpat	lacosamide	Partial-onset seizures	PREA Only
10/13/2017	Butrans transdermal system	buprenorphine	Moderate-to severe chronic pain requiring continuous, around-the clock opioid treatment for an extended period of time	PREA Only
10/13/2017	Stelara	ustekinumab	Psoriasis	PREA Only
10/13/2017	Pegasys	peginterferon alfa-2a	Non-cirrhotic HBeAg-positive Chronic Hepatitis B virus infection	PREA Only
9/28/2017	Descovy	emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
9/25/2017	Genvoya	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA + BPCA
9/20/2017	Rapivab	peramivir	Acute uncomplicated influenza	PREA Only
9/15/2017	Adzenys ER	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
9/13/2017	Aptiom	eslicarbazepine acetate	Partial-onset seizures	PREA + BPCA
9/1/2017	Cubicin Injection	daptomycin	Staphylococcus aureus bacteremia	PREA + BPCA
8/31/2017	Afluria Quadrivalent	Influenza Vaccine	Active immunization for the prevention of influenza disease caused by virus types A and B contained in the vaccine	PREA Only
8/30/2017	Kymriah	tisagenlecleucel	B-cell precursor acute lymphoblastic leukemia (ALL)	BPCA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
8/27/2017	T.R.U.E TEST	Thin-Layer Rapid Use Epicutaneous Patch Test	Aid in the diagnosis of allergic contact dermatitis in persons whose history suggests sensitivity to one or more of the 35 allergens and 17 allergen mixes included on the T.R.U.E. TEST panels	PREA Only
8/25/2017	Dotarem	gadoterate meglumine	Contrast agent for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity	PREA Only
7/26/2017	Fycompa	perampanel	Partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy	PREA Only
7/6/2017	Vimovo	naproxen/esomeprazole magnesium	Juvenile idiopathic arthritis (JIA)	PREA Only
6/22/2017	Simponi	golimumab	Active polyarticular juvenile idiopathic arthritis	PREA Only
6/20/2017	Mydayis	mixed salts of a single-entity amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/19/2017	Cotempla XR-ODT	methylphenidate	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
6/15/2017	Calcium Gluconate	calcium gluconate	Acute symptomatic hypocalcemia	PREA Only
6/7/2017	Fibryna	Fibrinogen (Human)	Acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia	PREA Only
5/31/2017	Rebinyn	Coagulation Factor IX (Recombinant), GlycoPEGylated	Hemophilia B	PREA Only
5/30/2017	Zerviate	cetirizine	Ocular itching associated with allergic conjunctivitis	PREA + BPCA
5/26/2017	Isentress HD	raltegravir	HIV-1 infection	PREA Only
5/23/2017	Sensipar	cinacalcet	Secondary HPT in pediatric patients with Chronic Kidney Disease on dialysis	BPCA Only
5/17/2017	Jevtana	cabazitaxel	Solid tumors	BPCA Only
4/7/2017	Harvoni	ledipasvir/sofosbuvir	Chronic hepatitis C virus genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis	PREA Only
4/7/2017	Sovaldi	sofosbuvir	Chronic hepatitis C virus genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis	PREA Only
4/5/2017	Visipaque	iodixanol	Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation patients with suspected coronary artery disease	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
3/30/2017	Orencia	abatacept	Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (pJIA)	PREA + BPCA
3/29/2017	Cubicin Injection	daptomycin	Complicated skin and skin structure infections (cSSSI)	PREA + BPCA
3/21/2017	Ciloxan ophthalmic solution	ciprofloxacin	Bacterial conjunctivitis	BPCA Only
3/21/2017	Zymar	gatifloxacin	Bacterial conjunctivitis	BPCA Only
3/14/2017	Vigamox Ophthalmic Solution	moxifloxacin	Bacterial conjunctivitis	BPCA Only
3/3/2017	Rubber Panel T.R.U.E. TEST	Rubber Panel Thin-Layer Rapid Use Epicutaneous Patch Test	Diagnosis of allergic contact dermatitis in persons whose history suggests sensitivity to one or more of the 5 substances included on the Rubber Panel T.R.U.E. TEST	PREA Only
3/1/2017	Liquid E-Z-Paque	barium sulfate	Use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the gastrointestinal (GI) tract	PREA Only
3/1/2017	Cerebyx	fosphenytoin sodium	Generalized tonic-clonic status epilepticus, for the prevention and treatment of seizures occurring during neurosurgery, and for short-term substitution for oral phenytoin	BPCA Only
2/23/2017	RotaTeq	Rotavirus Vaccine, Live, Oral, Pentavalent	Prevention of rotavirus gastroenteritis caused by types G1, G2, G3, G4, and G9	PREA Only
2/15/2017	Spiriva Respimat Inhalation Spray	tiotropium bromide	Asthma	PREA + BPCA
1/28/2017	Vyvanse	lisdexamfetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
1/27/2017	Ofirmev	acetaminophen	Pain and fever	PREA + BPCA
1/27/2017	Symbicort Inhalation Aerosol	budesonide/formoterol fumarate dihydrate	Asthma	PREA + BPCA
1/27/2017	Stribild	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	HIV infection	PREA Only
1/27/2017	ArmonAir RespiClick	fluticasone propionate	Asthma	PREA Only
1/27/2017	AirDuo RespiClick	fluticasone propionate/salmeterol	Asthma	PREA Only
1/27/2017	Latuda	lurasidone hydrochloride	Schizophrenia Irritability associated with autistic disorder	BPCA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
12/22/2016	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Evaluation of suspected or known vesicoureteral reflux	PREA Only
12/22/2016	Lyrica	pregabalin	Fibromyalgia	PREA Only
12/22/2016	Adynovate	Antihemophilic Factor (Recombinant), PEGylated	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
12/16/2016	Ryzodeg 70/30	insulin degludec/insulin aspart	Type 1 and type 2 diabetes mellitus	PREA Only
12/16/2016	Tresiba	insulin degludec	Type 1 and type 2 diabetes mellitus	PREA Only
12/14/2016	Eucrisa ointment	crisaborole	Mild to moderate atopic dermatitis	PREA Only
11/25/2016	Renvela	sevelamer carbonate	Control of serum phosphorus in patients with chronic kidney disease on dialysis	PREA Only
11/18/2016	FluLaval Quadrivalent	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine	PREA Only
11/18/2016	FluLaval	Influenza Virus Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine	PREA Only
11/10/2016	Naftin	naftifine hydrochloride	Tinea corporis	PREA Only
11/4/2016	Selzentry	maraviroc	CCR5-tropic HIV-1 infection	PREA + BPCA
11/4/2016	Enbrel	etanercept	Chronic moderate to severe plaque psoriasis (PsO)	PREA Only
10/18/2016	Zemplar	paricalcitol	Secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3, 4 and 5	PREA Only
10/14/2016	Varibar Pudding	barium sulfate	Evaluate the oral and pharyngeal function and morphology	PREA Only
10/7/2016	Gardasil 9	Human Papillomavirus 9-valent Vaccine, Recombinant	Two-dose regimen	PREA Only
10/6/2016	Pertzye	pancrelipase	Exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	PREA Only
9/27/2016	Avelox	moxifloxacin hydrochloride	Complicated intra-abdominal infections (cIAI)	PREA + BPCA

