Pediatric Drug Development: Regulatory Expectations BASIC

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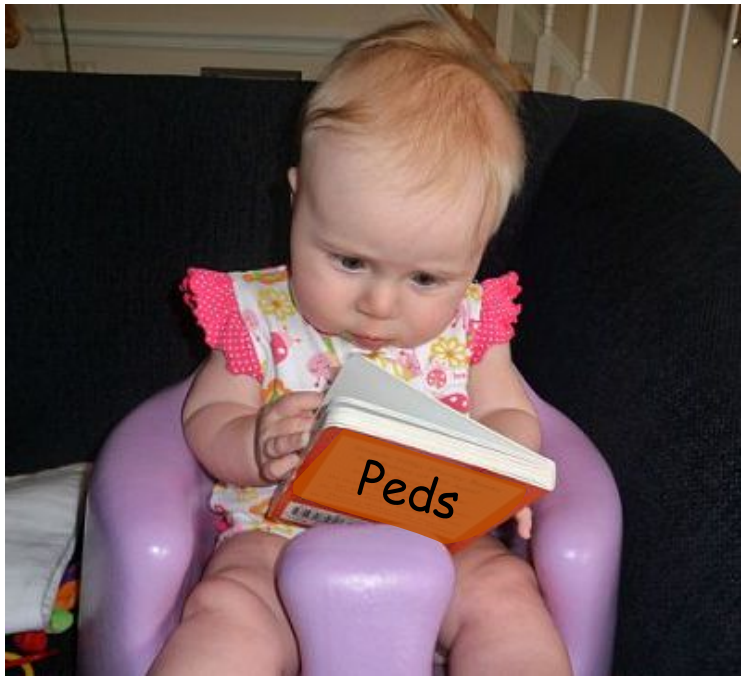
Disclosure Statement

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Objective

- Understand the basics of pediatric drug development laws



Outline

- The Past
- Current FDA Legislation
  - Pediatric Research Equity Act (PREA)
  - Best Pharmaceuticals for Children Act (BPCA)
  - Title V of FDA Safety and Innovation Act (FDASIA)

Acronyms

- BPCA Best Pharmaceuticals for Children Act
- EOP2 End of Phase 2
- FDAAA Food & Drug Administration Amendments Act
- FDASIA Food & Drug Administration Safety & Information Act
- PeRC Pediatric Review Committee
- PMHS Pediatric & Maternal Health Staff
- PPSR Proposed Pediatric Study Request
- PREA Pediatric Research Equity Act
- PSP Pediatric Study Plan
- WR Written Request

TOP 10 Pediatric Drug Development Questions

Question 10

Who are pediatric patients?

Pediatric Patients

- Age range depends on context
  - Labeling regulations for prescription drugs: 0 to 16 years old [21 CFR 201.57(c)(9)(iv)]
  - Clinical trials: *Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. [21 CFR 50.3(o)]

Question 9

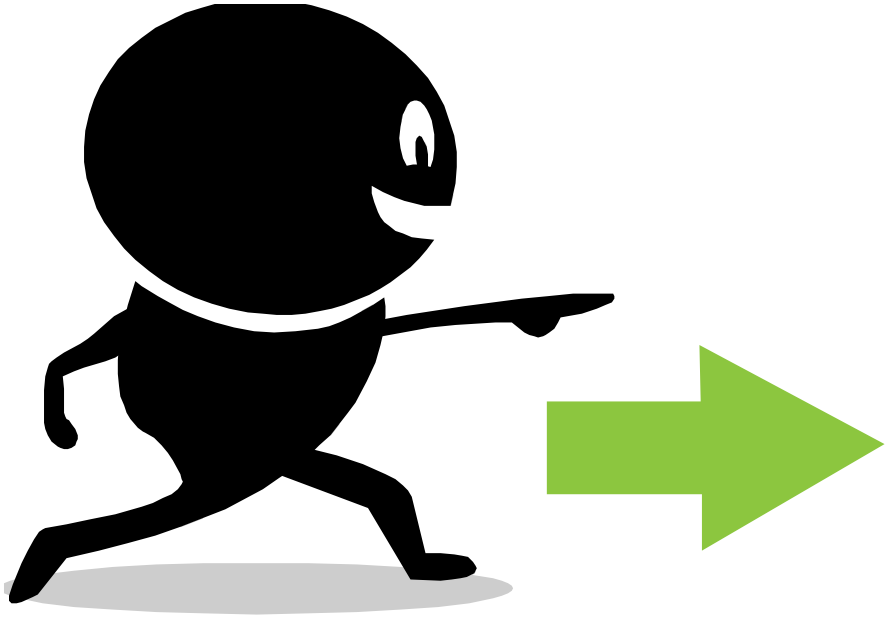
Why should we enroll children in clinical trials?

