The U.S. Regulatory Environment and Pediatric Cancer Drug Development: Orphan Drugs and Options for Changes to PREA and BPCA

Gregory Reaman, M.D.
Associate Director, Office of Hematology and Oncology Drug Products
Center for Drug Evaluation and Research
U.S. FDA
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• No financial relationships to disclose.
• Limited discussion of off label or investigational use of specific products/devices.
• The views expressed are those of the speaker and do not necessarily represent the opinion of the Food and Drug Administration.
Outline

• Legislative History
• Current provisions overview
• Maximizing authority
• Remaining challenges
• Options
Acronyms

• BPCA – Best Pharmaceuticals for Children Act
• FDAAA – Food and Drug Administration Amendments Act
• FDASIA – Food and Drug Administration Safety and Innovations Act
• PeRC – Pediatric Review Committee
• PPSR – Proposed Pediatric Study Request
• PREA – Pediatric Research Equity Act
• iPSP – initial Pediatric Study Plan
• WR – Written Request
Early pediatric legislation reflected a response to products that caused harm.

- 1902 Biologics Control Act
- 1906 Pure Food and Drug Act
- 1938 Food Drug and Cosmetic Act
- 1962 Kefauver-Harris Amendment
Cont’d

The laws created from the above legislation were based on incidents in children but largely benefited adults.

Evaluations of drugs in children were limited and discouraged

- ethical issues,
- fears of harming children
- perceived increased liability of testing drugs in children
Later pediatric legislation encourages pediatric investigations to inform labelling

- 1979 – *Pediatric Use* Subsection under *Precautions* required in the product label (21 CFR 201.57 (f)(9))
- 1994 – Pediatric Rule added subsection to this regulation regarding use of extrapolation as basis for pediatric use
- 1997 – FDAMA/Pediatric exclusivity provision
- 2002 - *Best Pharmaceuticals for Children Act (BPCA)*
- 2003 - *Pediatric Research Equity Act (PREA)*
- 2007 - *Food & Drug Administration Amendments Act (FDAAA)* reauthorized BPCA and PREA
- 2012 - *FDA Safety and Innovation Act (FDASIA)* made BPCA and PREA permanent
Pediatric Research Equity Act (PREA)

• Authorizes FDA to require pediatric assessments

• Triggered by NDA/BLA submission or a supplement with a new indication, active ingredient, dosage form, dose regimen or route of administration

• Applies only to indication(s) included in the submission

• Drugs with Orphan Designation do not trigger PREA

• FDA can grant full or partial waiver or deferral for pediatric studies if specific criteria are met

Best Pharmaceuticals for Children Act (BPCA)

• Provides a financial incentive to companies to voluntarily conduct pediatric studies under a Pediatric Written Request (WR)

• A sponsor may request the FDA to issue a WR by submission of a Proposed Pediatric Study Request (PPSR) OR FDA may issue WR without PPSR

• PPSR should contain rationale for studies, detailed study designs and plans for formulation development
BPCA: Written Request (WR)

- Considerations when reviewing a PPSR for a potential WR
  - What is the public health benefit?
  - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
  - Have all populations and conditions been addressed?
  - Are there other products already approved for the condition?
Cont’d

• Pediatric exclusivity
  – Applicants who fulfill requirements of the WR are eligible to receive an additional 6 months of exclusivity
  – Attaches to all existing exclusivities and patents for the drug moiety
  – Does not require positive studies or a pediatric indication
PREA and BPCA Programs

**PREA**
- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

**BPCA**
- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled
FDA Safety and Innovations Act (FDASIA)

- PREA and BPCA made permanent part of the Food Drug and Cosmetic Act (no ‘sunset’ provisions)
- NIH BPCA program reauthorized to Oct. 1, 2017
- Pediatric humanitarian device exemption (HDE) profit incentive and Pediatric Device Consortia program reauthorized to Oct. 1, 2017
- Rare Pediatric Disease Priority Review Voucher Program
- Requires FDA to hold a public meeting and issue a report on efforts to accelerate development of drugs for pediatric rare diseases
Changes to PREA and BPCA under FDASIA

**PREA**
- Submission of an iPSP within 60 days of End of Phase 2 meeting
- Provision for extension for deferred studies if general criteria are met
  - Delay in development could not have been prevented/foreseen.
  - Sponsor still able to complete studies.
  - Provide general consistency with reasons for delayed FDAAA PMRs
- Issuance and publication of non-compliance letters for late PREA PMRs

**BPCA**
- Requires BPCA requests for pediatric studies to include a rationale for not including neonatal studies if none are requested
  - If inclusion of neonates is not warranted a justification must appear in the WR
Ramifications of FDASIA changes to PREA

• More closely aligned PIP and PSP
• iPSPs – plans for waiver based on indication
• Provided opportunity to solicit interest in product from investigator community
• Feedback to sponsor (iPSP review) to assess potential relevance in pediatric tumor(s)
• Enabled product review and selection for possible invitation to Pediatric Subcommittee of ODAC
• Issuance of WRs earlier in product lifecycle
PPSR process under BPCA

• A sponsor may request FDA to issue a WR with the submission of a PPSR which contains:
  – Rationale for studies and detailed study designs (clinical, nonclinical)
  – Plans for age-appropriate formulation development

• Historically:
  – PPSR was submitted after an NDA/BLA was submitted (or after approval)
  – Submitted earlier for rare diseases or oncology indications
  – sufficient safety data to initiate pediatric studies?
Currently:
– PPSR may be submitted before NDA/BLA submission
– Agency may consider issuing a WR earlier in the drug development process with the following considerations:
  • Are children included in the later clinical studies?
  • Are there sufficient safety data to initiate pediatric studies?
Rare Pediatric Disease Priority Review Voucher Program

