Best Pharmaceuticals for Children Act
and
Pediatric Research Equity Act

July 2016
Status Report to Congress

Department of Health and Human Services
Food and Drug Administration

_____Date_____

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EXECUTIVE SUMMARY

The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, required in section 508 that the Secretary of Health and Human Services report by July 9, 2016, and every 5 years thereafter, on various activities resulting from the implementation of sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act. This report, submitted in accordance with that provision, contains a brief discussion of various pediatric drug development laws, regulations, and guidances; an assessment of the pediatric programs; as well as suggestions for improving pediatric research.

The first pediatric drug development incentive legislation was enacted as part of the Food and Drug Administration Modernization Act (FDAMA) in 1997. The 2001 Status Report to Congress, as required by FDAMA,[1] identified a number of gaps in pediatric labeling information and an inadequate focus on certain important drug categories and age groups. With the subsequent enactment of the Best Pharmaceuticals for Children Act (BPCA) in 2002, amended in 2007,[2] and the Pediatric Research Equity Act (PREA) in 2003, amended in 2007,[3] we have made significant progress in terms of the number, timeliness, and successful completion of studies of drugs in pediatric populations. FDASIA made BPCA and PREA permanent.

Assessment of the Pediatric Programs

FDASIA permanently authorized sections 505A and 505B; however, FDASIA only authorized funding for section 409I, which establishes the pediatric drug testing research program at the National Institutes of Health (NIH), for 5 years (through FY 2017). Almost all stakeholders involved asserted permanence was an important aspect for future drug development planning. These included individuals in industry, academia, consumer groups, the Food and Drug Administration (FDA or the Agency), and NIH. Integration of pediatric planning and exclusivity requests has become a regular part of product development. This has led to enormous progress in obtaining pediatric studies and has permitted new pediatric labeling of more than 600 products, 149 of which occurred since the passage of FDASIA. Despite this, studies in neonates, infants, and rare diseases remain a challenge. The establishment of pediatric clinical trial networks and the

[1] In 1997, as part of FDAMA Public Law 105-115, 111 Stat. 2296 (Nov. 21, 1997), Congress enacted a new law that provides marketing incentives to manufacturers who conduct studies of drugs in children. This law, which provided 6 months exclusivity in return for conducting pediatric studies, is commonly known as the pediatric exclusivity provision. The pediatric exclusivity provision had a sunset date of January 1, 2002, and included a requirement that the Secretary report by January 1, 2001, on the experiences under the new law. The report is at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf.

[2] Food and Drug Administration Amendments Act of 2007 (FDAAA), Title V (Public Law 110-85) (Sept. 27, 2007)

[3] Id., Title IV

development of regulatory science upon which to base pediatric endpoints for some drugs remain works in progress.

The important need to coordinate pediatric trials on an international basis has resulted in monthly—and often more frequent—scientific exchanges with our international colleagues. This need is driven by the limited pediatric patient population available for study participation, which, in many instances, necessitates a global development program. Additional efforts in this area have included both development of international working groups for various scientific challenges, such as for certain rare diseases and endpoints, and a number of joint scientific and regulatory publications. Both the International Neonatal Consortium (INC) and the Global Pediatric Clinical Trials Network are undertaking pediatric activities that have moved beyond the planning stages and into implementation.

Within FDA, success beyond labeling encompasses such diverse areas as the highly effective weekly Pediatric Review Committee (PeRC) meeting. Consultative reviews of pediatric information (e.g., pediatric plans, assessments, and protocols) are provided by many of the pediatricians and subject matter experts from the Office of Pediatric Therapeutics (OPT), the various product Centers and divisions at FDA, and numerous other technical experts involved in biopharmacology, statistics, ethics, neonatology, and international aspects of pediatric product development. This review process has facilitated consistency across the Agency in both pediatric product development and implementation of new process components of the pediatric program, such as the public posting of regulatory documents.

FDA continues to carry out the congressionally-mandated Postmarketing Pediatric Safety Review Process with reporting to the Pediatric Advisory Committee (PAC).[4] The success of the process is reviewed in a recent publication.[5] The enormous resources needed for this ever-expanding activity have required FDA to assess new approaches to conducting regulatory activities pertaining to BPCA and PREA.

One of the most difficult program areas to assess impact over the last 15 years has been the pediatric development of products for which sponsors have declined a Written Request (WR) issued under BPCA. These declinations are most typical for products that are generic drugs, for indications addressing small populations or neonates, or when receipt of additional exclusivity is not deemed useful to the sponsor. These declined WRs often include some of the most difficult products to study. Without a commercial sponsor agreeing to the studies, these products and requests are referred to the National Institute of Child Health and Development (NICHD) for consideration for the Priority List and funding by NIH for study. After years spent resolving many of the scientific and

[4] Section 505(B)(i) of the FD&C Act.
[5] See Cope JU, Rosenthal GL, Weinel PJ, Odegaard AJ, and Murphy DM. "FDA's Pediatric Advisory Committee and Safety Reviews: Drugs, Biologics and Vaccines, 2007-2013." Pediatrics. 2015 Nov. 23.

logistical issues surrounding implementation of these pediatric trials, the studies of these products are now submitted on a regular basis to FDA. Over the last few years, four products have been labeled with new pediatric information resulting from this process, and many more are in progress.

INTRODUCTION

Since the enactment of legislation (referred to as BPCA and PREA) that both incentivizes and requires pediatric studies, we have made significant progress in terms of the number, timeliness, and successful completion of studies of drugs in pediatric populations. Prior to the passage of the first incentive provisions for the completion of pediatric studies in 1997, more than 80 percent of approved drugs had no pediatric-specific labeling information. Of the 600-plus labeling changes with pediatric-specific information made in the last 19 years, 149 were completed since the passage of FDASIA. These labeling changes are largely the result of the successful implementation of both BPCA and PREA.

I. BACKGROUND: PEDIATRIC LAWS, REGULATIONS, AND GUIDANCES

Overview

Pediatric drug studies and labeling are governed largely by two sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act): section 505A (BPCA) and section 505B (PREA). To incentivize sponsors to conduct pediatric studies of drugs when the Agency believes the studies may produce benefits in pediatric populations, BPCA allows FDA to issue WRs to sponsors to conduct studies and establishes a framework whereby sponsors can qualify for 6 months of additional marketing exclusivity. BPCA also allows FDA to request studies that cannot be required under PREA because the applications or supplements are not subject to the requirements of PREA. PREA requires that sponsors of certain new drug applications, biologics license applications, or supplements thereto, submit assessments regarding the drug's safety, effectiveness, dosing, and administration in pediatric populations. Together,[6] these statutes encourage more effective labeling of drugs and biological products for use in neonates, infants, and children.

History of Pediatric Laws and Regulations

Over the last two decades, FDA has worked to address the problem of inadequate testing of drugs in pediatric populations and inadequate pediatric use information in drug and biological product labeling. In 1994, FDA published a final rule requiring manufacturers of marketed drugs to survey existing data to determine whether those data were sufficient to support adding pediatric use information to the drug's labeling.[7] However, the 1994 rule did not impose a general requirement that manufacturers conduct studies when existing information was not sufficient to support adding pediatric use information. This initial attempt to encourage sponsors to submit pediatric studies and plans to sufficiently

[6] 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). Further discussion of these laws will be included as appropriate or relevant to this report.

[7] See "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling" (59 FR 64240, Dec. 13, 1994).

inform use of drugs in pediatric patients was unsuccessful in achieving adequate labeling for most drugs and biological products regarding use in pediatric subpopulations; product labeling frequently continued to fail to provide directions for safe and effective pediatric use.

To address this problem, FDAMA contained provisions creating section 505A of the FD&C Act to establish incentives for conducting pediatric studies on drugs for which exclusivity or patent protection exists.[8] In addition, on December 2, 1998, FDA published a regulation known as the Pediatric Rule,[9] a regulation designed to work in conjunction with the pediatric exclusivity provisions of section 505A of the FD&C Act. The Pediatric Rule partially addressed the lack of pediatric use information by requiring manufacturers of certain new and marketed drugs and biologics to conduct studies to provide sufficient data to support directions for pediatric use for the claimed indications. The Pediatric Rule required that applications submitted on or after April 1, 1999, involving new active ingredients, indications, dosage forms, dosing regimens, or routes of administration include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. These two programs—the exclusivity incentive under section 505A and the Pediatric Rule—worked together to require or incentivize pediatric studies of drugs.

A few years later, the pediatric legal landscape changed again. On January 4, 2002, BPCA (Public Law 107-109) was enacted. The BPCA reauthorized and amended the pediatric exclusivity incentive program and created new mechanisms for funding pediatric studies that sponsors or holders of approved applications declined to voluntarily conduct. On October 17, 2002, however, the U.S. District Court for the District of Columbia held that FDA exceeded its statutory authority in issuing the Pediatric Rule, suspended the rule's implementation, and enjoined its enforcement.[10]

Not long afterward, on December 3, 2003, Congress passed PREA,[11] which adopted many of the provisions previously in place under the Pediatric Rule. This law, codified at section 505B of the FD&C Act, has been amended over the years. PREA requires sponsors of certain drug and biologic applications filed on or after September 2007[12] (i.e., those for a new active ingredient, new indication, new dosage form, new dosing regimen,

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[8] Under this provision, sponsors or holders of approved applications could qualify for an additional 6 months of marketing exclusivity if they voluntarily performed pediatric studies described in a WR issued by FDA.

[9] See "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (63 FR 66632, Dec. 2, 1998).

[10] *Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

[11] Public Law 108-155, 117 Stat. 1936 (Dec. 3, 2003).

[12] PREA also permits FDA to require the sponsor of already-marketed drugs and biological products to submit assessments if it finds that "(A)(i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and (ii) adequate pediatric labeling could confer a benefit on pediatric patients; (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; or (C) the absence of adequate pediatric labeling could pose a risk to pediatric patients" (section 505B(b)(1) of the FD&C Act).

or new route of administration) to submit data to assess the safety and effectiveness of the drug, and to support dosing and administration of the drug in pediatric populations unless the sponsor has obtained a waiver or deferral (see section 505B(a) of the FD&C Act). In addition, the FDAAA amendment to section 505B states "[u]nless the Secretary requires otherwise by regulation, [Section 505B] does not apply to any drug for an indication for which orphan designation has been granted under section 526" of the FD&C Act. FDAAA also required FDA to create a committee (PeRC) to review pediatric issues. FDA's PeRC reviews pediatric study plans, including planned requests for waiver or deferral.

FDA's most recent draft guidance pertaining to pediatric issues, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans,"[13] was issued in March 2016.[14] When finalized, this guidance will represent the Agency's current thinking regarding the submission of initial pediatric study plans.

Additionally, FDAAA required the Government Accountability Office (GAO) to evaluate and report upon the effects of BPCA and PREA since the 2007 reauthorization. Further, as directed by Congress, FDA asked the Institute of Medicine (IOM) to review aspects of pediatric studies and changes in product labeling resulting from BPCA and PREA and their predecessor policies, and to assess the incentives for (and the extent to which) there had been pediatric studies of biologics. The GAO findings were reported to Congress in May 2011,[15] and the IOM findings were reported to Congress in February 2012.[16]

II. ASSESSMENT OF EFFECTIVENESS OF DRUGS AND BIOLOGICS

A. Overview of FDA Implementation and Impact of Pediatric-Specific Provisions Under FDASIA

This section reviews the specific changes to BPCA and PREA under FDASIA, FDA's implementation of these changes, and the impact of these changes on pediatric drug and biological product development. This section will also review the implementation and impact of the rare pediatric disease priority review voucher program as established under section 908 of FDASIA.

[13] See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf

[14] FDA also issued a draft guidance for comment entitled "Rare Pediatric Disease Priority Review Vouchers" (Nov. 2014).

[15] See "Pediatric Research: Products Studied under Two Related Laws, but Improved Tracking Needed by FDA;" GAO-11-457 Report to Congressional Committee.

[16] See "Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act" at http://iom.nationalacademies.org/Reports/2012/Safe-and-Effective-Medicines-for-Children/Report-Brief.aspx.

Importantly, FDASIA (Title V, section 501) permanently reauthorized BPCA and PREA, and ensured acknowledgement by drug developers that pediatric product development programs must be considered during overall product development. The permanent reauthorizations eased concerns that drug developers may have felt in initiating pediatric studies conducted under BPCA or PREA. In addition, the permanent reauthorizations provided assurance the program would continue, and decisions on timing of this aspect of product development could be designed with confidence in the program's future availability. Title V of FDASIA includes amendments to both BPCA and PREA. Additionally, Title IX, section 908, amends subchapter B of chapter V of the FD&C Act (21 USC 360aa et seq.) to establish a priority review voucher program to encourage treatments for rare pediatric diseases.[17]

1. Changes to BPCA Under FDASIA

Including Neonates in WR Studies

FDASIA, Title V, section 502, generally requires studies included in a WR issued by FDA under BPCA to include neonates. If studies in neonates are not included in a WR, then a statement describing the rationale for not requesting studies must be included. This provision is in keeping with FDA's internal approach, prior to FDASIA, of routinely ensuring, through the PeRC, that all WRs address neonates. Doing so has identified important scientific challenges for sponsors and FDA, in that expertise in development of neonatal clinical trials is sparse and implementation extremely difficult. FDASIA also requires implementation within 1 year of enactment of an internal standard operating procedure providing for review of any significant modifications to initial pediatric study plans, agreed upon initial pediatric study plans, and WRs (see Title V, section 503). The standard operating procedure was made publicly available on the FDA website on July 9, 2013.[18]

Public Access to Pediatric Data Under BPCA

As required under FDASIA (Title V, section 504) for certain studies conducted under BPCA, FDA has made certain information about the pediatric trials underpinning these labeling changes publicly available. We have done so by posting medical, statistical, and clinical pharmacology reviews on the FDA website, as well as the corresponding WRs issued for studies, as required by FDASIA. Specifically, FDASIA required posting the reviews and corresponding WRs submitted under BPCA between January 4, 2002, and September 27, 2007, for which 6 months of market exclusivity was granted and that resulted in a labeling change. All required reviews were posted by July 29, 2015.

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

[18] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM359958.pdf.

Responses to Written Requests

Since passage of FDASIA, from July 9, 2012, through June 30, 2015, FDA issued 53 WRs to 59 sponsors under BPCA.[19] During that same time frame, 53 sponsors agreed to conduct the studies and 4 sponsors declined to conduct the studies in a WR they received. Notably, because sponsors have 180 days to respond to a WR, some of the responses were for WRs issued prior to July 9, 2012, and sponsors had not yet responded to some of the WRs issued on or before June 30, 2015. Thus, the numbers do not match and appear to create a discrepancy.

Those sponsors who declined the WR cited [20] the following reasons:

- Product is no longer being marketed
- Sponsor disagreed with the requirements of WR and did not believe it warranted expenditure of further business resources
- Sponsor would not be able to complete the studies before the due date
- Sponsor could not complete studies before expiration of patent or exclusivity

In summary, FDA has successfully implemented all changes to BPCA under FDASIA. FDA continues to monitor the impact of changes to BPCA on the overall success of the pediatric program.

2. Changes to PREA Under FDASIA

Extension of Deadline for Deferred Studies

FDASIA, Title V, section 505, amends PREA for the purpose of ensuring the completion of pediatric studies and authorizes FDA to grant an extension of assessments deferred under PREA. This provision applies to all deferred studies, including those already considered delayed (i.e., expired deferral). In order to alert applicants that certain deferrals were expired or due to expire within 180 days of the implementation date, FDA sent reminder or courtesy letters to each applicant. Between November and December 2012, FDA issued 102 reminder letters. The total number of deferral extensions (DE) requested and granted by year and by center is presented in Table 1.

Table 1: Deferral Extensions Granted by CDER (CBER)*

	2012	**2013**	**2014**	**2015**	**Total**
Requested	47	138 (8)	68 (0)	34 (1)	287 (9)
Granted	0	126 (7)	60 (1)	17 (0)	203 (8)
Denied	0	29 (0)	7 (0)	11 (0)	47 (0)

[19] The same WR can be issued to more than one sponsor; therefore, the number WR issued is not equal to the number of sponsors who received a WR.

[20] Because sponsors have 180 days to respond to a WR, some of the responses received may be for WRs issued prior to passage of FDASIA. Furthermore, sponsors will not yet have responded to some of the later WRs. Therefore, the number of WRs accepted and declined during the specified period of time will not equal the number of WRs issued during the same time interval.

*Because the Agency has 45 days to respond to a deferral extension request, the number of requests granted and denied may not equal the number of requests in a given year.

Overall, the number of DE requests submitted has decreased since the initiation of the program, a decline likely attributed to completion of the review of the "backlog" of deferrals delayed as of January 5, 2013. The vast majority of DE requests were granted by FDA; only 14 percent were denied. The most common reasons for denial of a deferral extension request is that the sponsor did not provide adequate justification for the delay in completion of the studies (i.e., the deferral criteria in section 505B(a)(3) of the FD&C Act are no longer met). For example, failure to demonstrate any communication with FDA about problems encountered in completing the studies may be grounds for denial of a deferral extension request.

Table 2 shows five general categories of reasons for granting DE requests, with examples of various scenarios for each category:

Table 2: Categories of Reasons for Deferral Extensions

Reasons cited for DE request	Examples of scenarios associated with each reason
Delays due to issues with the study drug and/or comparator drug.	• Delays developing an age-appropriate formulation • Product quality and stability issues • Comparator drug shortage
Delays involving study participants, sites, and/or management.	• Difficulty recruiting study participants • High rate of site personnel turnover • Additional time needed to address unexpected issues in study conduct
Delays due to safety and/or pharmacokinetic issues.	• Additional safety data required • Must review new pharmacokinetic data before proceeding with the study • Study proceeding with a more cautious approach due to new potential safety signals
Delays due to continuing interaction between the applicant and FDA.	• FDA placed study on clinical hold • FDA requested change in the protocol • The applicant and FDA are negotiating a different study to fulfill the PREA requirement
Additional time required to prepare the study report and/or submission.	• Delays collecting and compiling study data • Additional time required to analyze study data • Additional time required to prepare a supplemental NDA with appropriate pediatric labeling

Authority to Issue Noncompliance Letters

In addition to the authority to grant DEs for PREA-required studies, section 505 also authorizes FDA to issue, and publicly post, noncompliance letters for failure to submit

required pediatric assessments under PREA. The first noncompliance letters were posted on August 26, 2013. Since that date, FDA has issued 43 noncompliance letters for failure to submit required pediatric assessments; letters that have been posted to date may be found on the FDA website.[21]

Pediatric Study Plans

FDASIA, Title V, section 506, amends PREA to require submission of pediatric study plans before the assessments are submitted and no later than 60 days after an end-of-phase 2 (EOP 2) meeting with FDA or at a time agreed upon with FDA. The content and process for submission of initial pediatric study plans (iPSP) and amendments to agreed initial pediatric study plans is described in the statute. FDA implemented this new requirement within 180 days of the enactment of FDASIA as required by section 506(c).

The total number of initial pediatric study plans reviewed and agreed by year is presented in Table 3.

Table 3: Pediatric Study Plans Reviewed

	2012-13*	2013-14*	2014-15*	Total^
Initial Pediatric Study Plans	20	275	274	569
Agreed Pediatric Study Plans	4	125	235	360
Amended Agreed Pediatric Study Plans	0	0	2	2
Non-agreed Initial Pediatric Study Plans	0	5	16	21

*Data collected each period is July to June.
^There is a 120-day lag in review of an initial pediatric study plan and finalization of an agreed initial pediatric study plan.

Under section 506, FDA was also required to issue guidance and promulgate proposed regulations for pediatric study plans within one year of enactment. A draft guidance, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans," was publicly posted on FDA's website in July 2014. Given the substantial comments to the draft guidance, and the consequent revisions thereto, FDA reissued this guidance in draft form in March 2016. [22] FDA also continues the process of developing a proposed rule as required under this section of FDASIA; the Agency concluded that it would benefit the rulemaking process to review the public comments relating to the draft guidance before issuing a proposed rule. Therefore, the proposed rule is being developed on a parallel track with the guidance.

FDASIA Reports and Public Meetings

Under section 508, FDA was required to submit this report to Congress regarding implementation of BPCA and PREA within 4 years of enactment of FDASIA. In addition, stakeholder comments were to be obtained at least 180 days prior to the

[21] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm.
[22] See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf.

submission of the report. On March 25, 2015, in compliance with this section, the Agency convened a public stakeholder meeting entitled "Stakeholder Input on BPCA and PREA." The agenda and recording of the meeting are publicly available.[23]

In addition, under Section 510, FDA was required to convene, within 18 months of the enactment of FDASIA, at least one public meeting to discuss ways to encourage and accelerate development of new therapies for pediatric rare diseases. A public meeting was convened on January 7, 2014, entitled "Complex Issues in Developing Drug and Biological Products for Rare Diseases."[24] Under section 510, FDA was also required, within 180 days of the public meeting, to issue a report that includes a strategic plan for encouraging and accelerating development of new therapies for treating pediatric rare diseases. The report, entitled "Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Diseases," was publicly posted in July 2014.[25]

Rare Pediatric Disease Priority Review Voucher Incentive Program

FDASIA (Title IX, Section 908) established the Rare Pediatric Disease Priority Review Voucher Incentive Program. As of October 2015, four rare pediatric disease priority review vouchers were awarded (see Table 4). All but one have been resold for values between $67 million and $350 million.

Table 4: Rare Pediatric Disease Priority Review Vouchers Awarded

Product Name	Sponsor	Approved Indication	Date Awarded	Sold/Amount
Vimizim	BioMarin	Mucopolysaccharidosis Type IV	02/14/2014	Sanofi/$67 million
Unituxin	United Therapeutics	High risk neuroblastoma	03/10/2015	AbbVie/$350 million
Cholbam	Asklepion Pharmaceuticals	Bile acid synthesis disorders due to single enzyme defects, and for patients with peroxisomal disorders (including Zellweger spectrum disorders)	03/17/2015	Sanofi/$245 million
Xuriden	Wellstat Therapeutics	Hereditary Orotic Aciduria	09/04/2015	Unsold

[23] http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm433552.htm.
[24] The agenda and recording of the meeting are publicly available at: http://www.fda.gov/drugs/newsevents/ucm367820.htm.
[25] See http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM404104.pdf.

Products may also be designated as a "drug for a rare pediatric disease" under this program. However, designation is neither required for voucher eligibility, nor does designation require FDA to award a voucher to the designee. As of October 2015, 19 products were designated under this program. In addition, a draft guidance for industry, "Rare Pediatric Disease Priority Review Vouchers," was publicly posted in November 2014.[26]

FDA strongly supports the goal of incentivizing drug development for rare pediatric diseases. However, this program adversely affects the ability of FDA to set public health priorities because this program provides priority reviews of new drug applications that would not otherwise qualify for a priority review because the drug does not treat a serious condition or provide a significant improvement in safety or effectiveness. This can divert agency resources away from drugs more likely to benefit the public health.

Other Pediatric-focused Provisions Under FDASIA

In addition to the implementation of several new provisions under FDASIA as described above, other pediatric-focused provisions are described below:

- The PAC was permanently reauthorized under section 507 and the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee was extended for the duration of the Oncologic Drugs Advisory Committee.
- The Humanitarian Device Exemption Program was extended to 2017 under section 507.
- The Program for Pediatric Study of Drugs in the Public Health Service Act was extended to 2017 under section 507. This program is discussed in more detail in section 2.C of this report.
- FDA was required to implement an internal standard operating procedure for review of initial pediatric study plans, agreed initial pediatric study plans, and WRs within one year of enactment under section 503. The standard operating procedure was made publicly available on the FDA website on July 9, 2013.[27]
- FDA was required to hire an expert in neonatology and an expert in pediatric epidemiology under section 511. These positions were recruited and filled within OPT by October 2015.

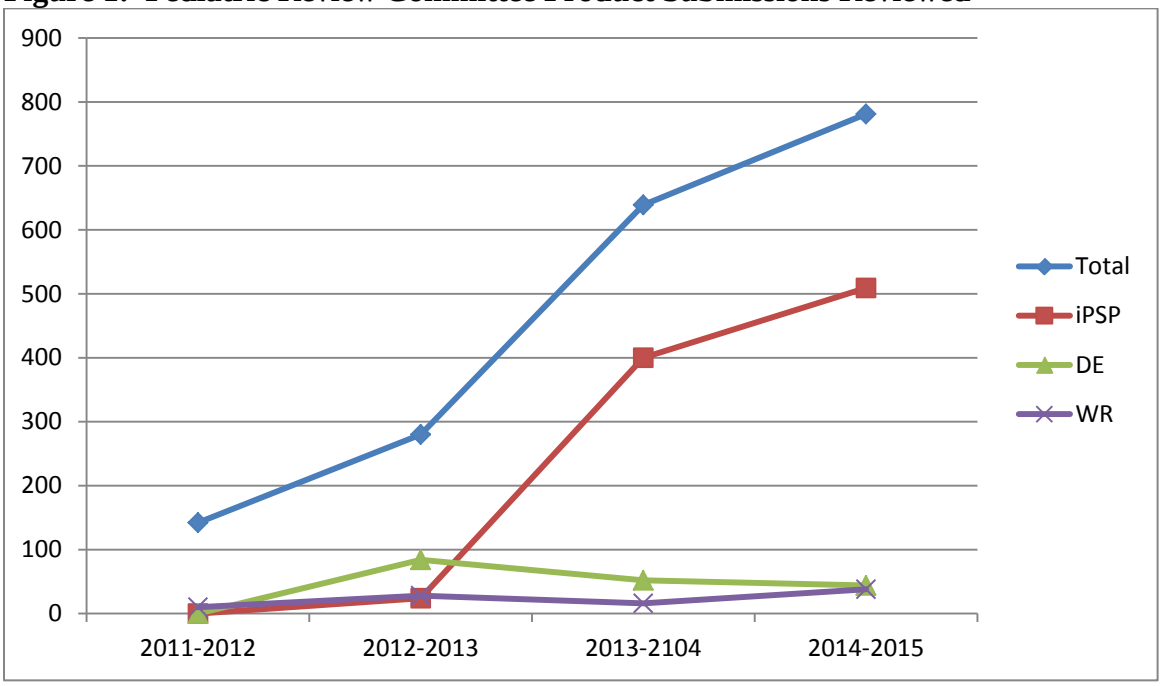
3. Summary of Implementation of Pediatric-focused Provisions Under FDASIA

FDA's implementation of pediatric-focused provisions under FDASIA has been tremendously successful. Some of the new programs implemented include DEs, public noncompliance letters, pediatric study plans, and the rare pediatric disease priority review voucher, which were accomplished under timelines established by the statute. However,

[26] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf.
[27] http://inside.fda.gov:9003/downloads/cder/officeofnewdrugs/officeofnonprescriptionproducts/pediatricandmaternalhealthstaff/ucm359955.pdf.

it should be noted that the implementation of these provisions has led to a substantial increase in workload within FDA. Figure 1 shows the total submissions reviewed by the PeRC over the last 4 years, and reflects a significant increase in submissions reviewed since the implementation of pediatric provisions required under FDASIA. The majority of the workload increase arose because of the requirement to submit pediatric study plans. The increase in workload due to review of DE requests peaked during the first year of implementation largely because of the backlog of delayed studies that required review at the start of the deferral extension implementation process.[28] The workload for review of WRs and amended WRs has been largely stable over this same period and constitutes less than ten percent of the overall number of submissions reviewed by the PeRC.

Figure 1: Pediatric Review Committee Product Submissions Reviewed



4. Impact of FDASIA on Pediatric Product Development

FDA believes that amendments to BPCA and PREA under FDASIA have strengthened these two important laws. The successful completion of pediatric studies under BPCA and PREA has led to the addition of new pediatric information on labeling for over 600 products since the enactment of these two laws. Moreover, 149 of these labeling changes have occurred since the passage of FDASIA. Furthermore, an additional important impact of these laws has been the improvement of the science needed to understand differences between children and adults and how these differences impact drug and biological product development. Important progress is also being made in pediatric-

[28] Data provided in Figure 1 cannot be directly compared to information Table 2 included because the data provided in Figure 1 represent products submitted for review, not individual PMRs.

specific study design issues, including endpoints, biomarkers, and exposure-response relationships, though much work is still needed—especially for neonates and for children with rare diseases.

In summary, the implementation of pediatric-focused provisions under FDASIA has been successful. BPCA and PREA complement each other in helping to encourage the collection of quality data to support new pediatric information in product labeling. However, it is still premature to state with any assurance the impact of some pediatric-focused provisions of FDASIA. For example, the impact of the pediatric study plan program on increasing the efficiency of pediatric product development is yet unclear because pediatric product development often requires several years to complete. In addition, the impact of voucher programs on increasing the efficiency of rare pediatric disease product development and the availability of products used to treat rare pediatric diseases is also not yet known. All of the products to date that have received rare pediatric disease priority review vouchers were already near completion of product development. Therefore, there has been no evidence that such a program would provide an incentive to directly or indirectly improve drug development for pediatric rare diseases.[29] Also, as stated above, this program adversely affects the ability of FDA to set public health priorities because the program provides priority reviews of new drug applications that would not otherwise qualify. Additional experience may provide further opportunity to assess the impact of these programs.

B. Important Changes as a Result of BPCA and PREA

Improved Product Labeling for Children

There have been over 600 pediatric labeling changes pursuant to BPCA and PREA, of which 149 changes for various diseases or conditions occurred since the enactment of FDASIA. Some of the noteworthy pediatric labeling changes are highlighted in the bullets below:

- **Asthma**: There were two noteworthy pediatric labeling changes for asthma: ProAir RespiClick (albuterol sulfate) for the prevention of exercise-induced bronchospasm in patients 12 years of age and older, and Spiriva Respimat (tiotropium bromide) for long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older.

- **Influenza Vaccines:** There were four notable pediatric labeling changes for new influenza vaccines for the active immunization for the prevention of influenza A and B: FluLaval, FluLaval Quadrivalent, Fluzone Quadrivalent, and Fluarix Quadrivalent.

[29] GAO issued a report in March 2016 and concluded it was too early to gauge the effectiveness of the program. See http://www.gao.gov/assets/680/675544.pdf.

- **Seizure Disorders:** There were six important pediatric labeling changes for the treatment of various types of seizures: Fycompa (perampanel), Banzel (rufinamide), Keppra (levetiracetam), Keppra XR (levetiracetam), Sabril (vigabatrin), and Oxtellar XR (oxcarbazepine).

- **Rare Diseases:** Two notable pediatric labeling changes were made for rare diseases, including Bethkis (tobramycin) for the management of cystic fibrosis in patients 6 years of age and older with P. aeruginosa, and Procysbi (cysteamine bitartrate) for the treatment of nephropathic cystinosis in pediatric patients 2 years of age and older.

- **HIV:** There were four pediatric labeling changes for products with once-daily dosing for the treatment of HIV: Epzicom (abacavir sulfate and lamivudine), Epivir (lamivudine), Ziagen (abacavir), and Prezista (darunavir).

- **Migraine:** Two products were approved for the treatment of migraine in pediatric patients 12 years and older: Zomig Nasal Spray (zolmitriptan) and Treximet (sumatriptan/naproxen). One product, Topamax (topiramate), was approved for the prevention of migraine in pediatric patients 12 years and older. In this category of products we learned a great deal from failed studies, including a greater understanding of the basic diseases and their differences between adults and pediatric patients. For example, pediatric migraine trials failed to establish safety and efficacy until we developed a better understanding of the differences in the rate of resolution of migraines between adolescents and adults.

Drugs Approved for Use in Neonates

Several products were approved for use in neonates since FDASIA's enactment, including Gadavist (gadobutrol) for the detection and visualization of areas with disrupted blood-brain barrier and/or abnormal vascularity of the central nervous system; Merrem I.V. (meropenem) for the treatment of complicated intra-abdominal infections; and Nitropress (sodium nitroprusside) for the immediate reduction of blood pressure in hypertensive crisis. Meropenem and sodium nitroprusside were studied under the off-patent WR process which involved NICHD; these two labeling changes are an important example of collaboration between FDA and NICHD. Neonatal studies that lead to safety, efficacy, and dosing information for drugs used in neonates are essential. Trials in the neonatal population are sparse due to multiple scientific, regulatory, and ethical challenges. Neonates are a difficult population to study because of the lack of data to identify appropriate endpoints and the inability to extrapolate efficacy from adults because the diseases are different.

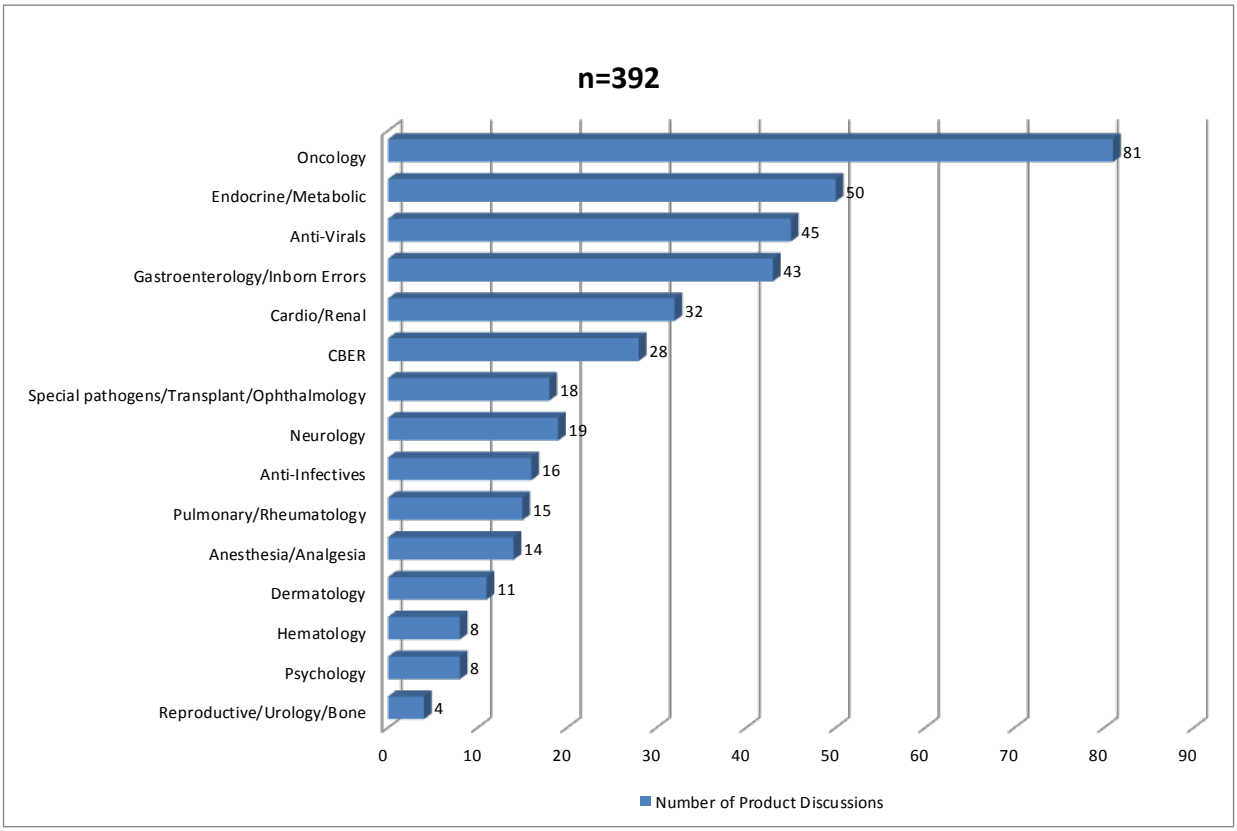
Global Harmonization of Pediatric Research

Since 2007, FDA has been engaged in a global effort to improve what is known about therapies for pediatric populations and include this knowledge in prescribing information. Even before full implementation of recent European Union (EU) pediatric regulations

and directives,[30] it became clear that pediatric trials must be coordinated on an international level in order to prevent children from being enrolled in duplicative trials. It also became clear that FDA would need to encourage international harmonization in order to maximize the informational benefits from pediatric trials, decrease unnecessary exposure or trials, and increase the efficiency of enrollment of limited study populations.

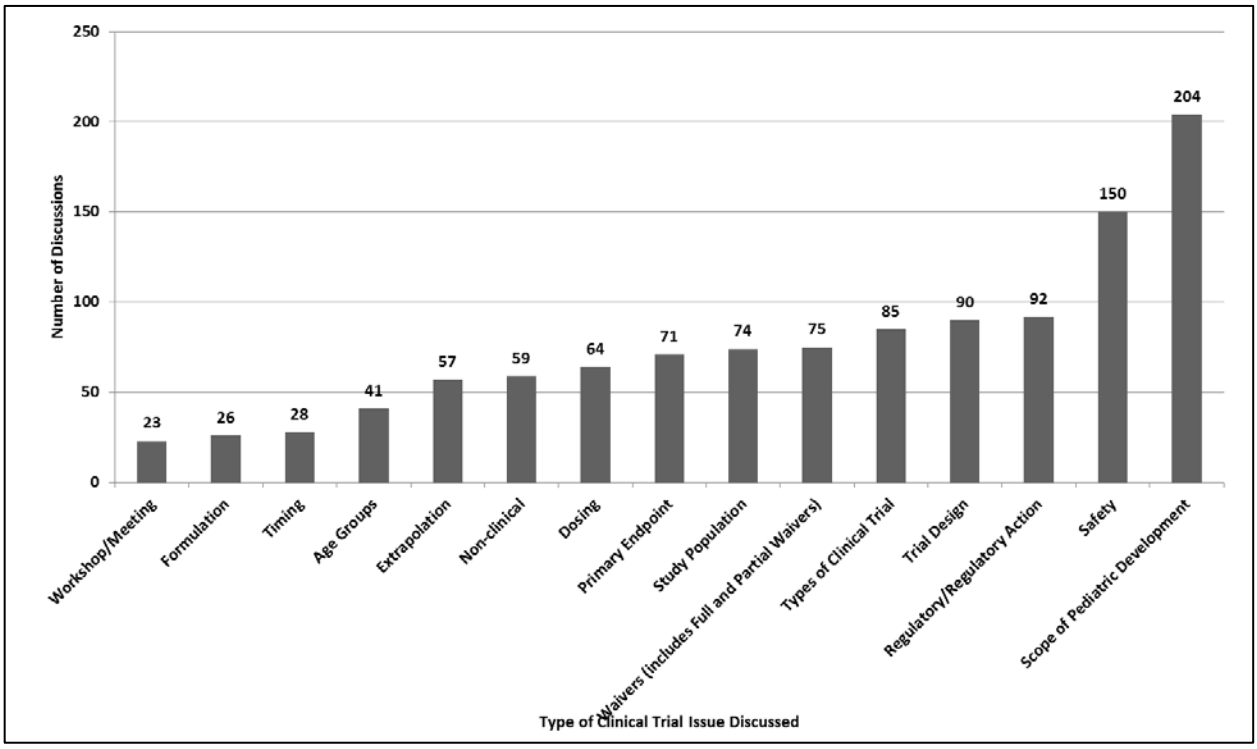
To facilitate this process, OPT is working with the scientific experts in the various FDA Centers to coordinate monthly conference calls with pediatric colleagues in Europe, Japan, Canada, and Australia. This collaboration is commonly termed the "Pediatric Cluster," as it is one of several similar groups addressing a variety of topics related to medical product development and regulation. From July 2012 to July 2015, the Pediatric Cluster discussed 107 products proposed for studies in pediatrics (see figure 2). Over two dozen different issues were discussed, with the most common topics being the scope of pediatric development, safety issues, and study design (see figure 3). This international collaboration resulted in the resolution of many pediatric trial and safety issues, and it has been critical to development of common trial designs and publications. Since 2012, for topics meeting certain criteria, FDA and the European Medicines Agency (EMA) developed a one-page "Common Commentary" document to inform sponsors about the discussion and any high-level conclusions by the regulators.

Figure 2: Pediatric Cluster Products Discussed by Division 2007-2015



[30] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf.

Figure 3: Frequency of Clinical Trial Issues Discussed at Pediatric Cluster 2007-2015



Three specific examples—one in type 2 diabetes and two related to Gaucher's Disease—where differences existed and were either partially or completely resolved demonstrate the value of a strategic collaborative approach between FDA and EMA.

In the first example, trials of type 2 diabetes products in pediatric patients were problematic on a global basis because of the paucity of children with the condition relative to the number of products sponsors were trying to develop. FDA and EMA collaborated to recommend a trial with multiple products compared to the standard-of-care to maximize the information gained from the study and allow one "control" arm for a number of products.

However, in this example, FDA and EMA differed on an appropriate length of treatment on the control arm. The United States was requiring 12 months of controlled data, while the EMA was requiring only 6 months. The agencies collaborated on a solution to require submission of 12 months of data to the United States, but allow for flexibility in design of the study so that at 6 months, those for whom HbgA1C was not controlled within certain parameters could opt out of the control arm. This was acceptable to both agencies.

The second example is in the case of Gaucher's Disease and the issue of extrapolation of efficacy. FDA and EMA discussed the extent to which extrapolation could be applied across subtypes of Gaucher's Disease and across similar products with the same mechanism of action to treat this disease. It was agreed that extrapolation was

appropriate from adults to children for visceral and hematologic endpoints within Type 1 Gaucher's Disease. In addition, FDA and EMA agreed on a single rather than a composite primary endpoint irrespective of prior treatment status.

The third example reflects another difference in perspectives relating to Gaucher's Disease. EMA's position was that change in normalized hemoglobin for treatment-naïve patients and a composite endpoint (change in hemoglobin, platelet count, liver and spleen volume) for pre-treated patients should be the primary endpoint in clinical trials. By contrast, FDA proposed a specific single primary endpoint, considering change in hemoglobin scientifically robust and acceptable for prior approvals. Through collaboration, EMA accepted FDA's position, and the agencies proposed a common commentary and joint publication.

Pediatric Advisory Committee: Postmarketing Safety Reviews

There remains a critical need for reporting of adverse events (AE) in the pediatric population. FDA's ongoing pediatric-focused postmarket surveillance with safety reviews presented to the PAC often results in important new safety information and sometimes reveals unexpected AEs in children. Since the passage of FDASIA, from July 2012 to July 2015, the PAC was presented 87 products for review (60 drug reviews, 13 biological product reviews, and 14 device reviews). The identified safety signals may not be seen in adults, and children may be particularly vulnerable to accidental or secondary exposures that were not studied, such as in the case of AndroGel (testosterone gel). FDA received several pediatric reports of secondary exposure to topical testosterone gel through contact with other persons using the drug product, and the exposed children developed severe AEs including precocious pubertal development, enlarged genitalia, advanced bone age, and aggressive behavior. In some cases, surgery was being performed on young girls because of the enlargement of the genitalia resulting from these exposures. The identification of this safety signal led to a Boxed Warning (FDA's strongest warning) for AndroGel, and the manufacturers of topical testosterone products were required to develop safety strategies to protect children from secondary exposure.

The pediatric postmarket surveillance and public reporting to the PAC is unique in that it is triggered by the pediatric information that results in new labeling, irrespective of the success or failure of the trials. Recognizing that pediatric trials are difficult and small in number, it is required that even "negative trial findings" for pediatric studies are included in labeling. This is important because we know that products that are available for adults may be used in children, even when they have not been proven to work effectively in children. Therefore, this 18 month post-labeling activity provides a window on "real world" use of these products in children.

C. Program for Pediatric Study of Drugs Under the Public Health Service Act (NIH-BPCA Program for Pediatric Studies of Drugs)

1. Background

One of the most challenging areas in the last 15 years has been the development of those products for which sponsors have declined the FDA-issued WR. These declinations often involve products that are generics or intended to treat small populations or neonates, or for which the receipt of additional exclusivity was not deemed useful to the sponsor. Section 409I of the Public Health Service Act was enacted in 2002 as part of BPCA, and it authorizes testing of pediatric therapeutic products by NIH. Consequently, for those FDA-issued WRs for pediatric testing that are declined by sponsors, the products are referred to the NIH for consideration for its priority list and potential study. The NICHD, which leads the trans-NIH BPCA Working Group, established and funded the Pediatric Trials Network (PTN) to conduct clinical trials aimed at filling in the critical gaps in information on pediatric therapeutic product use. After resolving many of the scientific, motivational, and logistical issues surrounding implementation of these pediatric trials, the NIH now regularly submits data packages to FDA, with four products newly labeled for pediatric use and many more products in the labeling pipeline.

The NIH prioritization process is based on identifying gaps in information on pediatric therapeutics, the health benefits of further research, and the need for infrastructure to carry out these research goals (e.g., training for clinical pharmacologists to enable them to participate in clinical trials with pediatric patients and a pediatric trials network structure). Public input to inform these research priorities is obtained via various mechanisms, including mailing solicitations for input, convening working groups in specific therapeutic areas composed of leading researchers and health care professionals, and awarding contracts to evaluate the frequency of medications used and the prevalence of conditions.

2. Current process

NIH is directed to prioritize therapeutic areas and/or medications prescribed to pediatric patients that need further study and specific labeling for pediatric use, to perform or sponsor pediatric clinical trials, and to submit study data to FDA as evidence for pediatric labeling. NIH may receive WRs that have been declined by the pharmaceutical industry (common with off-patent medications) or develop draft WRs (Proposed Pediatric Study Requests, or PPSRs).

The NIH BPCA process consists of the following steps:

- NIH prioritization of a therapeutic area and drug product(s)
- Funding of the clinical trial
- Submission of data to FDA
- Acceptance of the data by FDA and opening of an FDA docket
- Submission of de-identified data to the FDA docket
- FDA review of submission

- FDA publication in the *Federal Register* of the labeling change (time=180 days)

3. Results

From 2002 to date, NIH prioritized 96 drugs in 46 therapeutic areas. NIH received 24 WRs from FDA and submitted 7 PPSRs to FDA. In the early years of the program, WRs received from FDA for off-patent drugs constituted the original pipeline for studies performed in the NIH BPCA program. In addition, following passage of the original 2002 legislation, the NIH awarded seven contracts to perform pediatric clinical trials to academic centers with expertise in a particular clinical area. Within a few years, it became clear there was a need for a centralized network to perform pediatric clinical trials and other trial-related activities (such as protocol, assay, and formulations development), improve trial design and patient recruitment, and generate a new pipeline of studies in pediatric therapeutics. In 2010, a contract was awarded to Duke University for PTN.[31] The Duke contract now performs 40 small and larger clinical trials with 60 academic sites as subcontractors.

As previously noted, since the NIH program's inception, FDA has approved four labeling changes to drug products and approved one device related to this program (although not related to BPCA). Due to the complexity of conducting studies that manufacturers declined to perform, product drug label changes for sodium nitroprusside and meropenem took an average of 10 years to complete from the time the WR was received, the contract awarded, the study completed, the data reviewed, the data submitted to the docket, and the label changed. Labeling changes for pralidoxime (for a pediatric indication to treat nerve agent exposure) and propylthiouracil were the result of cooperative efforts between NIH and FDA. NIH provided a total of 21 submissions to FDA review divisions for 14 products as of July 2015; 2 of these submissions (ampicillin and lorazepam) were posted to FDA's docket in December 2015. FDA expects 10 more submissions by 2017.

In an effort to expand outreach and research capacity, the NICHD developed a trans-NIH BPCA Working Group to determine interests from other NIH Institutes and Centers (IC). NICHD also collaborated with several other NIH ICs on specific areas of pediatric therapeutic interest. The National Heart, Lung, and Blood Institute's Baby HUG trial for hydroxyurea in very young children with sickle cell disease [32] was co-funded by NICHD under BPCA, as were several NCI-Children's Oncology Group trials. In addition, the NICHD is working closely with other federal agencies and non-governmental organizations, such as the Health Resources and Services Administration (HRSA) and the American Academy of Pediatrics' (AAP) "Pediatric Research in the Office Setting Network," on use of atypical antipsychotics and AEs in these pediatric primary care practices.

[31] Contract number HHSN275201000003I.
[32] Data to be submitted in 2016.

To address the substantial issue of developing pediatric formulations (dosage forms that children can easily swallow and are palatable), in 2010 NIH and FDA entered into a two year Interagency Agreement to devise approaches to developing such dosage forms.[33]

In the 2012 reauthorization of BPCA, Congress specifically included neonates as a population in which studies should be encouraged. In response, the NIH BPCA program collaborated with the NICHD Neonatal Research Network to determine the dosing, efficacy, and safety of dopamine, a drug commonly used in the Neonatal Intensive Care Unit (NICU) to treat hypotension (low blood pressure). The study identified a surprising number of scientific gaps in our knowledge, including lack of a clear definition of hypotension, lack of information about normal blood pressure in extremely premature infants, and the health outcomes of children who had been treated (or not treated) for low blood pressure. As a result of this study, we have much more relevant information to help answer these questions.

D. Neonates

Since the enactment of BPCA and PREA, FDA has made efforts to increase the number of studies conducted in the neonatal population. FDA encourages the conduct of appropriate studies in neonates by sponsors of products with sufficient safety and other information to ensure the ethical and safe conduct and results of such studies. In 2012, the Agency established a Neonatal Subcommittee of the PAC to address the challenges associated with the neonatal population, with the intent of fostering the development of therapeutics for neonates and overcoming the challenges and obstacles to advancing neonatal regulatory science. The subcommittee met in 2013 to discuss the challenges impeding the advance of neonatal product development across all therapeutic areas of FDA-regulated medical products (biologics, devices, drugs, etc.). These challenges were broadly grouped into three categories—study design, study implementation, and ethics.

Additionally, under FDASIA, FDA was required to hire a neonatologist and to have the neonatologist serve as a member of the PeRC. This was accomplished in the fall of 2015. In September 2015, the neonatologist launched a consultation service offering neonatal-oriented consultation on drugs, devices, biologics, and nutritional products throughout the Agency. The consultation service addresses adverse event reporting in NICUs, neonatal therapeutic gaps, and expansion of databases to include more detailed neonatal data. This service has been promoted in face-to-face meetings with FDA Center leadership; consultations with FDA's Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health (CDRH); and meetings with sponsors.

Development of an International Neonatal Consortium

In October 2014, FDA co-sponsored the "First Annual Neonatal Scientific Workshop—Roadmap for Applying Regulatory Science to Neonates." This workshop determined

[33] See http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx.

interest in developing an International Neonatal Consortium (INC). Today, INC is a global consortium with international stakeholders from academia, industry, regulatory bodies (FDA, NIH, EMA, Health Canada, and the Japan Pharmaceutical and Medical Devices Agency), neonatal advocacy groups, family/patient advocacy groups, and neonatal nursing organizations.[34] After discussions with stakeholders, INC was launched by the Critical Path Institute (CPath) with a workshop at the EMA in London on May 18-19, 2015. Four initial working groups (Seizures, Data, Bronchopulmonary Dysplasia, and Clinical Pharmacology) were established. These working groups reported at the second annual workshop held on March 7-8, 2016.[35]

ORISE Faculty Fellowship

Until resources were available to hire a neonatologist, FDA was able to leverage internal resources to establish an Oak Ridge Institute for Science and Education (ORISE) Senior Faculty Fellowship that allowed a part-time neonatologist to join FDA. The ORISE fellow worked on numerous projects inside the Agency and developed external collaborations to advance neonatal science and clinical trials. This included the development of a research program involving an academic researcher's evaluation of potential study endpoints for neonates with pulmonary arterial hypertension. Subsequently, the work continues under an Interagency Personnel Agreement with OPT. The neonatologist partnered with the AAP Section on Neonatal-Perinatal Medicine to launch the Task Force for Neonatal Therapeutics Development and presented the FDA regulatory perspective to neonatology training program directors, neonatology fellows, and early-career neonatologists, with a goal of expanding training opportunities in clinical trial design, pharmacology, and neonatal regulatory science.

In 2015, the International Life Sciences Institute-Health and Environmental Sciences Institute's Developmental and Reproductive Toxicology Technical Committee voted to support a project on nonclinical neonatal pediatric models. Working groups, including FDA participants, were established to identify nonclinical models of neonatal disease, construct a general framework for nonclinical neonatal models, and use nonclinical neonatal models to identify safe and effective starting doses for studies in neonates. The ORISE fellow participated on these working groups.

E. Oncology

Since the enactment of FDASIA, there have been a number of advances in the pediatric oncology arena. Six new drugs were approved for oncology indications in the pediatric population: asparaginase Erwinia chrysanthemi, mercaptopurine, everolimus, denosumab, palifermin, and dinutuximab. All of these products were approved to treat cancer with the exception of palifermin, which was approved for the amelioration/prevention of mucositis, a complication specifically associated with hematopoietic stem cell transplantation. Two of these drugs are essential elements of the multi-agent treatment

[34] http://c-path.org/programs/inc/.
[35] http://www.fda.gov/Drugs/NewsEvents/ucm475626.htm.

regimen for childhood acute lymphoblastic leukemia. Asparaginase Erwinia chrysanthemi represents the only alternative therapy for children who develop hypersensitivity reactions to other asparaginase preparations, an unfortunately frequent problem that directly affects response to therapy and outcome. In other advances, a new formulation (solution for oral administration) of mercaptopurine was approved; this formulation is intended to improve accuracy of dosing and therapeutic efficacy by decreasing toxicities. Denosumab is the only approved therapy for a rare bone tumor which, before the approval, was managed only with aggressive surgical excision associated with disfiguring and debilitating complications. The approval of dinutuximab for high-risk neuroblastoma was based on the results of large multi-center clinical trials conducted over a period of 9 years, resulting in the first improvement in observed survival rates in over 20 years. Prior to enactment of FDASIA, only one of these products (denosumab) had been studied in children. However, from 2012 to present, three additional products (erlotinib, capecitabine, and bortezomib) had pediatric information added to product labeling as a result of completed studies.

In addition, in response to WRs issued under BPCA before FDASIA, 21 oncology products are being evaluated in clinical trials in one or more specific pediatric cancers. From 1998 to July 2012, FDA issued 54 WRs for oncology products. Since the enactment of FDASIA to the present, FDA issued 12 WRs for oncology drug and biological products. Four additional WRs are currently under discussion with sponsors; we anticipate some of these will be issued prior to the approval of these new drugs.

Review staff have been proactive in identifying new drug and biologic products which, based on their mechanisms of action or efficacy in a cancer type commonly seen in adults, might be effective in the pediatric population. This has contributed to the significant increase in the rate of issued WRs. Quarterly meetings between FDA staff and representatives of the pediatric oncology investigator community aid in the identification of prospective new products with a strong rationale for pediatric evaluation. Sponsors of products of interest are invited to meetings of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee to present background on mechanisms of action, pre-clinical studies, and early adult clinical efficacy trial and toxicity results. These outreach initiatives result in valuable discussions about the specific cancers in children for which a drug might be effective, create the potential for effective treatment and possible study designs, and inform decisions regarding issuance of WRs.

BPCA is a significant piece of legislation with the goal of encouraging pediatric drug development. The current emphasis on personalized/precision therapy in cancer medicine drives the development of new targeted drugs that inhibit specific cellular pathways or genetic mutations/deletions associated with the causation or progression of specific types of cancer in selected individuals. Given this current emphasis, we plan on expanding such outreach efforts. To date, precision medicine has benefited mainly adults with cancer. Increasing opportunities for communication with pediatric cancer subject-matter experts and investigators will promote earlier identification of new drugs of interest for potential evaluation in children. Continuing efforts may include increasing the frequency of meetings of the Pediatric Subcommittee of the Oncologic Drugs

Advisory Committee, increasing participation by the Office of Hematology and Oncology products pediatric oncology medical officers in meetings of the various pediatric cancer clinical trial networks, formalizing an annual Pediatric Cancer Advocacy Outreach Program, and increasing the frequency of quarterly teleconferences of the BPCA Pediatric Oncology Working Group.

FDA understands the limitations of PREA with regard to certain pediatric diseases, most notably pediatric cancers. Because most oncology products are developed for adult cancer indications that do not occur in children (e.g., breast, lung, prostate, colorectal), products that would otherwise be studied under PREA are generally not applicable to pediatric cancers. The Agency has granted full waivers when studies would be impossible or highly impracticable. However, in some types of childhood cancers, the same molecular targets for which new drugs are developed in adults may be important in the etiology of a specific, albeit different, cancer type seen in the pediatric population. Examples include mutations, amplifications of the ALK gene in neuroblastoma, SHH pathway mutations in medulloblastoma, BRAF mutations in gliomas, and ABL family genes (PDGFRB, CSF1R) in Ph+-like acute lymphoblastic leukemia. Early clinical evaluation of targeted drugs developed for adult cancers in children with relapsed/refractory cancers presents an opportunity to address a significant unmet medical need. Therefore, expanding the scope of PREA to require pediatric studies based on a pediatric tumor's expression of a molecular target or the known molecular mechanism of a new drug could significantly increase the number of pediatric studies conducted under PREA. ***We recommend an amendment of PREA to require certain drugs (including biological products) developed for adult cancer indications to be evaluated for a pediatric cancer indication, when there is evidence the drug affects specific molecular targets and/or molecular mechanisms shared between adult and pediatric cancers.*** This would include a drug that targets, inhibits, or suppresses a cell surface receptor, an aberrant fusion protein, or cell signaling pathway (molecular target) in an adult cancer reportedly associated with the causation and/or progression of one or more pediatric cancers.

One significant limitation of PREA that negatively affects pediatric cancer drug development is the PREA exemption resulting from orphan designation (disease prevalence of < 200,000 in the United States) for "rare" adult cancers that also occur in children. Because PREA does not apply to drugs for indications for which orphan designation has been granted even when the same cancer types occur in the pediatric population, there are substantial delays in the evaluation of highly effective cancer drugs in children. Examples include the BCR-ABL tyrosine kinase inhibitors, imatinib, dasatinib, nilotinib, and ponatinib for chronic myelogenous leukemia (CML) that also occurs, albeit rarely, in children. In addition, brentuximab vedotin, an anti-CD30 monoclonal antibody now approved for two different clinical indications in Hodgkin Disease (which also occurs in children), is only now being studied in the pediatric population. Timely evaluation and approval of these drugs in children would not jeopardize the exclusivity associated with orphan-designation. ***Therefore, we recommend eliminating the exemption under PREA for relevant orphan-designated***

adult oncology products, found in section 505B(k) of the FD&C Act, which could be useful for pediatric indications.

F. Improving Pediatric Drug Research

While BPCA and PREA (and the FDASIA amendments to BPCA and PREA) have been instrumental in improving pediatric labeling and drug research, some future modifications may be warranted for further improvements. Specifically, the Secretary recommends the following modifications:

1. Yearly Review of HDEs

The Pediatric Medical Device Safety and Improvement Act (PMDSIA) of 2007 provides for an exemption from the restriction on profit-making for devices approved under humanitarian device exemption (HDE) that are labeled for the treatment or diagnosis of a disease/condition that occurs in pediatric patients or a pediatric subpopulation. Such devices must undergo an annual review by the PAC of the appropriateness of the HDE. As of September 16, 2015, 11 devices were presented to the PAC, with 9 devices continuing to undergo PAC annual reviews (2 were removed, as they are no longer Humanitarian Use Devices).

Devices that undergo annual reviews by the PAC vary greatly in their annual distribution numbers (ADNs) and safety profile. For example, the Elana Surgical Kit was first reviewed by the PAC in September 2012, followed by three annual PAC reviews, with a low ADN and no new safety issues identified for the device. However, the Gastric Enterra Therapy System underwent an initial PAC review in 2014 and a subsequent annual review in 2015. In response to PAC recommendations, the sponsor made labeling changes for the device and, in their annual report, submitted AE information for patients younger than 22 years. ***To better utilize the PAC and FDA staff generating materials for the annual reviews to the PAC and to focus on HDE-approved devices with new and/or serious safety signals, FDA recommends enhancing the current "annual" review requirement by changing the threshold for review of a pediatric HDE-approved device to be based on a "periodic" risk-based review.*** Independent of the PAC review, CDRH receives an annual report from the sponsor with a summary of all mandatory Medical Device Reports (MDRs), the ADN for the device, and any post-approval study results. In addition, CDRH conducts a separate pediatric-focused postmarket review of both mandated and voluntary MDRs. A requirement for "periodic" risk-based (rather than "annual") PAC review would allow for some flexibility in deciding when to bring a pediatric HDE-approved device to the PAC based on the review of the pediatric safety data.

2. Possible Modification of Orphan-designated Products from PREA

One aspect of PREA that negatively affects pediatric drug development is the current PREA exemption resulting from orphan designation (disease prevalence of < 200,000 in the United States) for "rare" diseases that also occur in children. As previously

mentioned, because PREA does not apply to any drug for an indication for which orphan designation has been granted even when the same cancer types occur in the pediatric population, there are substantial delays in the evaluation of highly effective cancer drugs in children.

Timely evaluation and approval of these cancer drugs in children would not jeopardize the exclusivity associated with orphan designation. ***Thus, we recommend modification of the exemption under PREA for certain oncology products with orphan designation, found in section 505B(k) of the FD&C Act.*** Targeted amendments to PREA and issuance of WRs under BPCA earlier in product development to incentivize industry sponsors can improve the timeliness of pediatric evaluations of certain oncology products, resulting in their safe and effective use for children with cancer.

3. Potential Removal of Vaccines from PREA

FDA recognizes the importance of PREA in the successful development of drugs for use in pediatric populations. However, in the development of preventive vaccines for which there is a need in the pediatric populations, pediatric studies are almost always completed early, because these vaccines are intended for use in the pediatric population. For preventive vaccines, intensive pediatric development predates, and is irrespective of, PREA. Yet the Agency has spent a large amount of resources addressing PREA requirements, including administrative expenses, communications, recordkeeping, reviewer work time, and presentations at the PeRC and the PAC. Exempting preventive vaccines from PREA would allow reallocation of resources to other important pediatric activities, including review of pediatric cancer indications and other rare pediatric diseases.

PREA is duplicative of the existing national structure aimed at incentivizing development of vaccines for pediatric populations that was in place prior to PREA, and that structure is actually more expansive than the PREA requirements. Programs and factors that incentivize development of vaccines for pediatric use include federal funding of vaccine research, the Vaccines for Children program, state laws mandating vaccination, recommendations for vaccine use, and the National Vaccine Injury Compensation Program. The National Vaccine Program Office[36] coordinates federal activities related to research, development, testing, production, procurement, distribution, and use of vaccines. Furthermore, the advisory body oversight on pediatric issues as stipulated by PREA is largely redundant of other mechanisms, programs, and advisory committees already in place that have helped ensure that children have access to safe and effective preventive vaccines. These include the CDC/FDA Vaccine Adverse Events Reporting System, FDA's Post-Licensure Rapid Immunization Safety Monitoring program, FDA's Vaccines and Related Biological Products Advisory Committee, CDC's Advisory Committee on Immunization Practices, and the National Vaccine Advisory Committee. As a result of the long-standing, robust national structure aimed at ensuring the availability of safe and effective preventive vaccines, the impact of PREA on pediatric

[36] 42 U.S.C. 300aa-1, et. seq.

testing and labeling for preventive vaccines is estimated to be negligible. ***Thus, we believe it is appropriate to remove preventive vaccines from the scope of PREA in order to redistribute Agency resources for focus on needed pediatric activities.***

G. Response to Findings of GAO and IOM Reports to Congress

In accordance with the 2007 legislative provisions, both the IOM and the GAO assessed and reported upon the effectiveness of BPCA and PREA since the 2007 reauthorization of FDAAA. The IOM report included a suggestion for expanding public access to information from pediatric studies conducted under BPCA and PREA, specifically those conducted prior to 2007. Both the IOM and the GAO reports noted a need to improve the timeliness of neonatal studies and long-term safety studies. In terms of expanding public access, the Agency has posted certain information from all studies conducted under BPCA prior to 2007 on its website.[37] The website also makes available the WRs issued for studies submitted between January 4, 2002, and September 27, 2007, and the status of pediatric exclusivity and label changes.[38] In regards to the timeliness of neonatal and long-term safety studies, the Agency has made concerted efforts to focus on the neonatal population, including hiring of additional expert staff and sponsoring workshops with outside expertise.[39]

H. Stakeholder Input on BPCA and PREA Mandated under FDASIA

1. General Conclusions

In response to FDA's March 2015 request for comments and public meeting, stakeholders from the pharmaceutical industry and advocacy organizations were in general consensus on a number of conclusions relating to BPCA and PREA. Without exception, stakeholders who provided comments agreed that BPCA and PREA have been successful in improving information about pediatric uses for approved drugs and biologic products, creating more treatment options for children and significantly improving pediatric patient safety and children's health.