Pediatric Drug Development – *The Past*

Choices for Pediatric Practitioners

- Not treat children with potentially beneficial medications because they are not approved for use in children
- Treat with medications based on adult studies with limited or anecdotal pediatric experience (off-label use)

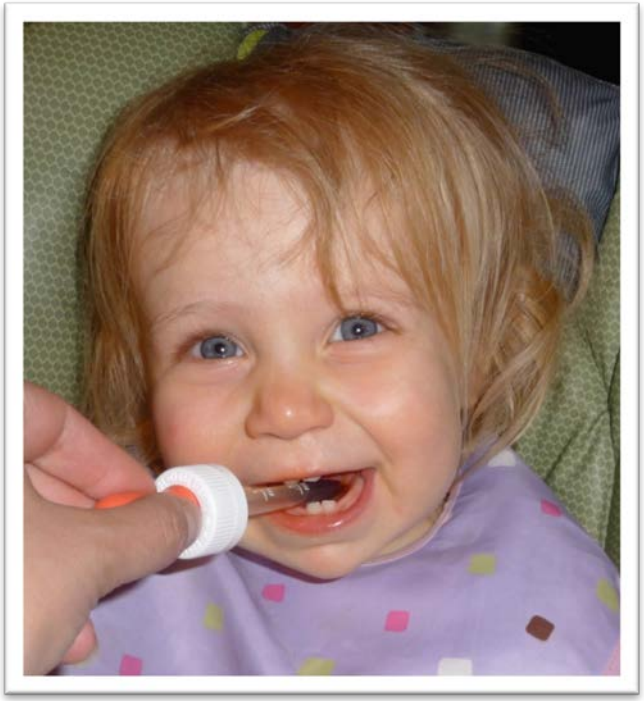
The Present



Pediatric Drug Development
General Principles

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population*, December 2000

- Give pediatric patients products that have been appropriately evaluated for them
- Product development programs should include pediatric studies when anticipate pediatric use



Why We Need Pediatric Trials

- Children get sick - they need medication
- Children should have access to medicines that have been properly evaluated for use in the intended population
- Thoughtful drug development and inclusion of children in trials is critical to pediatric health

Question 8

What are the main U.S. pediatric drug development laws?

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
- Title V of FDA Safety and Innovation Act (FDASIA)

PREA and BPCA

- **Pediatric Research Equity Act (PREA)**
  - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients (Pediatric Assessment)
- **Best Pharmaceuticals for Children Act (BPCA)**
  - **Provides a financial incentive** to companies to voluntarily conduct pediatric studies

PREA vs. BPCA

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

Pediatric Review Committee (PeRC)

- Established by legislation to carry out the activities described under PREA and BPCA
- Intended to increase the consistency of implementation of provisions of PREA and BPCA across FDA
- Committee membership
  - Expertise in Pediatrics, Neonatology, Pediatric Ethics, Biopharmacology, Statistics, Chemistry, Law required
  - Appropriate expertise pertaining to the product under review

Ultimate Goal of PREA and BPCA

PREA  ***BPCA***

New Pediatric Labeling

to encourage appropriate use of medications to treat pediatric patients

Importance of PREA and BPCA[1]

- Before these laws, 22% of drug labeling had pediatric information[1]
- In 2009, 46% with pediatric information[1]
- Now 500+ pediatric labeling changes[2]
- Still a lot of work to be done[1]

[1]Sachs et al. Pediatric Information in Drug Product Labeling, *JAMA*, 2012:1914-5.