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/13/2016	Cuvitru	Immune Globulin Subcutaneous (Human), 20% Liquid	Primary humoral immunodeficiency (PI)	PREA Only
9/9/2016	Noxafil	posaconazole	Prophylaxis of invasive fungal infections	PREA + BPCA
9/9/2016	Q-Pan	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted	Prophylaxis of influenza A (H5N1)	PREA Only
9/2/2016	Canasa Suppositories	mesalamine	Mildly to moderately active ulcerative proctitis	PREA Only
8/30/2016	Blincyto	blinatumomab	Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	BPCA Only
8/16/2016	Kapvay Extended Release Tablets	clonidine	Juvenile animal toxicity study	PREA Only
7/29/2016	Dysport	abobotulinumtoxinA	Lower limb spasticity	PREA Only
7/12/2016	Effient	prasugrel	Vaso-occlusive crises in patients with sickle cell disease	BPCA Only
7/8/2016	Dexilant	dexlansoprazole	Healing of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD)	PREA Only
7/6/2016	Xolair	omalizumab	Moderate to severe persistent asthma	PREA Only
6/29/2016	Kovanaze Nasal Spray	tetracaine HCl/oxymetazoline HCl	Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J	PREA Only
6/9/2016	Tivicay	dolutegravir	HIV-1 infection	PREA Only
5/27/2016	Ativan Injection	lorazepam	Status epilepticus	409I(BPCA)
5/27/2016	Teflaro Injection	ceftaroline fosamil	Acute Bacterial Skin and Skin Structure Infections (ABSSI) and Community Acquired Bacterial Pneumonia (CABP)	PREA Only
5/25/2016	Afstyla	Antihemophilic Factor (Recombinant), Single Chain	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
5/23/2016	Flucelvax Quadrivalent	Influenza Vaccine	Active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine	PREA Only
5/23/2016	Flucelvax	Influenza Vaccine	Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
4/29/2016	Fycompa	perampanel	Partial-onset seizures; primary generalized tonic-clonic seizures	PREA Only
4/29/2016	Entocort EC	budesonide	Crohn's disease	PREA Only
4/29/2016	Otovel Otic Solution	ciprofloxacin/fluocinolone acetonide	Acute otitis media with tympanostomy tubes	PREA Only
4/28/2016	ProAir Digihaler	albuterol sulfate	Asthma	PREA Only
4/27/2016	Gadavist	gadobutrol	Evaluation of known or suspected supra-aortic or renal artery disease	PREA Only
4/14/2016	Trumenba	Meningococcal Group B Vaccine	Active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B	PREA Only
4/4/2016	Descovy	emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
3/31/2016	Lumason	Sulfur Hexafluoride Lipid-Type A Microspheres	Ultrasonography of the liver for characterization of focal liver lesions	PREA Only
3/23/2016	Cinqair	reslizumab	Asthma	PREA Only
3/18/2016	OraVerse Injection	phentolamine mesylate	Reversal of soft-tissue anesthesia	PREA Only
3/18/2016	Anthim	obiltoxaximab	Inhalational anthrax	PREA Only
3/16/2016	Kovaltry	Antihemophilic Factor (Recombinant), Full Length	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
3/10/2016	Truvada	emtricitabine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
3/1/2016	Odefsey	emtricitabine/rilpivirine/tenofovir alafenamide	HIV-1 infection	PREA Only
2/29/2016	Tetracaine Hydrochloride Ophthalmic Solution	tetracaine hydrochloride	Ophthalmic anesthesia	PREA Only
2/24/2016	Aczone Gel	dapsone	Acne vulgaris	PREA Only
2/23/2016	Complera	emtricitabine/rilpivirine/tenofovir disoproxil fumarate	HIV-1 infection	PREA Only
2/3/2016	Prilosec	omeprazole magnesium	Erosive esophagitis due to gastroesophageal reflux disease	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
1/27/2016	Adzenys XR-ODT	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
1/15/2016	Readi-Cat 2; Readi-Cat 2 Smoothie	barium sulfate	CT of the abdomen in pediatric patients	PREA Only
1/14/2016	Hiberix	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)	Active immunization for the prevention of invasive disease caused by Haemophilus influenzae type b	PREA Only
1/11/2016	E-Z-HD	barium sulfate	For use in double contrast radiographic examinations of the esophagus, stomach and duodenum to visualize the gastrointestinal tract	PREA Only
12/17/2015	Emend	aprepitant**	Chemotherapy induced nausea and vomiting	PREA + BPCA
12/10/2015	Otiprio	ciprofloxacin otic suspension	Bilateral otitis media with effusion undergoing tympanostomy tube placement	PREA Only
12/4/2015	Gamunex-C	Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified	Primary Humoral Immunodeficiency	PREA Only
12/4/2015	QuilliChew ER	methylphenidate hydrochloride	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
11/20/2015	Caldolor Injection	ibuprofen	Mild to moderate pain; moderate to severe pain as an adjunct to opioid analgesics; fever	PREA + BPCA
11/18/2015	Narcan Nasal Spray	naloxone hydrochloride	Opioid overdose	PREA Only
11/13/2015	Adynovate	Antihemophilic Factor (Recombinant), PEGylated	Hemophilia A (congenital factor VIII deficiency)	PREA Only
11/5/2015	Genvoya	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	HIV-1 infection	PREA Only
11/4/2015	Nucala	mepolizumab	Severe asthma with an eosinophilic phenotype	PREA Only
10/19/2015	Dyanavel XR Oral Suspension	amphetamine	Attention Deficit Hyperactivity Disorder (ADHD)	PREA Only
9/24/2015	Reyataz Oral Powder	atazanavir	HIV-1 infection	PREA + BPCA
9/17/2015	Epzicom	abacavir sulfate/lamivudine	HIV-1 infection	PREA Only