Additionally, respondents generally agreed that the FDASIA permanent reauthorization of BPCA and PREA enabled a "comprehensive and integrated approach to pediatric drug development,"[40] and inspired the "confidence and predictability necessary to invest in the scientific capacity and infrastructure to advance pediatric research."[41]

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[37] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm328603.htm.
[38] See http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase.
[39] See Section II.D. of this report.
[40] Eli Lilly and Company response to Docket No. FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (Feb. 25, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.
[41] Biotechnology Industry Organization response to FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (Feb. 25, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.

Stakeholders also lauded international coordination efforts in pediatric product development to date and encouraged the Agency to continue working with global regulatory health authorities to further pediatric drug development.[42] This included the development of a global pediatric clinical trial network that leverages existing efforts to help shorten the development process by minimizing existing barriers that make it challenging to enroll subjects in pediatric studies. One organization suggested increased transparency of existing collaboration meetings between FDA and the EMA, "such as disclosure of summary reports and discussions…, acceptance of innovative approaches, and safety concerns." The organization further stated that this "would likely result in additional positive impact on pediatric product development."[43] Responding stakeholders further recommended FDA and EMA continue their efforts to develop common processes."[44]

FDA initiated the Common Commentary process in October 2012 to provide feedback to stakeholders on product development issues discussed with international regulatory colleagues in Europe, Canada, Japan, and Australia (i.e., the Pediatric Cluster). To date, 16 Common Commentaries have been completed in the following therapeutic areas: oncology, gastroenterology, cardiovascular, and neurology. In addition, FDA collaborated with EMA in writing a manuscript for publication comparing pediatric clinical trial waivers granted by each Agency from January 2007 through December 2013, and that article has been accepted for publication. Furthermore, because the development of pediatric medicines is largely driven by legislation in the United States, the EU, FDA, and EMA are collaborating on a strategic document for potential publication on how the regulatory processes can be integrated within the constraints of different pediatric legislations and timelines guiding the two regulatory bodies.

2. Specific Concerns

Several stakeholders expressed concern over remaining limitations under the current BPCA/PREA legislation. The most notable comments related to the limitations in encouraging pediatric oncology drug development, given the PREA requirements which involve dependency on the adult indications, exclusion of drugs with orphan indications, late award of BPCA incentives, and perceived risk in testing new agents in children. Responding stakeholders recommended that the legislation be amended to give FDA authority to require pediatric studies of an adult oncology agent based on common mechanisms of action or common effects on molecular pathways, and to eliminate the orphan drug exclusion.

[42] http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm433552.htm.
[43] Pharmaceutical Research and Manufacturers of America response to FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (Feb. 25, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.
[44] Pfizer response to Docket No. FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (April 24, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.

In recognition of the changing science of drug development and associated challenges for pediatric oncology, another stakeholder commented on the introduction of the Kids' Innovative Drug (KIDS) initiative for Congress' consideration and enactment. The KIDS initiative would extend PREA to mechanism of action for children, with the goal of fulfilling PREA's legislative intent. It would also provide companies additional incentives for undertaking their PREA obligations in a timely fashion.

Another stakeholder suggested the expediting of clinical trials in children. The organization further urged support for the KIDS initiative, which seeks to reform BPCA as well as PREA in this regard[45] and to substantially increase the supply of investigational drugs for pediatric cancer patients.

Stakeholders specifically recommended empowering FDA to require pediatric plans at the end of Phase 1 testing for a drug being developed to treat adults and the award of 6-month exclusivity at the earliest possible point, "even prior to approval of an adult indication, upon a company's completion of a Written Request."[46]

In terms of the challenges relating to perceived risk in testing investigational drugs in children, one stakeholder inquired about the Agency's efforts in addressing ethical questions. In responding to this issue of how to be inclusive while still minimizing risk for children, the Agency's legislatively mandated pediatric ethicist represents an integral part of the decision-making process and has been active in the PeRC in addressing such ethical concerns. Additionally, FDA has established and brought numerous issues to an ethics subcommittee of the PAC.[47]

3. Other Key Recommendations

To encourage the earliest possible start to, and ultimate success of, pediatric drug studies, responding stakeholders urged FDA to clarify timelines for review and response to PPSRs and review of amendments to WRs. Respondents identified the goals to be consistency in the process, predictability for sponsors, and promotion of timely drug development for pediatric populations. Additionally, respondents recommended the Agency consider updating and finalizing existing FDA draft guidances on BPCA and PREA, as well as ensuring consistency between the guidances on PREA, BPCA, and PSPs.[48]

In commenting on the effect of particular processes, several stakeholders noted the positive impact of the FDASIA requirement for PREA PSPs not later than 60 days following the

[45] See comments from The Max Cure Foundation, pp. 229-235 of the transcript from the "Stakeholder Input on BPCA and PREA" meeting held on March 25, 2015; http://www.fda.gov/newsevents/meetingsconferencesworkshops/ucm433552.htm.
[46] See Children's Cause Cancer Advocacy March 25, 2015, presentation in response to Docket No. FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (Feb. 25, 2015).
[47] See http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm116525.htm .
[48] See AAP Comments/Section in Transcript from Pediatric Stakeholder Meeting of March 25, 2015.

End of Phase II meeting (or a proposed alternate timeline in the absence of an End of Phase II meeting) in drug development programs.

Stakeholders suggested sponsors should include information in PSPs to support plans for submission of future PPSRs, as appropriate. Stakeholders further suggested that FDA should clarify this in the final draft guidance on PSPs by explicitly allowing sponsors to include optional BPCA information in PSPs and by providing feedback on potentially beneficial pediatric uses of the product as it may apply to the sponsor's future PPSR, and ultimately issuance of a WR, under BPCA.[49] FDA's revised draft of the guidance regarding PSPs addresses this recommendation.

Stakeholders also expressed appreciation for "FDA's implementation of the rare pediatric disease priority review vouchers (PRVs) in a manner that stimulates new drug development of new therapies for devastating childhood diseases and serious conditions through additional incentive mechanisms." They recommend legislation to make this program permanent and remove the three voucher cap, "which introduces significant uncertainty and unpredictability for sponsors…considering the risky, long, and costly investment into a clinical development program for [a] rare pediatric condition."[50] As noted earlier in this report, FDA strongly supports the goal of incentivizing drug development for rare pediatric diseases. However, this program adversely affects the ability for FDA to set public health priorities because it provides priority reviews of new drug applications that would not otherwise qualify for a priority review if the drug does not treat a serious condition or provide a significant improvement in safety or effectiveness.

Finally, responding stakeholders expressed a desire to have FDA address feasibility issues such as "formulation development, disease indication and age, and recruitment competition for limited numbers of affected pediatric patients [with a]…more flexible approach…towards clinical trial designs or alternatives to developing data outside of actual clinical trials." FDA noted its collaboration with NICHD to address formulation issues. FDA's chemists worked on a contract to evaluate the formulations of most of the products newly labeled with pediatric information and publish the basic components of those formulations; this information is now posted as the Pediatric Formulations Platform on the NICHD BPCA website.[51]

[49] Pharmaceutical Research and Manufacturers of America response to FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (Feb. 25, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.
[50] Biotechnology Industry Organization response to FDA-2015-N-0456: Pediatric Stakeholder Meeting: Requests for Comments; 80 FR 10493 (February Feb. 25, 2015); see http://www.regulations.gov/#!docketDetail;D=FDA-2015-N-0456.
[51] http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/Pages/index.aspx.

III. CONCLUSIONS

There has been significant progress made since the enactment of pediatric legislation in 1997, with over 600 products containing new pediatric information in labeling. The permanency of the programs has been critical to the sponsors, the regulators, and the patients in providing a foundation of certainty to pursuing research in this arena. However, section 409I should be permanently authorized. The implementation of new programs, including deferral extensions, issuance of public noncompliance letters, pediatric study plans, and rare pediatric disease priority review vouchers were accomplished by the timelines established by the statute but without authorization of appropriate funding to FDA. Many of the provisions led to a significant increase in the work required for review by FDA. Although implementation of these programs is ongoing, it is still premature to estimate the resulting impact on the efficiency and success of pediatric product development, which often requires several years to complete.

Created by the NIH BPCA program, the PTN is a major step forward in expanding clinical trial capabilities and is the future of pediatric clinical research. Challenges remain, including the need for development of new clinical trial designs for small populations and the need for better oral dosage forms for all age groups. These challenges increase geometrically in conducting research with neonates, where scientific gaps include measurement of neurodevelopmental outcomes, development of standardized pain scales, research on the etiologies of neonatal conditions, and development of specific drug targets that can lead to specific therapies. As they become available, data from these and other federally supported pediatric drug studies need to be shared openly to enable the field to advance more rapidly.

In addition, targeted amendments to PREA and issuance of WRs under BPCA earlier in product development to incentivize industry sponsors can improve the timeliness of pediatric evaluations of relevant products, resulting in their safe and effective use for children with cancer.

In conclusion, the areas that still require additional attention are the need for a global pediatric trials network, in coordination with existing networks, to more efficiently and effectively manage the even more difficult studies that must now be addressed. This includes the advancement of the science required to address the product development needs of neonates and pediatric cancers;, the removal of the exclusion from PREA requirements for rare diseases; and the expansion of PREA to require pediatric studies based on a pediatric tumor’s expression of a molecular target, the known molecular mechanism of a new drug, or both.