

SOPP 8421: Complying with Requirements under the Pediatric Research Equity Act (PREA)

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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) are met.
- B. This SOPP serves as a first-line 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.

II. Scope

- A. This SOPP applies to Investigational New Drugs (INDs), 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.
- B. This SOPP does not recapitulate existing PREA related resources for CBER staff, but rather provides general information and expectations on how CBER and sponsors/applicants will comply with PREA. For CBER specific instructions on:

1. The processing and review of Pediatric Study Plans (PSPs) received under an IND see *JA 851.05: Instructions for Processing Pediatric Study Plans*,
 2. Completing a review of an applicant's postmarketing commitment/postmarketing requirement (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 review of any applicant proposed PREA Post Marketing Requirement (PMR) 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 paperwork, see the PeRC SharePoint Online (SPO) site, and;
 5. Posting Food and Drug Administration Amendments Act (FDAAA) required documents to the Biologics PREA Review and Labeling Changes web page, see Job Aid (*JA*) *910.07: Posting Procedures for BLA/NDA Supplements* and *T910.01: Transmittal Memo - NDA/BLA/ANDA Originals and Supplements*
- C. This SOPP is specific to PREA and does not discuss other pediatric regulatory issues such as:
1. Procedures under Best Pharmaceuticals for Children Act (BPCA) for proposed pediatric study requests (PPSRs) or Written Requests (WR),
 2. Procedures for presenting products to the FDA's Pediatric Advisory Committee (PAC), and;
 3. Rare pediatric disease priority review vouchers

NOTE: Consult the Senior Advisor for Pediatric Regulatory Review, in CBER's Office of Regulatory Operations, for regulatory questions on any of these issues.

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 in 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 (or supplements to an application) for drugs submitted under section 505 of the Act (21 U.S.C. 355) or biologics under section 351 of the Public Health Service Act (PHSA) (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).

1. The pediatric assessments shall contain data gathered using appropriate formulations for each age group for which the assessment is required that are adequate to:
 - a. Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations.
 - b. Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective.
 - c. 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 16 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.

C. A sponsor of an IND subject to PREA is required to submit an initial pediatric study plan (iPSP) to identify needed pediatric studies early in drug development and begin planning for these studies. 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. See the *Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

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

1. Waiver for some/all age groups if (in most cases only if 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 pediatric patients. 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;

timeframe a required pediatric assessment 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 sponsor's response are made public on the CBER PREA Non-Compliance Letters web page.

- H. PREA PMRs are not fulfilled by submission of final study reports (FSRs). 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.
- I. 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."
- J. FDA has required tracking and reporting requirements under PREA.
 - 1. All PREA PMRs (deferred pediatric assessments) are annually reported in the Federal Register and quarterly on FDA's Postmarket Requirements and Commitments 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. FDASIA 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, "Status Report to Congress July [insert date] - Best Pharmaceuticals for Children Act and Pediatric Research Equity Act" is 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. 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 will track &

report 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

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 initial pediatric study plans (iPSP), agreed upon initial pediatric study plans, assessments, deferrals, deferral extensions (DE) and waivers.
- 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 and the Associate Director for Medicine in the Immediate Office/OD.
- D. 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

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 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.

Note: For NDAs, BLAs, or supplements subject to PREA, applicants must include an agreed iPSP in the submission when a deferral of pediatric studies is being requested. In such cases, submission of the agreed iPSP fulfills the requirement of the applicant to submit a PSP. Any planned requests for waivers and/or deferrals included in the agreed iPSP serve as the official request with the application submission.

I. Amended PSP: Sponsor's proposed changes made to an agreed PSP.

J. Amended Agreed PSP: FDA's agreement of the sponsor's changes made to the amended PSP.

K. PREA non-compliance letter: Issued when FDA has determined that the applicant has failed to submit a required pediatric assessment for a PREA PMR or has failed to submit a request for deferral extension of that PREA PMR.

V. Policy

A. Product Offices will engage sponsors/applicants early in product development (i.e., under the 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. For submissions subject to PREA and PeRC review, the Product Office will:

1. Review the sponsor's pediatric plans under the 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 sufficient 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.
- C. Product Offices will utilize their office representatives to the CBER PWG and consult with the Senior Advisor for Pediatric Regulatory Review to provide PREA oversight and to discuss 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.
 - D. 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.
 - E. CBER will utilize the PMR/PMC Annual Report Review Form (PARRF) to review the applicant's PMR/PMC Annual Reports to determine whether PREA PMRs are proceeding on schedule.