Pediatric Labeling Date	*Trade Name*	*Generic Name*	*Conditions Evaluated**	*Pursuant to Statute*
9/15/2015	Spiriva Respimat Inhalation Spray	tiotropium bromide	Asthma	PREA Only
9/14/2015	Velcade	bortezomib	Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)	BPCA Only
9/9/2015	Delzicol	mesalamine**	Mildly to moderately active ulcerative colitis	PREA + BPCA
9/4/2015	Nuwiq	Antihemophilic Factor (Recombinant)	Hemophilia A (congenital Factor VIII deficiency)	PREA Only
8/28/2015	Emend	aprepitant**	Chemotherapy induced nausea and vomiting	PREA + BPCA
8/26/2015	Edurant	rilpivirine	HIV-1 infection	PREA + BPCA
8/24/2015	Promacta	eltrombopag	Chronic immune (idiopathic) thrombocytopenia (ITP)	BPCA Only
8/14/2015	Procysbi	cysteamine bitartrate	Nephropathic cystinosis	BPCA Only
8/13/2015	Oxycontin Extended Release Tablets	oxycodone hydrochloride	Severe pain in opioid-tolerant patients	BPCA Only
8/5/2015	Wilate	von Willebrand Factor/Coagulation Factor VIII Complex (Human)	Control of bleeding episodes and perioperative management of bleeding	PREA Only
7/30/2015	Gammaplex	Immune Globulin Intravenous (Human) 5% Liquid	Primary immunodeficiency (PI)	PREA Only
7/15/2015	Epiduo Forte	adapalene/benzoyl peroxide	Acne vulgaris	PREA Only
7/15/2015	TachoSil	Absorbable Fibrin Sealant Patch	Local bleeding in patients undergoing hepatic resection surgery	PREA Only

* Conditions provided in this table do not necessarily represent an approval in pediatric patients. In some cases, the condition may have been evaluated in pediatric patients and found to be ineffective or unsafe.

Note that not all pediatric labeling changes have resulted from pediatric studies. In some cases, labeling may be updated based on other data sources such as pediatric extrapolation from adult data or the literature.

For complete details regarding these labeling changes, please see https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes.