SOPP 8421: Complying with Requirements under the Pediatric Research Equity Act (PREA) & Best Pharmaceuticals for Children Act (BPCA)

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I. Purpose

A. This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff to ensure that the provisions of the Pediatric Research Equity Act (PREA) & the Best Pharmaceuticals for Children Act (BPCA) are met.

B. This SOPP serves as a resource for product offices/review divisions to ensure that sponsors/applicants as well as CBER staff are following the required procedures and timeframes under PREA & BPCA.

II. Scope

A. This SOPP applies to Investigational New Drugs (INDs) and New Drug Applications (NDAs) under section 505 of the Federal Food, Drug, & Cosmetic (FD&C) Act, Biologics License Applications (BLAs) under section 351 of the Public Health Service Act (42 USC 262), and related NDA and BLA supplements for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

NOTE: It also applies to initial pediatric study plans (iPSPs) submitted in the absence of an IND when clinical programs have been conducted outside the United States in support of a BLA.

B. This SOPP does not repeat existing PREA & BPCA related resources for CBER staff but rather provides general information and expectations on how CBER and sponsors/applicants will comply with PREA & BPCA. For CBER specific instructions on:

1. The processing and review of Pediatric Study Plans (PSPs) received under an IND or Pre-IND, refer to *JA 851.05: Instructions for Processing Pediatric Study Plans*.

2. Completing a review of an applicant's postmarketing requirement/ postmarketing commitment (PMR/PMC) Annual Report (to determine whether PREA PMRs are proceeding on schedule), refer to *JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)*.

3. Processing and reviewing any applicant proposed PREA Postmarketing Requirement (PMR) final study report milestone schedule changes (Deferral Extension Requests), refer to *JA 860.08: Instructions for Processing Applicant Deferral Extension Requests for Pediatric Postmarketing Requirements*.

4. Scheduling a Pediatric Review Committee (PeRC) meeting and preparing and submitting the required materials, see the PeRC SharePoint Online (SPO) site.

5. Posting documents to the FDA/CBER Biologics PREA Review and Labeling Changes web page (as required by the Food and Drug Administration Amendments Act of 2007 (FDAAA)), see *JA 910.07: Posting Procedures for BLA/NDA Supplements* and *T910.01: Transmittal Memo - NDA/BLA/ANDA Originals and Supplements.*

6. Processing and reviewing proposed pediatric study requests (PPSRs) and Written Requests (WRs) under the Best Pharmaceuticals for Children Act (BPCA), including procedures for qualifying for pediatric exclusivity, consult the respective Office pediatric leadership, the Office Associate Director for Pediatrics (OTP)/Review Division Senior Advisor for Pediatrics (OVRR/DCTR) and/or the Senior Advisor for Pediatric Regulatory Review (CBER).

C. This SOPP excludes:

1. Procedures for presenting products to the FDA's Pediatric Advisory Committee (PAC) (consult CBER's Senior Advisor for Pediatric Regulatory Review for regulatory questions on FDA's Pediatric Advisory Committee).

2. Rare pediatric disease priority review vouchers (for more information regarding priority review vouchers, refer to *SOPP 8427: Procedures for Priority Review Vouchers*).

III. Background

A. The Pediatric Research Equity Act (Public Law 108-155), enacted in December 2003, amended the FD&C Act by adding section 505B (21 U.S.C. 355B) to give FDA the authority to require pediatric studies for certain drugs and biological products. The goal of these studies is to obtain pediatric labeling for the product. PREA was re-authorized as part FDAAA in 2007 and made permanent as part of FDASIA in 2012.

B. PREA requires that all applications, and supplements to an application, for drugs submitted under section 505 of the FD&C Act (21 U.S.C. 355) or biologics under section 351 of the Public Health Service Act (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, contain pediatric assessments, unless the applicant has obtained a waiver or deferral (section 505B(a) of the FD&C Act).

C. In 2010, the Biologics Price Competition and Innovation Act of 2009 extended provisions of the BPCA to biological products. The BPCA defines pediatric studies to mean at least one clinical investigation in “pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies.” The BPCA and PREA are designed to work together to encourage the development of data to inform the safe and effective use of drugs in pediatric populations.

IV. Definitions

A. Pediatric Review Committee (PeRC) - A CDER led committee, established under FDAAA, with additional membership from CBER, Office of Pediatric Therapeutics (OPT) and Office of the Chief Council (OCC), that regularly meets to provide consultations to review divisions on **all** PREA-required studies to include iPSP, agreed upon iPSP, assessments, deferrals, deferral extensions (DE) and waivers; also reviews BPCA submissions: Proposed Pediatric Study Requests (PPSR), inadequate letters, and Written Requests (WR).

B. Oncology subcommittee of PeRC - A committee established by the Oncology Center of Excellence (OCE) to implement provisions under FDARA regarding the development of safe and effective new drugs and biologics to treat cancer in children.

C. CBER Pediatrics Working Group (PWG) - A collaborative forum used in CBER to discuss and develop both policy and procedures regarding product development in the pediatric population in a manner which will provide for participation by all CBER offices. This working group is overseen by the Associate Director for Policy (ADP) and the Associate Director for Medicine (ADM) Office of the Center Director (OCD) or designee.

D. **PREA Post Marketing Requirement (PREA PMR) -** A deferred pediatric study required under PREA that is implemented as a PMR.

E. **Pediatric Deferral Extension (DE) Request -** A request from an applicant to extend the final study report submission date (milestone) of an outstanding PREA PMR.

F. **Pediatric Study Plan (PSP) -** An outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any planned request for a deferral, partial waiver, or waiver if applicable, along with any supporting information; and other information specified in the regulations issued by the FDA.

G. **Initial PSP (iPSP) -** The initial submission under the pre-IND/IND of a sponsor's plans for addressing PREA for any planned new application or supplement.

H. **Agreed iPSP -** FDA's agreement to an iPSP.

I. **Amended iPSP -** Sponsor's proposed changes made to an agreed iPSP.

J. **Agreed Amended iPSP -** FDA's agreement to the sponsor's changes made to the amended iPSP (30 day review clock).

K. **PREA Non-Compliance Letter -** Issued when FDA has determined that the applicant has failed to submit a pediatric assessment for a PREA PMR or has failed to submit a request for deferral extension of that PREA PMR.

L. **Written Request (WR) -** A document issued by FDA requesting submission of a study or studies intended to provide meaningful health benefits in the pediatric population. The WR specifies the elements of the study or studies that the sponsor or application holder must complete to qualify for pediatric exclusivity. FDA can issue a WR at the request of an interested party or on its own initiative. Completion of studies described in a WR is voluntary.

M. **Proposed Pediatric Study Request (PPSR) -** A sponsor's submission describing proposed pediatric studies to obtain a WR under BPCA. The PPSR should describe the studies the sponsor or application holder proposes to conduct to qualify for pediatric exclusivity. The PPSR should include:

   1. A background section,

   2. Nonclinical studies,

   3. Drug information,

   4. Clinical studies,

5. Known drug safety concerns and monitoring,

6. Statistical information, including power of studies and statistical assessments, and

7. Time frame for submitting reports of the study or studies.

N. Pediatric Exclusivity - A 6-month extension of existing patent or exclusivity protections granted for completing studies in response to a WR. For biologics, pediatric exclusivity only attaches to reference product and orphan drug exclusivity periods. In addition, unlike other drug products, pediatric exclusivity does not attach to patents for biological products.

O. Pediatric Exclusivity Board (PEB) - The Pediatric Exclusivity Board reviews pediatric studies that can be submitted in response to a Written Request (WR), issued by FDA, that addresses a public health need. The Board reviews the materials provided by the review division to make a determination. The determination must be made within 180 days of receipt of the application.

V. Policy

A. Product Offices will engage sponsors/applicants early in product development (i.e., under the pre-IND, if submitted without an IND or IND phase) regarding any required plans for developing products subject to PREA. Specifically, Product Offices will ensure that the following key points are discussed:

1. Rationale for the sponsor's plan to request either a waiver or deferral for pediatric studies in accordance with PREA and the PSP guidance.

2. Reasonably agreed upon timelines for completing planned pediatric studies.

B. In the absence of an IND (e.g., when the clinical development program is conducted outside the United States), sponsors are strongly encouraged to contact the appropriate CBER Office as early as possible to avoid any delay to ensure that an agreed iPSP is included in any future NDA, BLA, or supplement that is required by PREA to include pediatric assessments. All applicable review timelines, PeRC review requirements, and communication procedures outlined in this SOPP and in *JA 851.05: Instructions for Processing Pediatric Study Plans* remain in effect regardless of a submitted iPSP and are reviewed without an IND.

C. The pediatric assessments shall contain data gathered using appropriate formulations for each age group for which the assessment is required that are adequate to:

1. Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations.

2. Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective.

3. Applicants must provide an assessment of the data gathered to support the safety and effectiveness of the product in the entire pediatric population (from birth through younger than 17 years of age).

   NOTE: While the **entire** pediatric age range must be addressed, depending on the product, not all age groups (neonates, infants, children, and adolescents) will necessarily require completed studies.

D. A sponsor of an IND subject to PREA is required to submit an initial pediatric study plan (iPSP), typically no later than 60 days after an end-of-phase 2 meeting, to identify needed pediatric studies.

E. Under PREA, an applicant may request and be granted a:

1. Waiver for some/all age groups if (in most cases only one of the following is applicable):

   a. Studies in pediatric age group(s) are impossible or highly impracticable (because, for example, the number of patients is so small, or the patients are geographically dispersed);

   b. There is evidence strongly suggesting that the product would be ineffective or unsafe in some/all pediatric age groups. If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product;

   c. The product does not represent a meaningful therapeutic benefit over existing therapies *AND* is not likely to be used in a substantial number of pediatric patients; or

   d. The applicant can demonstrate that reasonable attempts to develop a pediatric formulation necessary for a specific age group have failed (partial waiver only).

2. Deferral for some/all age groups if (in most cases only one of the following is applicable):

   a. Product is ready for approval for use in adults before pediatric studies are complete;

   b. Pediatric studies should be delayed until additional safety or effectiveness data have been collected; or

c. There is another appropriate reason for deferral; and the applicant submits to the Secretary (i) certification of the grounds for deferring the assessments; (ii) a description of the planned or ongoing studies; and (iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; (iv) a timeline for completion of such studies.

F. Deferred studies identified in the agreed PSP may become PREA PMRs with specific milestones at the time of BLA or supplement approval. If unanticipated difficulties arise, applicants may later request revised (new) final study report (FSR) milestones for their deferred PREA PMRs under a deferral extension (DE) request (which must be submitted not less than 90 days prior to the date the original deferral FSR milestone and no earlier than one year prior to the date the original deferral FSR milestone).

G. Generally, products designated as orphan under the Orphan Drug Act are exempt from meeting the requirements of PREA. However, Section 505B of the FD&C Act, as amended by FDA Reauthorization Act (FDARA), requires that any original NDA or BLA submitted on or after August 18, 2020, for a new active ingredient, must contain reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act, unless the requirement is waived or deferred, if the drug that is the subject of the application is: (1) intended for the treatment of an adult cancer, and (2) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer in accordance with the Guidance for Industry: *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*. FDA maintains a current list of pediatric molecular targets, The Relevant Molecular Target List & The Non-Relevant Molecular Target Leading to Waiver List on FDA's Pediatric Oncology web page.

H. Under section 505B(d)(1) of the FD&C Act, FDA may issue a PREA Non-Compliance letter to an applicant who failed to submit a required pediatric assessment (i.e., FSR containing data to support pediatric labeling of the product) or report of a molecularly targeted pediatric cancer investigation (usually in the form of a supplemental application that includes proposed labeling). FDA may also issue a letter if a sponsor failed to request approval for a pediatric formulation. FDA Non-Compliance letters and applicant's response are made public on the CBER PREA Non-Compliance Letters web page.

I. PREA PMRs cannot be fulfilled only by the submission of FSRs as product correspondence or in an annual report. PREA requires the results of all required pediatric studies be in the label (whether negative, positive, or inconclusive data); therefore, a labeling or efficacy supplement is required as a condition of fulfillment of a PREA PMR.

J. Applicants are required to annually report the progress of all PREA PMRs as part of the requirements under 21 CFR 601.70 “Annual progress reports of postmarketing studies.”

K. FDA has tracking and reporting requirements under PREA.

1. All PREA PMRs (i.e., deferred pediatric assessments) are annually reported in the Federal Register and quarterly on FDA’s Postmarketing Requirements and Commitments Searchable Database web page. FDA is required to report on the status of each milestone for all PREA PMRs. The applicant and FDA reporting requirements are detailed in the Guidance for Industry: *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*. Refer to *SOPP 8413: Postmarketing Requirement/Commitment Related Submissions – Administrative Handling, Review, and CBER Reporting* for more information and procedures.

2. Section 508 of FDASIA requires 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, “Status Report to Congress July [insert dates] - Best Pharmaceuticals for Children Act and Pediatric Research Equity Act” is submitted in accordance with that provision and 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. CBER contributes to these Congressional reports.

3. FDAAA requires that the FDA track and make publicly available certain pediatric information resulting from pediatric clinical trials. CBER provides data at the end of each calendar year to both the Office of Pediatric Therapeutics (Office of Commissioner level) and the Division of Pediatric Maternal Health in the Center for Drug Evaluation and Research (CDER) to satisfy annual reporting requirements under PREA. CBER tracks & reports the following data on the “Pediatric Tracking Requirements Under FDAAA” web page:

a. Waivers requested and granted.

b. Deferrals requested and granted.

c. Deferral extensions requested and granted.

d. Products approved with a pediatric indication.

e. Pediatric study characteristics for the clinical trials conducted to support each pediatric labeling change also are provided, including the type of study, study design, number of pediatric participants, and ages studied.

f. The status of all PREA PMRs.

L. For submissions subject to PREA and PeRC review, the Product Office will:

1. Review the sponsor's pediatric plans under the IND/pre-IND to determine the adequacy of the proposed studies.

2. Review the adequacy of a completed pediatric assessment in the applicant's original application to provide pediatric data in the label.

3. Review the adequacy of an applicant's efficacy/labeling supplement containing pediatric data (submitted in support of an outstanding PREA PMR) to provide sufficient pediatric data in the label and to fulfill the PREA PMR.

M. Product Offices will utilize their Associate Director for Pediatrics (OTP) or Review Division Senior Advisor for Pediatrics (OVRR/DCTR) and office representatives to the CBER PWG for clinical questions pertaining to PREA, and consult with the Senior Advisor for Pediatric Regulatory Review (CBER) for questions that could affect consistency of PREA oversight across CBER Product Offices with regard to regulatory and policy questions related to INDs and applications that are subject to PREA and other relevant pediatric topics. If warranted, the questions/topics will be discussed at the monthly PWG.

N. CBER will utilize PeRC/Oncology subcommittee PeRC to review all Pediatric Plans, Assessments, Deferrals, and Waivers prior to the approval of an application or supplement for which a pediatric assessment is required.

O. CBER will utilize the PMR/PMC Annual Report Review Form (PARRF) to review the applicant's PMR/PMC Annual Reports to monitor that PREA PMRs are proceeding on schedule.

P. Studies conducted under the BPCA are optional because sponsors have the option of declining to undertake them in response to a written request (WR). While sponsors may qualify for pediatric exclusivity under the BPCA for completed PREA studies when those studies are described in a WR issued by FDA before the sponsor submits any study reports, FDA does not expect to issue WRs solely for PREA-required studies. In general, a WR that includes PREA-required studies will also encompass additional indications or populations that may produce health benefits in the pediatric population If FDA determines that "information relating to the use of a new drug in the pediatric population may produce health benefits in that population" and issues a WR, a sponsor may qualify for 6 months of exclusivity under the BPCA for conducting studies that are required under PREA.

Q. For submissions under BPCA and PeRC review, the Product Office will:

1. Review Proposed Pediatric Study Requests (PPSRs) submitted to the IND and determine whether to issue an inadequate letter or issue a Written Request (WR) for pediatric studies. The Product Office will communicate the planned action to PeRC to facilitate appropriate scheduling and discussion time allocation.

2. Review and discuss amendments to the Written Request at PeRC to ensure alignment on study design, endpoints, and pediatric study requirements.

3. Review completed pediatric studies submitted to the (s)BLA, in response to a Written Request to determine whether:

   a. All objectives outlined in the WR have been met.

   b. The data are adequate to support pediatric labeling.

   c. The sponsor has fulfilled requirements for pediatric exclusivity consideration.

4. Present at the Pediatric Exclusivity Board (currently housed in CDER) after the BLA/sBLA midcycle meeting, to evaluate whether the sponsor has met all requirements for pediatric exclusivity, including completion of all WR objectives and timely submission of study reports.

5. Present pediatric exclusivity determinations to PeRC following the pediatric exclusivity board meeting for awareness and to solicit additional comments or considerations.