- Enacted under FDASIA
- Awarded upon approval of NDA/BLA for a rare pediatric disease indication
- Incentivizes development of products for rare pediatric disease
  - Relies on clinical data from studies in a pediatric population
  - Does not seek approval for an adult indication
  - A rare disease affects < 200,000 people 0-18 years old
Cont’d

• Voucher gives a sponsor ‘priority review’ of a subsequent drug application
• Voucher is transferable
• Does not have to be used for a pediatric or orphan disease application
• Re-authorized (21st Century Cures Act) Omnibus budget until 2018
• Success under review by the GAO
Promoting efficient development of new drugs for pediatric cancers

• BPCA Pediatric Oncology Working Group holds quarterly meetings with representatives of the academic community to discuss promising new agents for pediatric evaluation

• OPT coordinates a monthly Pediatric Cluster meeting with international regulators for information exchange and discussion of specific product development, safety concerns and general scientific issues
Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

• Forum where industry sponsors can obtain input from key academic and community opinion leaders regarding an ongoing or potential pediatric development program
  – gauge investigator interest in exploring pediatric development programs for products in various stages of adult development
  – select possible drug candidates for a Written Request
Cont’d

– provide feedback to industry on trial design, pediatric regulations

– Interactive discussion of key topics in designing/conducting trials for pediatric patients with cancer
  • PRO instruments in pediatric trials

• Ideal to come early in drug development

• Sponsors are encouraged to seek an invitation if there are questions regarding a specific pediatric development program
Expanding the Authority of PREA

- Indication-based to MOA-based
- Requiring pediatric studies based on known molecular mechanism of action could significantly increase the number of earlier pediatric studies under PREA
- PREA be amended to require that certain drugs (including biologic agents) developed for adult cancer indications be evaluated for a pediatric cancer indication when there is evidence that the drug affects specific molecular targets and/or molecular mechanisms that are shared
- Eliminate orphan exemption
Cont’d

• A drug which targets, inhibits, or suppresses a cell surface receptor, an aberrant fusion protein or cell signaling pathway in an adult cancer which has been reported to be associated with the causation and/or progression of one or more pediatric cancers.
Addressing the Challenge of New Drug Development when No Adult Indication Exists

- No current legislative fix
- Substantial and early incentives to industry require expansion
- Continued success of current special initiatives (Pediatric Rare Disease Priority Review Vouchers) – subject to dilution of benefit and competing priority review mechanisms/”early” development incentive lacking
- Public/Private Partnerships – Role of NCI
  - Ch 14.18 (dinutuximab) in NBL
  - AMG479 in Ewing sarcoma
Rare Disease History at FDA: The Orphan Drug Act

- Orphan Drug Act (ODA) – signed into law in 1983
  - Purpose
    - To promote the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases
  - Orphan Designation – Requirements:
    - Disease/condition with a prevalence <200,000 Americans
    - Drug shows “promise” for treating disorder
  - Mainly provides financial incentives
    - Exempt from PDUFA fees ($2,374,000 FY 16)
    - 50% tax credit for clinical study costs
    - Eligible to apply for FDA Orphan grants program to support clinical research
      - Clinical trials, $14 million/year, ~80 studies
    - 7 years marketing exclusivity for approved Orphan product
Diseases/Conditions with Orphan Designations

- Oncologic: 36%
- Metabolic: 11%
- Hematologic-immunologic: 7%
- Neurologic: 7%
- Infectious/parasitic: 6%
- Cardiovascular: 5%
- Transplantation: 4%
- Gastrointestinal: 4%
- Respiratory: 4%
- Endocrinologic: 2%
- Dermatologic: 2%
- Ophthalmic: 2%
- Musculoskeletal: 2%
- Injury/poisoning: 2%
- Perinatal: 1%
- Congenital abnormalities: 1%
- Others: 27%

Slide courtesy of FDA Office of Orphan Products Development
Orphan Drug Act (ODA)

• ODA intended to make development of drugs to treat small populations financially viable
  – Does not define standards for approval
  – Intention: Patients with rare diseases are as entitled to safe and effective medications as those with common diseases

• Orphan drugs held to the same approval standards as drugs for common diseases
  – Both require “substantial evidence” of safety and effectiveness for approval
  – However, regulations allow for “flexibility” and “scientific judgment” in how this is achieved
Level of Evidence

• Substantial clinical trial design diversity\(^4\)
• Analysis of CDER applications 2006-2011 showed:
  – RCTs, OL single-arm trials, enrichment trials, etc.
  – Concurrent or historical controls
  – Wide variety of endpoints
    • Determined by disease characteristics, expected effects of intervention, population under study, etc.
  – Efficacy trial size
    • <20 to >1,000 (median ~250)

PDUFA V: Regulatory Science and Expediting Drug Development

• Expedited Pathways and Designation
  • **Breakthrough** (new under PDUFA V) Many/most Rare Disease Programs will be eligible for one or more expedited pathway

  • **Priority Review** (existing)
  • **Accelerated Approval** (existing + PDUFA V)
  • **Fast Track** (existing)
Future Direction

• Maximize Regulatory Authority
  – Aid in Legislative amendments when warranted
  – Expand opportunities for evaluating Precision Medicine approaches to improve outcomes
  – Paradigm shifts in study design, conduct, initiation, and F/U
  – Rational science-based strategy for prioritizing which/when new products to test in what diseases; successful integration with “standard” therapy