VI. Responsibilities

A. Regulatory Project Manager (RPM)

1. Ensures the timely review of all incoming PREA 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.

NOTE: Not all PSPs include plans for clinical studies; those that do should include timelines. Pre-IND meetings may be too early for meaningful discussion of timelines.

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 Senior Advisor for Pediatric Regulatory Review.
4. Assists, as needed, the clinical reviewer to complete the required PeRC documentation and submits the required PeRC documents to the PeRC RPMs in CDER's Division of Pediatric and Maternal Health (DPMH).
5. Attends the PeRC meetings, and after internal review team concurrence, follows up (telecon, email, letter) with the sponsor/applicant based on the meeting outcome.
6. Ensures the Senior Advisor for Pediatric Regulatory Review and the Product Office Representatives to the CBER Pediatric Working Group are copied on

all communications with the PeRC (refer to the internal CBER Pediatrics webpage for current members).

7. Drafts relevant PSP communications (emails/letters), DE granted/denial letters and non-compliance letters for delayed PREA PMRs when applicable.
8. Ensures the correct PREA letter template language is used in the approval letter for new applications or relevant supplements.

B. Senior Advisor for Pediatric Regulatory Review

1. Serves as the project manager for the CBER Pediatrics WG.
2. Works with CBER Regulatory Information Branch (RIB) to prepare the monthly pediatric related tracking tables for office review.
3. Represents CBER as a voting member of the PeRC.
4. Reviews all draft letters (original, supplement, non-compliance, DE extension) containing PREA language.
5. Reviews PeRC paperwork for completeness and accuracy.
6. Maintains FDAAA-required web posting content of CBER pediatric labeling page as well as the FDASIA required web posting of FDA PREA non-compliance letters and corresponding responses from applicants.
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.

C. Product Office Representatives to the CBER PWG

1. Serves as a first line resource within their respective office for questions related to PREA and provides guidance on whether discussion with the CBER PWG is warranted.
2. Attends the monthly CBER PWG Meetings.
3. Reviews monthly pediatric related tracking tables to help ensure that timelines are met.
4. Assists review committee as needed to prepare for PeRC.
5. Reviews PeRC paperwork for completeness and accuracy as needed based on specific office procedures.

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

D. Clinical Reviewer

1. Ensures the timely review of any incoming PREA related submissions.
2. Ensures IND 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. Completes and provides to the RPM the necessary PeRC documentation within the required timeframe for the scheduled PeRC presentation.
4. Attends the PeRC meetings as lead presenter and responds to any committee questions.
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 related correspondence (emails, letters, etc) to ensure that all correspondence reflects review division/office decisions.
10. Completes the PARRF upon the review of the applicant's PMR/PMC Annual Report (to determine whether PREA PMRs are proceeding on schedule).

E. Office of Regulatory Operations (ORO), Division of Informatics and Information Technology (DITT), Regulatory Information Branch (RIB)

1. With the assistance of the Senior Advisor for Pediatric Regulatory Review:
 - a. Prepares external reports for Agency posting.

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

NOTE: PSPs (iPSPs, agreed PSPs, amended PSPs, agreed amended PSPs) are received under the IND. In rare situations in which there is no active U.S. IND, RPMs should contact RIB *and* the Senior Advisor for Pediatric Regulatory Review for guidance.

2. For PeRC scheduling and preparation, refer to the “PeRC Information Page” Sharepoint Online (SPO) site for necessary instructions and guidance on scheduling a PeRC meeting and preparing and submitting the required paperwork. **[RPM, Clinical Reviewer]**

B. BLA and Supplement Phases

1. For applications and supplements subject to PREA and/or supplements submitted in response to an outstanding PREA PMR, refer to the “PeRC Information Page” SPO site for necessary instructions and guidance on scheduling a PeRC meeting and preparing and submitting the required paperwork. **[RPM, Clinical Reviewer]**

NOTE: A PeRC review should generally occur after the mid-cycle meeting (6-8 weeks prior to the action date).

C. Post Approval Phase (PREA PMR changes, Non-compliance)

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)*.
2. For any substantive changes to an outstanding PREA PMR (i.e., major protocol changes, a request from the applicant to release and replace a PREA PMR, or Deferral extension Requests, i.e., changes to the established PMR milestones), refer to the “PeRC Information Page” SPO site for necessary instructions and guidance on scheduling a PeRC meeting and preparing and submitting the required paperwork. **[RPM, Clinical Reviewer]**
3. For specific procedures on the management of applicant submitted Deferral Extension request, refer to *JA 860.08: Instructions for Processing All Applicant Deferral Extension Requests*. **[RPM, Clinical Reviewer, RIB]**
4. For any PREA non-compliance issues that may warrant a PREA non-compliance letter, contact the Senior Advisor for Pediatric Regulatory Review.

D. Reports

1. For the Quarterly Postmarket Requirements and Commitments Web page 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 Coordinator, Senior Advisor for Pediatric Regulatory Review, RIB]**
2. For the Status Report to Congress July [insert date] - 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, Senior Advisor for Pediatric Regulatory Review]**
 - c. Send the final data to OPT for inclusion into the final aggregated FDA report. **[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, Senior Advisor for Pediatric Regulatory Review]**
 - c. Send the final data to OPT for web posting. **[Senior Advisor for Pediatric Regulatory Review]**

VIII. Appendix

- A. Timelines for Review of the Initial PSP, Agreed Initial PSP, Amended PSP, and Agreed Amended PSP

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 SharePoint Online site

B. References below are found on the Internet:

1. [Draft Guidance for Industry: How to Comply with the Pediatric Research Equity 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. FDA's designated [Pediatric molecular targets](#) web page
4. [CBER's PREA Non-Compliance Letters web page](#)
5. FDA's [Postmarket Requirements and Commitments](#) web page
6. [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](#)
7. [Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling](#)
8. [Guidance for Industry: FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act](#)
9. [Pediatric Research Equity Act \(PREA\) website](#)
10. [PREA statute](#)
11. [SOPP 8413: Postmarketing Requirement/Commitment Related Submissions - Administrative Handling, Review, and CBER Reporting](#)
12. [Pediatric Tracking Requirements Under FDAAA](#)

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
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 PSP, and Agreed Amended PSP¹

A. Review of the Initial PSP (iPSP)

- Sponsor should submit the iPSP within 60 days of the end-of-Phase 2 (EOP2) meeting.
- The review division and the PeRC must review initial PSP within 90 days.
 - As a best practice, the PeRC review should ideally occur before Day 75.
- The review division must provide written comments (feedback on the initial PSP) via email to the sponsor by day 90.

B. Review of the Agreed Initial PSP (Agreed iPSP)

- The sponsor should review and negotiate any further edits to the iPSP with the review division within 90 days of receipt of FDA's written comments.
- The sponsor must submit an Agreed iPSP within 90 days of receipt of FDA's comments. Note: This 90-day clock on the sponsor is not tracked by FDA.
 - Prior to the review division responding to the agreed initial PSP, it must consult the PeRC and the PeRC must review.
 - As a best practice PeRC, review should ideally occur before Day 25.
- The review division should confirm agreement (via letter) with the agreed initial PSP within 30 days from the date the sponsor's submission of the Agreed iPSP.

C. Timeline for Review of the Amended PSP

- The review division must review the amended PSP. CBER considers Amended PSPs to be significant changes to Agreed iPSPs. Minor changes can be reviewed without a review clock & do not require a PeRC review.
- If the proposed changes are significant, the PeRC must also review the amended PSP during that timeframe.
 - As a best practice PeRC review of the amended PSP, if needed, should ideally occur before Day 75.
- The review division must provide written comments via email to the sponsor by day 90 to provide feedback on the amended PSP.

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>.

D. Timeline for Review of Agreed Amended PSP

- The sponsor must incorporate recommendations and submit the Agreed Amended PSP within 90 days of receipt of written comments.
- Prior to the review division responding to the agreed amended PSP, it must consult the PeRC and the PeRC must review if the changes are significant.
 - As a best practice PeRC review of the agreed amended PSP, if needed, ideally should occur before Day 25.
- The review division must confirm agreement with the agreed amended PSP within 30 days of submission of the agreed amended PSP.