VI. Responsibilities

A. Regulatory Project Manager (RPM)

1. Ensures the timely review of all incoming PREA and BPCA related submissions.

2. Ensures sponsors are provided standard language regarding the submission of an iPSP within 60 days of the End-of-Phase 2 (EOP2) meeting. When there are clinical development topics at meetings (i.e., EOP2, and pre-BLA), ensures that timelines for completion of pediatric studies are included.

3. Schedules PeRC presentations with the PeRC RPMs in a timely manner (based on the availability of the relevant review staff) and communicates the PeRC meeting date to the Associate Director for Pediatrics (OTP), Review

Division Senior Advisor for Pediatrics (OVRR/DCTR), and Senior Advisor for Pediatric Regulatory Review (CBER).

4. Ensures relevant review team members and senior leadership are aware of the PeRC meeting.

5. Assists the clinical reviewer in completing the required PeRC documentation, as needed.

6. Submits the required PeRC/Oncology Center of Excellence Pediatric Review Committee (OCE PeRC) documents and follows up if there are scheduling delays or issues.

7. Attends the PeRC meetings, and after internal review team concurrence, follows up (telecon, email, letter) with the sponsor/applicant based on the meeting outcome.

8. Notifies the Pediatric Exclusivity Board (PEB) as soon as a PPSR is submitted.

9. Keeps the Senior Advisor for Pediatric Regulatory Review (CBER), Associate Director for Pediatrics (OTP), Division Senior Advisor for Pediatrics (OVRR/DCTR), and the Product Office Representatives to the CBER Pediatric Working Group informed of high priority communications with the PeRC.

10. Drafts relevant PSP communications (emails/letters), Deferral Extension (DE) granted/denial letters, release/replace letters, and non-compliance letters for delayed PREA PMRs when applicable. Drafts relevant Inadequate PPSR letters or WR following PeRC recommendations.

11. Ensures the correct PREA letter template language is used in the approval letter for new applications or relevant supplements.

12. Ensures the correct BPCA letter template language is used in Inadequate PPSR letters or WRs.

13. Follows applicable CBER procedures for the web posting of PREA non-compliance letters in accordance with FDASIA requirements.

B. Senior Advisor for Pediatric Regulatory Review (CBER)

1. Serves as the project manager for the CBER PWG.

2. Works with CBER RIB to prepare pediatric related tracking tables for office review.

3. Represents CBER as a voting member of the PeRC.

4. Serves as the first line resource for regulatory questions that could affect consistency of review of PREA and BPCA related submissions across CBER Product Offices.

5. Reviews all draft letters (original, supplement, non-compliance, and deferral extension request) containing PREA and BPCA language. Reviews approval letters as needed, at the discretion of the Office. Reviews any modifications or changes made to templated language.

6. Utilizes web posting notifications from the Offices, including updates to CBER's Biologics PREA Reviews and Labeling Changes web page (FDAAA-required) and CBER PREA Non-Compliance letters and corresponding applicant responses (FDASIA-required) to support annual reports and Competing Products Lists.

7. Prepares data to support congressional pediatric reports and annual OPT reports.

8. Performs a quality review of the quarterly PMR/PMC report to ensure the accuracy of PREA PMR statuses before web posting.

9. Leads the PREA Tab Coordination Team.

C. Product Office Representatives to the CBER PWG

1. Attends the monthly CBER PWG Meetings.

2. Elevates any high priority pediatric issues to the monthly CBER Pediatric Workgroup Meetings.

3. Reviews data available in the CBER iPSP Dashboard.

D. Clinical Reviewer

1. Ensures the timely review of any incoming PREA & BPCA related submissions.

2. Completes and provides to the RPM the necessary PeRC documentation within the required timeframe for the scheduled PeRC presentation.

3. Attends the PeRC meetings as lead presenter and responds to any committee questions.

4. After the PeRC Meeting, reviews PeRC meeting minutes to ensure accuracy and captures PeRC recommendations in clinical memorandums.

   NOTE: The PeRC has requested notification of instances where the Division decides not to follow the PeRC’s recommendations.

5. Ensures PREA-required clinical studies are clearly delineated from any other pediatric non-PREA studies in the clinical review.

6. Reviews proposed labeling to ensure added pediatric data are presented in the relevant sections of the label in accordance with the Guidance for Industry: *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling.*

7. Reviews all draft approval and supplement letters for original and supplement submission, respectively, that contain PREA language to ensure there is consistency between the final label and approval letter pertaining to the "Pediatric Use" section and/or age range in the "Indication and Usage" statement.

8. Reviews PREA non-compliance and PREA DE extension letters.

9. Assists the RPM with any PREA and BPCA related correspondence (emails, letters, etc.) to ensure that all correspondence reflects review division/office decisions.

10. Completes the PARRF upon review of the applicant's PMR/PMC Annual Report to determine whether PREA PMRs are proceeding on schedule.

11. Attends the PEB meetings as lead presenter and responds to any committee questions.

E. CBER's Regulatory Information Branch (RIB)

1. With the assistance of the Senior Advisor for Pediatric Regulatory Review (CBER):

   a. Prepares external reports for Agency posting.

   b. Prepares monthly pediatric tracking tables for discussion with the CBER PWG.

   c. Follows up and alerts the appropriate Office when tracking updates are needed.

2. Ensures the RPM and Senior Advisor for Pediatric Regulatory Review (CBER) are notified of all IND amendments containing PSPs.

F. Associate Director for Pediatrics (OTP)/ Review Division Senior Advisor for Pediatrics (OVRR/DCTR)

1. Serves as a first line resource within their respective office for questions related to PREA & BPCA.

2. Provides guidance on whether discussion with the CBER PWG is warranted.

3. Provides input on congressional related pediatric reports and annual OPT reports.

4. Assists the review team with timely review of any incoming PREA and BPCA related submissions.

5. Reviews documentation (e.g., PeRC paperwork) for completeness and accuracy and ensures it is in alignment with Office/Center precedents.

6. Assists review committee in determining whether PREA requirements and justifications for deferral and waivers have been appropriately applied.

7. If the Associate Director for Pediatrics (OTP) or OVRR/DCTR is a PeRC Member, attends all PeRC presentations/meetings.

8. Reviews all draft letters (original BLA, BLA supplement, non-compliance, release/replace, DE extension) containing PREA language. Reviews all draft letters and communications regarding PPSRs and WRs.

G. Office of the Center Director

1. Provides oversight and guidance to offices as needed. **[ADM & ADP or designee]**

2. Attends all PeRC meetings where CBER products are being presented **[ADM, ADP or designee]**

3. Serves as a liaison between PeRC and the review divisions at the center level. **[ADM & ADP or designee**]

4. Leads the CBER PWG to ensure continued compliance with the PREA and BPCA provisions. **[ADM & ADP or designee]**

VII. Procedures

A. IND Phase (Review of PSPs)

1. For processing of all PSPs received under the IND, follow *JA 851.05: Instructions for Processing Pediatric Study Plans*. **[RIB, RPM, Reviewers]**

   NOTE:

   - In rare situations in which there is no active U.S. IND, a PTS submission should be created to house the PSP. RPMs should contact RIB *and* the CBER Senior Advisor for Pediatric Regulatory Review for guidance. Pediatric study plan submissions received under an IND are characterized as an “iPSP” (e.g., initial, agreed, or amended, as applicable). The iPSP should be provided no later than either 60

calendar days after the date of the end-of-phase 2 meeting or such other time as agreed upon between FDA and the sponsor. In the absence of an end-of-phase 2 meeting, the sponsor should submit the iPSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 studies, of the drug that is the subject of the iPSP.

- The sponsor should submit the iPSP no later than 210 calendar days before it submits a marketing application or supplement. See the Guidance for Industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.*

2. For PeRC scheduling and preparation, refer to the "PeRC Information Page" SPO site for necessary instructions and guidance on scheduling a PeRC meeting, preparing and submitting the required information. **[RPM, Clinical Reviewer]**

B. BLA/NDA and Supplement Phases

NOTE: The "iPSP" becomes the "PSP" upon submission of the marketing application (BLA or NDA). Any planned requests for waivers and/or deferrals included in the agreed iPSP serve as the official request with the application submission.

1. For applications and supplements subject to PREA and/or postmarketing submissions submitted in response to an outstanding PREA PMR: **[RPM, Clinical Reviewer]**

a. Refer to the FDA/CDER/OND "PeRC Information Page" SPO for necessary instructions and guidance on scheduling a PeRC meeting, preparing and submitting the required information.

NOTE: For a BLA or BLA Supplement, PeRC review should generally occur after the mid-cycle meeting (6-8 weeks prior to the Goal Date).

C. Post-Approval Phase (i.e., PMR/PMC Annual Reports, Requests for PREA PMR changes such as Deferral Extension Requests or Request for Release/Replace, and Issuance of Non-Compliance Letters)

1. For specific instructions on completing the PARRF to review the applicant's PMR/PMC Annual Reports (to determine whether PREA PMRs are proceeding on schedule), refer to *JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)*. **[RPM, Office PMR/PMC Coordinator]**

2. For specific procedures on the management of applicant submitted Deferral Extension Request, refer to *JA 860.08: Instructions for Processing Applicant Deferral Extension Requests for Pediatric Postmarketing Requirements.* **[RPM, Clinical Reviewer]**

3. Schedule a PeRC Meeting to present applicant's substantive changes to an open PREA PMR (i.e., major protocol changes), Deferral Extension Requests (i.e., request to change the established PMR final study report milestone), or a request from the applicant to release and replace a PREA PMR. Refer to the CDER/OND "PeRC Information Page" SPO for necessary instructions and guidance on scheduling a PeRC meeting, preparing and submitting the required information. **[RPM, Clinical Reviewer]**

   Note: For 45-Day Deferral Extension Requests and 90-day Correspondence Status Updates (CSU) submission requests for Release/Replace, PeRC review should be scheduled as soon as possible and presented to PeRC no later than 7 days prior to the Goal Date.

4. Contact the Office PMR/PMC Coordinator and Associate Director for Pediatrics (OTP)/ Review Division Senior Advisor for Pediatrics (OVRR/DCTR) to discuss whether a non-compliance letter should be issued if an applicant fails to meet deadlines specified in postmarketing requirements (PMRs). Notify the Senior Advisor for Pediatric Regulatory Review (CBER) for awareness. **[RPM, Clinical Reviewer]**

D. Pediatric Exclusivity (PPSR & WR)

1. For guidance on the review of requests for pediatric exclusivity, refer to the Guidance for Industry*: Qualifying for Pediatric Exclusivity Under Section 505(A) if the Federal Food, Drug, and Cosmetic Act* and consult the Associate Director for Pediatrics (OTP)/Senior Pediatric Advisor (OVRR/DCTR) and the Senior Advisor for Pediatric Regulatory Review (CBER). **[RPM, Clinical Reviewer]**

   NOTE: PPSRs and WRs are distinct from and serve a different statutory purpose than PSPs. PPSRs are submitted by sponsors to request a WR from FDA, which, if issued, may qualify the sponsor for an additional six months of pediatric market exclusivity under the BPCA. FDA must respond to a PPSR within 120 days. All PPSRs, WRs, and Inadequate PPSR Letters must be reviewed by the PeRC prior to issuance.

E. Reports

1. For the Postmarketing Requirements and Commitments Searchable Database, quarterly updates, or preparation of the Annual Federal Register Report on PMRs/PMCs, see *SOPP 8413: Postmarketing Requirement/Commitment Related Submissions - Administrative Handling,*

Review, and CBER Reporting. **[CBER PMR/PMC Liaison, Office PMR/PMC Coordinators, CBER Senior Advisor for Pediatric Regulatory Review, CBER/RIB]**

2. For the Status Report to Congress July 2026 - Best Pharmaceuticals for Children Act and Pediatric Research Equity Act (required every five years):

   a. Organize and analyze reportable data. **[RIB]**

   b. Perform quality review of data to ensure correct data. **[RIB, CBER Senior Advisor for Pediatric Regulatory Review]**

   c. Send the final data to OPT for inclusion into the final aggregated FDA report. **[CBER Senior Advisor for Pediatric Regulatory Review]**

3. For Pediatric Tracking Requirements Under FDAAA (required annually):

   a. Organize and analyze reportable data. **[RIB]**

   b. Perform quality review of data with Product Offices to ensure correct data. **[RIB, CBER Senior Advisor for Pediatric Regulatory Review]**

   c. Send the final data to OPT for web posting. **[CBER Senior Advisor for Pediatric Regulatory Review]**

VIII. Appendix

A. Timelines for Review of the iPSP, Agreed iPSP, Amended iPSP, and Agreed Amended iPSP

IX. References

A. References below are CBER internal:

1. JA 860.03: Instructions for Completing the PMR/PMC Annual Report Review Form (PARRF)

2. JA 860.08: Instructions for Processing All Applicant Deferral Extension for Pediatric Postmarketing Requirements

3. JA 851.05: Instructions for Processing Pediatric Study Plans

4. JA 910.07: Posting Procedures for BLA/NDA/Supplements

5. T 910.01: NDA/BLA/ANDA Originals and Supplements

6. PeRC SPO site

B. References below are found on the Internet:

1. Draft Guidance for Industry: Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act
2. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans
3. Draft Guidance for Industry: Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations
4. FDA's designated Pediatric molecular targets web page
5. CBER's PREA Non-Compliance Letters web page
6. FDA's Postmarket Requirements and Commitments Searchable Database web page
7. Guidance for Industry: Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997
8. Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling
9. Guidance for Industry: FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act
10. Pediatric Research Equity Act (PREA) website
11. PREA statute
12. SOPP 8413: Postmarketing Requirement/Commitment Related Submissions - Administrative Handling, Review, and CBER Reporting
13. Pediatric Tracking Requirements Under FDAAA

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
LCDR Kelly Abraham	Sonday Kelly, MS, PMP, RAC Associate Director of Regulatory Programs	August 28, 2026	3	• Added BPCA and updated title • Added submission requirements if an IND doesn't exist • Added submission timelines if an EOP2 meeting not held • Updated Responsibilities • Updated Procedures to include PPSR and WRs • Revised Appendix A to be a table rather than text
Daniela Vanco (Reviewed content)	Regulatory Review Document Lead Coordinator	N/A	2	June 27, 2025: Reviewed for content and found to be current as part of the QMS initiative.
Monser	N/A	February 27, 2023	2	Technical Update for changes due to 2023 CBER reorganization
Erik Laughner/Adrienne Hornatko-Munoz/CBER PWG	Darlene Martin, MS, PMP ORO/DROP Director	August 1, 2022	1	Original

SOPP 8421 Appendix A: Sponsor and FDA Timelines for Submission and Review of the Initial PSP, Agreed Initial PSP, Amended iPSP, and Agreed Amended iPSP[1]

Section	Party Responsible	Action	Timeline
A. Review of Initial PSP (iPSP)	Sponsor	Submit iPSP after EOP2 meeting	Within 60 days of EOP2 meeting
A	Sponsor	Submit iPSP if no EOP2 meeting	Before initiation of Phase 3 studies, but no later than 210 calendar days before marketing application submission
A	Review Division & PeRC	Review iPSP	Within 90 days of receipt
A	PeRC	Review iPSP (best practice)	Ideally before Day 75 of receipt
A	Review Division	Provide written comments to sponsor via email	By Day 90 of receipt
B. Review of Agreed iPSP	Sponsor	Discuss changes and submit Agreed iPSP	Within 90 days of receipt of FDA's written comments
B.	Review Division & PeRC	Review Agreed iPSP	Within 30 days of receipt
B.	PeRC	Review Agreed iPSP (best practice)	Ideally before Day 25 of receipt
B.	Review Division	Confirm agreement or non-	Within 30 days of Sponsor's

[1] modified from PMHS Standard Operating Procedure (SOP) for Review of Pediatric Study Plans (PSPs) and Written Requests by the Pediatric Review Committee (PeRC). See: https://www.fda.gov/media/86061/download.

Section	Party Responsible	Action	Timeline
		agreement via letter	submission of Agreed iPSP
C. Review of Amended iPSP	Review Division	Review Amended iPSP and assess scope of changes	Within 90 days of receipt
C	PeRC	Review Amended iPSP if changes are significant	Ideally before Day 75 of receipt (best practice)
C	Review Division	Send email to PeRC confirming minor changes	Upon assessment of minor changes
C	Review Division	Provide written comments to sponsor via email	By Day 90 of receipt
D. Review of Agreed Amended iPSP	Sponsor	Incorporate recommendations and submit Agreed Amended iPSP	Within 90 days of receipt of FDA's written comments
D	Review Division	Review Agreed Amended iPSP, assess scope, and consult PeRC	Within 30 days of receipt
D	PeRC	Review Agreed Amended iPSP if needed (best practice)	Ideally before Day 25 of receipt
D	RPM (in consultation with review team)	Send email to PeRC confirming minor changes	Upon assessment of minor changes
D	Review Division	Confirm agreement via letter	Within 30 days of submission of Agreed Amended iPSP