

Overview of PREA, PSPs plus an Introduction to the Rare Pediatric Disease (RPD) Priority Review Voucher Program

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Why select only these topics for today?

- PREA has a broad regulatory impact & requirements for industry are in statute
- While requesting a RPD PRV is not a “requirement” on industry’s part, there is a fair amount of interest in this incentive program
- We are not able to cover all pediatric-related provisions/programs in one session (i.e., BPCA, Orphan Drug Act, etc.)

Learning Objectives



- Demonstrate knowledge of what “triggers” PREA
- Identify which submissions are subject to PREA and require a new initial Pediatric Study Plan (iPSP)
- Understand the purpose of submitting an iPSP
- Recognize potential gaps in information in PSP submissions
- Understand the basics of the Rare Pediatric Disease Priority Review Voucher program

Regulatory Background

- 2002 - [Best Pharmaceuticals for Children Act \(BPCA\)](#)
- 2003 - [Pediatric Research Equity Act \(PREA- Drugs & Biologics\)](#)
- 2007 - [FDAAA](#)
 - Required that the labeling include:
 - Information on pediatric studies and
 - *Whether or not* the studies demonstrate safety or efficacy or studies were inconclusive in pediatric populations
- 2010 - [Patient Protection and Affordable Care Act](#)
 - Biosimilars
 - Pediatric Exclusivity for biologics (+ 6 months)
- 2012 - [FDASIA](#)
 - Permanent reauthorization of PREA & BPCA
 - Enforcement/deferral extensions (DE)
 - Pediatric Study Plan (PSP) requirements
 - HDE (profit exemption provision)
- 2017-FDARA
 - <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/fda-reauthorization-act-2017-fdara>

Pediatric Research Equity Act

- Requires pediatric assessment of drugs & biological products* if application is for: (What “triggers” PREA?)
 - A new indication
 - New dosing regimen (any change in a single dose, maximum daily dose or dosing interval)
 - New active ingredient (including a new combination)
 - New dosage form (e.g., vial to transdermal patch)
 - A new route of administration (e.g., subcutaneous to intramuscular)
- Not subject to PREA:
 - Products granted orphan designation for the indicated disease (except FDARA carve-out/**pediatric cancer**)
 - Devices [Combination Products *are* if Primary Mechanism of Action (PMOA) is the biologic/drug]

**Does not generally apply to Blood and blood components intended for transfusion regulated by CBER under 21 CFR 606.*



Pediatric Oncology info

- Research to Accelerate Cures and Equity (RACE) for Children Act - incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted on August 18, 2017.
 - RACE Act amended PREA and went into effect on August 18, 2020.
- Oncology products with orphan designation are no longer exempt from PREA.
- Requires that marketing applications for **certain adult oncology drugs** (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a **pediatric cancer**) that are **submitted on or after August 18, 2020** contain reports of molecularly targeted pediatric cancer investigations.
 - Does not apply to supplements.

[Pediatric Oncology | FDA](#)

Molecular Targets

- Per the Guidance, the Agency interprets a “molecular target” in cancer drug development as a molecule in human cells (normal or cancer cells) that is intrinsically associated with a particular malignant disease process such as etiology, progression, and/or drug resistance.
 - [FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act | FDA](#)
- FDA is responsible for determining whether a molecular target is *substantially relevant* for purposes of section 505B of the FD&C Act.
- Molecular targets that lack sufficient evidence for FDA to determine whether they are “substantially relevant” or “not substantially relevant” will not be included in a target list.
- Sponsors submitting PSPs for oncology products must include a description of the cancer(s) in the pediatric population for which the drug may or may not warrant early evaluation based on the molecular mechanism of action of the drug.

What about Cord Blood regulated CBER?

- FDA made a determination in 2011 that cord blood is not subject to PREA provided that none of the PREA “triggers” are met.
- Hemacord (1st cord blood BLA approved) was subject to PREA
 - <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/hemacord-hpc-cord-blood>
- FDA determined that each successive BLA submission under 351(a),
 - provided it is prepared in accordance with the 2009 Guidance for Industry, Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications, **AND**
 - is for the same indications as listed in the above referenced guidance, with the same dosage form and dosing regimen, and route of administration, will not trigger PREA.

Updated Guidance: <https://www.fda.gov/media/86387/download>

What about other types of CBER/OTP products? Are they subject to PREA?

- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) solely regulated under PHS Act 361?
 - No. Not drugs or biologics under the regs
 - <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products>
- Autologous pancreatic islet cells?
 - No. Enforcement discretion
- Allogeneic pancreatic islet cells?
 - Potentially yes unless orphan-designated
- Devices solely regulated under 21 CFR 800s?
 - No. Why? Devices unto themselves are not subject to PREA

Factors to keep in mind

- A product might have orphan designation based on the disease covered in the original indication, but not necessarily for the supplemental indications. Some examples for CBER-regulated products:
 - Privigen
 - Wilate
 - Kymriah (non-Hodgkin lymphoma)
- An Applicant might be seeking multiple indications in an application but not all are orphan designated.
- *Why is this important?* PREA must be addressed unless exempt due to orphan status.

Pediatric Age Range

According to 21 CFR 201.57, the pediatric age group is defined as “birth to 16 years, including age groups often called neonates, infants, children, and adolescents”

- A useful description of pediatric age groups is found in the [ICH guideline. Clinical Investigation of Medicinal Products in the Pediatric Population E11](#) and are the following:

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents [12 to 16-18 years (dependent on region)]

NOTE: For medical devices: pediatric patients are defined as persons aged 21 or younger at the time of their diagnosis or treatment (up to but not including 22nd birthday)

Options for Fulfilling PREA



All pediatric ages must be addressed

- **Completed Studies Assessment** (pediatric data submitted) Section 505B(a)(2)
- **Full Waiver** (no pediatric studies) Section 505B(a)(4)(A)
- **Partial Waiver** (no pediatric studies in *some* age groups) Section 505B(a)(4)(B)
- **Deferral** (pediatric studies will be conducted later or are not yet completed) Section 505B(a)(3)
 - Common scenario = partial waiver + partial deferral

Pediatric Assessments



- Applicants are required to submit a pediatric assessment that contains data to support the safety and efficacy in pediatric subjects.
- Should contain data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data 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

Waivers [Sections 505B(a)(4)(A) & (B)]

- Must meet one of these criteria:
 - Necessary studies are **impossible or highly impracticable**
 - Evidence strongly suggests that the product would be **ineffective or unsafe** in pediatric patients
 - Product does not represent a meaningful therapeutic benefit over existing therapies **AND** is not likely to be used in a substantial number of patients
 - Applicant can demonstrate that **reasonable attempts to produce a pediatric formulation necessary for a specific age group have failed** (partial waiver only)
- Include scientific rationale to support waiver request
- Waiver requests based on safety or efficacy should be accompanied by proposed labeling
- Refer to Guidance for list of “adult-only” conditions
 - [Guidance for Industry \(Draft\): How to Comply with the Pediatric Research Equity Act \(posted 9/7/2005\) \(PDF - 116KB\)](#)

Deferrals [Section 505B(a)(3)]

- Must meet criteria
 - Product is **ready for approval** for use in adults before pediatric studies are complete
 - Pediatric **studies should be delayed until additional safety or effectiveness data have been collected**
 - Other appropriate reason for deferral
- Must include scientific rationale to support deferrals on the basis of need for additional safety or effectiveness data
- *Deferred studies included in the iPSP are considered PREA PMRs in the approval letter*

Pediatric Study Plans (PSPs)



- Implemented under FDASIA 2012
- A sponsor who is planning to submit a marketing application (or supplement to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an iPSP unless the drug is for an indication for which orphan designation has been granted.
- The intent of the iPSP is for a sponsor to identify needed pediatric studies early in development and begin planning for these studies.
- The plan should cover all pediatric age groups.

PSPs continued...

- When to submit?
 - Before the date on which the sponsor submits the required assessments or investigation and 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.
- Having early discussions with CBER are critical to discuss the pediatric plan particularly for those products under expedited review pathways

Pediatric Study Plan (PSP) Contents



- How am I (the sponsor) going to fulfill PREA? (see slide 12)
- Current PSP Guidance has template for including the following:
 - Overview of the disease in the pediatric population, the product under development
 - Potential plans and justification for use of extrapolation
 - Any plans to request a deferral, or full or partial waiver w/ supporting information
 - Plans for pediatric specific formulation development
 - **Outline** of nonclinical and clinical studies/data, complete or planned study (s) the applicant plans to conduct
 - *study objectives , Study design, age groups, relevant endpoints, and statistical approach (protocol details can be negotiated under the IND)*
 - Timelines for conducting pediatric studies
 - Provide any agreements with other Health authorities (e.g., Pediatric Investigation Plan for the European Medicines Agency (EMA))



For Sponsors & Applicants

Considerations for preparing your PSP

- What is the proposed indication?
 - Did you specify the age range for the intended population that you intend to seek with your initial submission?
 - If you are planning for either a waiver or deferral, then your proposed indication should be limited to adults.
- Did you address all age groups across the pediatric population in your iPSP?
- Did you cite the appropriate statutory reasons for any plans for any waivers or deferrals?

Remember that the PSP is a “plan”. It is not the “request”. Requests for deferrals and waivers are only granted at such an application or supplement is approved.

Additional considerations for preparing your PSP



- Length? Please refer to the PSP Guidance for suggested page limits.
- For any planned deferred studies, are the proposed timelines reasonable and achievable?
- Have you included sufficient information on the formulation? Needs for age-appropriate formulation?
- How many children are being studied per age group? Will the planned studies support safety & effectiveness in the pediatric population?

✓ PSP review/admin



- Sponsor should check “other” box on Form FDA 1571 when submitting the PSP as an IND amendment
- CBER has 90 days to review the iPSP and provide a response regarding the iPSP. (recommend any changes, etc.)
 - This review process includes consultation with FDA’s internal Pediatric Review Committee (PeRC) or OCE PeRC.
- The sponsor then has a second 90-day period during which it may review FDA comments and initiate any needed negotiations to discuss the iPSP. By the end of this second 90-day review period, the sponsor must submit an Agreed iPSP which is on a 30-day clock. (90+90+30)
- Sponsors should have an Agreed PSP in place before BLA/S submission
- Significant changes to the Agreed iPSP should be submitted as an Amended PSP before BLA/S submission.



Pediatric Review Committee (PeRC)

- An Agency-level committee established under FDAAA to carry out activities related to BPCA and PREA
- Comprised of Office of the Commissioner (OC), CDER & CBER (chaired by CDER)
- Makes recommendations - advisory
- Reviews all Pediatric Study Plans, Assessments, Deferrals (and deferral extension requests), and Waivers **prior to the approval of an application or supplement** for which a pediatric assessment is required
- Reviews **all Inadequate Letters & Written Requests** under BPCA prior to being issued

PeRC Oncology Subcommittee

- Started in 2018
- Specific expertise in oncology products
- Meets every Wednesday morning
- Different RPMs; led by CDER/OHOP
- Same paperwork applies
- Follows 'full' PeRC procedures & statutory timelines

“Full” PeRC versus OCE PeRC

- All oncology indications go to OCE PeRC
- Products for “immune reconstitution” post-transplant go to full PeRC
- Products to treat or prevent infections post-transplant go to full PeRC
- Benign hematology products go to full PeRC
 - i.e., bleeding disorders, clotting factors

What does CBER do after the BLA/S is approved?

- We continue to monitor the Applicant's ability to meet the timeline as listed in the approval letter for any deferred pediatric studies
- Deferred studies that are submitted in response to PREA PMRs are pediatric assessments
 - Pediatric assessments must come in a supplement (almost always efficacy; can be labeling).
 - Final Study Reports (FSR) **do not** fulfill PREA PMRs.
 - Require a PeRC review
- FDA posts an explanation of the status of all PREA PMRs
 - <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>
- **Delayed PREA PMRs are subject to PREA non-compliance letters**

Efficacy Supplements

Can “trigger” PREA (new indication, etc.)

- Is there an Agreed iPSP for ***this*** indication?
- Was the plan followed?
- Requires going back to PeRC

Can fulfill a Deferred PREA PMR

- Contains the completed pediatric assessments that were deferred in the original BLA
- Requires going back to PeRC

Outstanding PREA PMRs

How can an Applicant be “fulfilled”?

- Submit an efficacy supplement to support the peds indication (to fulfill the terms of PREA PMR)
- Submit a supplement (labeling or efficacy) to add negative or inconclusive data to 8.4 of the product label
 - No Peds indication is awarded but peds study is completed & informative info is added to label (e.g., Agriflu & Sevenfact)
- But, not by a stand-alone Final Study Report (FSR)
 - Why? We don’t update labels based on FSRs for PREA PMRs
 - Need a either a labeling or efficacy supplement

Deferral Extension (DE) requests

- Implemented under FDASIA 2012
- Provision for Applicants to request a new timeline for completing an outstanding PREA PMR
- Should include supportive rationale for the delay
- Requires a PeRC review; 45-day review clock
- DEs may either be granted or denied (letter is issued)
- For admin purposes, DEs are based on the 3rd milestone date in the AP letter (FSR)

A few Take-Home Messages

- Sponsors are required to have an Agreed iPSP in place before submitting a BLA/NDA or supplement subject to PREA
- Results of pediatric studies must be included in the label
 - Positive, negative or inconclusive
- Review teams will ensure consistency between the approval letter (indication & PREA section) and label
- PREA PMRs can not be changed without FDA approval
 - To revise PREA PMR milestones, a deferral extension request must be submitted

Challenge Question?



Which of the following is NOT a PREA trigger?

- A. New IND product intended for the treatment of High-grade, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer
- B. New efficacy supplement for approved IVIG indicated for primary immunodeficiency to add a new indication for treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
- C. Concomitant administration of two (2) licensed childhood immunizations

(What other info might we need to know?)

Pediatric Study Plan Resources



- Draft Guidance Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (July 2013/March 2016/July 2020)

[Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans \(PDF - 408KB\)](#)

- PSP template for sponsors:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>

- Division of Pediatric and Maternal Health (DPMH) Standard Operating Procedure (SOP) for Review of Pediatric Study Plans (PSPs) and Written Requests by the Pediatric Review Committee (PeRC)

<https://www.fda.gov/media/86061/download>

Resources

- **Draft Guidance: How to Comply with the Pediatric Research Equity Act**
 - [Guidance for Industry \(Draft\): How to Comply with the Pediatric Research Equity Act \(posted 9/7/2005\) \(PDF - 116KB\)](#)
- **Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling Good Review Practice (final Guidance)**
 - [<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good>](#)
- **“Adult-only conditions” that generally qualify for a waiver (see list)**
 - [<https://www.fda.gov/media/101440/download>](#)
- **Pediatric and Maternal Health Product Development**
 - [Division of Pediatric and Maternal Health | FDA](#)
- **New Guidance recently issued:**
 - [Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act | FDA](#)

Rare Pediatric Disease Priority Review Voucher program

Product development incentive
program

Priority Review Vouchers

- What is a PRV?
 - A voucher that is granted by FDA to an Applicant who receives marketing approval of a drug or biologic for a specific indication under predefined parameters of eligibility
- Once awarded, PRV can be held/retained by that Applicant or sold to another “entity” (no limits on the # of transfers)
- Owner of a voucher redeems that voucher with FDA, obtaining priority review for a subsequent application for a different product that wouldn’t otherwise qualify for priority review
- Three FDA Priority Review Voucher Programs (affects CDER & CBER)
 - Tropical Disease
 - Rare Pediatric Disease (we will discuss this today)
 - Material Threat Medical Countermeasure

Brief History of PRV programs



- **2007** (FDAAA) - Tropical Disease PRV Program Established
- **2012** (FDASIA) - Rare Pediatric Disease PRV Established (original 2017 Sunset)
- **2014** – Changes to Tropical Disease PRV Program
 - Ebola added to list of tropical diseases
 - Changed process for adding a tropical disease to the list
 - Unlimited transfers of PRVs
- **2016** (21st Century Cures Act) - Material Threat Medical Countermeasures (MCM) PRV Program established (2023 sunset)
 - GAO Study of Rare Pediatric Disease PRV published
 - Zika added to list of tropical diseases
 - Rare Pediatric Disease definition changed
 - Rare Pediatric Disease PRV Program extended to 2022
 - GAO Study of PRV Programs January 2020

History continued...

- **2017 (FDARA)- New Criteria Added to Tropical Disease PRV Program**
 - “New clinical investigations”
 - An attestation that studies not submitted to other regulatory authorities before 2007
- **December 27, 2020, RPD PRV Program was extended to 2026**
 - Under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024.
 - After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers.
- **2021 –Legislative change (The Act was amended) definition of new chemical entity (NCE)**

Why Are PRVs so Popular?

- Intended to act as an incentive where traditional incentives might not be sufficient
 - cost of development
 - lack of market opportunities
- Success tied to “market forces”
- Can be a windfall for companies
 - PRVs have been sold for \$67-350 million





Common Concerns Raised About PRVs

- Strain on FDA's resources to compress standard review into priority review
- Doesn't require innovation or investment
- Doesn't require availability or affordability*
- Not enough certainty
- Increasing number of PRV programs will lead to too many PRVs and prices for PRVs will drop

*Rare Pediatric Disease PRV requires "marketing"

CBER PRVs Awarded Since 2007

– MCM PRVs

- 4 issued by CBER
- <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/21st-century-cures-act-mcm-related-cures-provisions#MCM> PRVs issued

– Tropical Disease PRVs

- 3 issued by CBER (Cholera, Dengue, Ebola)
- <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program>
- <https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states>

– Rare Pediatric Disease PRVs

- 8 issued by CBER thus far (more on slide 54)



Requirements for all PRVs

- To **obtain** a PRV, Applicant must:
 - Submit either an NDA or 351(a) BLA
 - Contain no active ingredient of which has been previously approved in any other application under 505(b)(1), 505(b)(2), 505(j), 351(a), or 351(k)
 - NME or novel BLA
 - Not a supplement for a new use of previously approved product
 - Be eligible for Priority Review on its own merit
- To **redeem**, Applicant must:
 - Have notified FDA within 90-days before notice of intent to redeem
 - Pay the fee associated with redeeming (set annually)

Requirements for all PRVs (cont'd)

- To **obtain** a PRV, must be a drug or biologic for:
 - A tropical disease on the **list** in Section 524 of the FD&C Act
 - or**
 - A disease that meets the **definition** of rare pediatric disease in Section 529 of the FD&C Act
 - or**
 - Harm from a biological, chemical, radiological, or nuclear agent on the **list** published by HHS in PHEMCE Strategic Implementation Plan (or harm from administering a drug or biologic against such an agent)

Rare Pediatric Disease Priority Review Vouchers

What is a Rare Pediatric Disease (RPD)?



A disease that meets each of the following criteria:

- A. The disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
- B. The disease is rare disease or condition, within the meaning of Section 526 of the FD&C Act, which includes diseases and conditions that affect fewer than 200,000 persons in the United States (U.S.) and diseases and conditions that affect a larger number of persons and for which there is no reasonable expectation that the costs of developing and making available the drug in the U.S. can be recovered from sales of the drug in the U.S.

Advancing Hope Act 2016: Definition of “rare pediatric disease” changed

- *“serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect [children]”*

Who decides on designation?

- Both the FDA's Office of Pediatric Therapeutics (OPT) and the Office of Orphan Products Development (OOPD) have the lead in determining whether a disease is **designated** as a rare pediatric disease. (Agency level)
- Usually done under the IND or even before an IND
- Centers review the eligibility criteria & issue the PRV (in the approval letter)
- Sidenote, OOPD also makes the orphan designation determination (separate program). Orphan designation does not = rare peds designation (although there can be overlap)

Rare Pediatric Disease PRVs: Specific Requirements



- Designation available in advance of a PRV request
 - *Note: requesting RPD designation in advance is currently optional. Section 529(d)(2) specifically says that requesting designation is not a prerequisite for receiving a voucher. Designation will become a requirement again when the sunset kicks in on Sept. 30, 2024.*
- Applicant must request the RPD PRV when submitting application
- Relies on data derived from studies examining a pediatric population
- Does not seek approval for an adult indication (see Q5 of the RPD PRV Guidance)
- No 505(b)(2) NDAs
- FDA may revoke a RPD PRV if product not marketed within a year
- Postapproval Production Report due five years after approval



Where should the Applicant include the voucher request?

- **Cover letter** - RPD priority review voucher must be requested by the Applicant in their cover letter.
- **Additional information usually in eCTD Module 1.9**
Pediatric Administrative Information

RPD PRV Eligibility

- Meets the definition of a rare pediatric disease
- The candidate drug or biological product contains no active ingredient (including any ester or salt of the active ingredient)* that has been previously approved in any other application
- FDA deems eligible for priority review (on its own merits)
- Relies on clinical data from pediatric population(s) in doses intended for use in that population
- Does not seek approval for an adult indication in the original rare pediatric disease product application

*amended in 2021

New Chemical Entity language

- “active ingredient (including any ester or salt of the active ingredient)” replaced with “active moiety” defined as:
 - for a human drug, contains no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of the FD&C Act
- Or**
- for a biological product, contains no active ingredient that has been previously approved in any other application under section 351(a) or 351 (k) of the Public Health Service Act and is the subject of an application submitted under section 351(a) of the Public Health Service Act

CBER's Internal RPD PRV Process

- CBER has both an internal Job Aide and Checklist for guiding staff with the review of the RPD PRV eligibility criteria during the review cycle
- Substantive input by review team, OPT and OOPD; other experts as needed
- Final signatory authority is CBER's Associate Director for Review Management (ADRM)

CBER Policy

- As required under statute, the **RPD** priority review voucher must be requested by the Applicant in their cover letter.
- Applicants who are awarded vouchers are subsequently required to notify CBER when vouchers are sold or transferred. (Submit as Product Correspondence to the BLA).
- Review teams **will not** notify Applicants about voucher decisions prior to issuance of an approval letter.
- Applicants are not permitted to both redeem and request a priority review voucher in the same application.
- Cannot receive multiple vouchers for the same product application.



Sample approval letter language

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

- We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA #####. All correspondences related to this voucher should refer to this tracking number.
- This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.
- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

Approval letter language continued...

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

Agency requirements

- Post-approval, respective centers are required to issue a Federal Register notice regarding the awarding a RPD PRV (within 30 days).
- Agency tracking of RPD PRVs requested, awarded, denied, sold, transferred & redeemed
- Congressional reports/GAO reports
 - <https://www.gao.gov/assets/gao-20-251.pdf>

CBER's RPD PRV experience

- Several PRVs currently in-house (non-disclosable)
- Eight (8) vouchers have been issued (CBER/OTP)
 - Kymriah STN 125646
 - Luxturna STN 125610
 - Zolgensma STN 125694
 - Ryplazim STN 125659
 - Rethymic STN 125685
 - Skysona STN 125755
 - Zynteglo STN 125717
 - Vyjuvek STN 125774

RPD PRV resources

- From OOPD's webpage:
 - <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>
- Revised Draft Guidance (July 2019)
 - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-pediatric-disease-priority-review-vouchers>
 - Incorporates public comments received on the initial draft and provides FDA's thinking regarding the provisions of the Advancing Hope Act of 2016, which updated the definition of a rare pediatric disease as one that is a rare disease and one where the disease is serious or life-threatening with the serious or life-threatening manifestations primarily affecting individuals from age zero to 18.
 - Among the key changes from the initial draft are an explanation of the rare pediatric disease priority review voucher eligibility requirements, the rare pediatric disease designation process and examples to illustrate the agency's current thinking on these review determinations.

A final word about “redemption”

- Applicants are required to notify the reviewing Center 90 days prior of an intent to **redeem** a RPD PRV
- The Applicant will be assessed the PRV redemption fee (in addition to the user fee)
- That redemption fee is **non-refundable**
- *Specific Qs about fees should be directed to the Agency user fee staff :*
CBERUserFeeStaff@fda.hhs.gov

Summary

- Addressing PREA is required; submit PSPs early and as an IND amendment
- Early consultation with CBER for pediatric drug development is important
- The PRV programs offer incentives
- This is just a “snapshot” of FDA’s pediatric-related provisions

Questions?



- **Consumers:** ocod@fda.hhs.gov
- **Manufacturers' Assistance:** Industry.Biologics@fda.hhs.gov
Manufacturers include blood, plasma and tissue banks, clinical investigators and other members of regulated industry who are developing pharmaceuticals derived from blood and blood components, vaccines, or cellular and gene therapies.
- IND holders and Applicants should contact the respective CBER Office & Review Division
- Rare pediatric disease designation process:
orphan@fda.hhs.gov