[2] New Pediatric Labeling Information Database, http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase.

Pediatric Drug Development Laws

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Question 7

When does PREA apply?

Pediatric Research Equity Act (PREA)

- Is triggered by an application for:
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration
  - New active ingredient

Question 6

What is a Pediatric Assessment?

PREA: Pediatric Assessment

- **Data** from pediatric studies using appropriate formulations for each age group and other data
  - **To assess the safety and effectiveness** of a drug/biologic for the claimed indications in all relevant pediatric subpopulations AND
  - **To support dosing and administration** for each pediatric subpopulation for which the drug or biological product is safe and effective

Question 5

How does my company discuss with the FDA ahead of time our plans to fulfill PREA?

Pediatric Study Plan (PSP)

- Outline of the pediatric study(ies) the sponsor plans to conduct
- The intent of the PSP:
  - Encourage sponsors to identify pediatric studies as early as possible in product development
  - When appropriate, to conduct those studies prior to submitting the NDA/BLA

Timing of a PSP Submission (current)

- If End of Phase 2 (EOP2) Meeting will occur
  - PSP must be submitted within 60 days
- If no EOP2 Meeting to occur, then PSP should be submitted as early as possible and at a time agreed upon by FDA and sponsor
  - FDA strongly encourages PSP to be submitted prior to initiation of Phase 3 studies
  - PSP must be submitted no later than 210 days prior to submission of application

Question 4

What if our company believes we should wait to do pediatric studies until additional adult data is available?

PREA: Pediatric Deferral

- The submission of some or all assessments may be deferred until a specified date after approval

PREA: Deferral Criteria

- The drug/biologic is ready for approval for use in adults before pediatric studies are complete OR
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected OR
- There is another appropriate reason for deferral (e.g., scientific issues exists regarding study design or endpoints)

PREA: Deferral Requirements

The sponsor must submit

- ✓ Certification of the grounds for deferring the assessments AND
- ✓ A Pediatric Study Plan AND
- ✓ Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time AND
- ✓ A timeline for the completion of such studies

Question 3

What if the disease our product is treating doesn't exist in pediatric patients?

PREA: Pediatric Waiver

- The requirement for assessments may be waived
- May be a full waiver (all pediatric ages) or partial waiver (a subset of the pediatric population)

PREA: Waiver Criteria

- Necessary studies are impossible or highly impracticable OR
- Evidence strongly suggests the drug/biologic would be ineffective or unsafe OR
- Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used by a substantial number of pediatric patients OR
- Reasonable attempts to produce a pediatric formulation necessary for that age group have failed (partial waiver only)

PREA: Deferrals and Waivers

- OND review divisions and sponsors should discuss PREA requirements early in the drug development process
- PSP needs to include plans to request deferrals, waivers or partial waivers with supporting data
- Final deferral and waiver decisions are made at the time of NDA/BLA approval

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Question 2

How does the incentive under BPCA work?

Best Pharmaceuticals for Children Act (BPCA)

- Provides for **voluntary** pediatric drug studies via a Written Request (WR)
- Reflects need for information that may produce health benefits in the pediatric population
- Authorizes FDA to **request pediatric studies of approved and/or unapproved indications**

BPCA and the Written Request

- A sponsor may request the FDA to issue a WR by submitting a Proposed Pediatric Study Request (PPSR)
- PPSR should contain:
  - Rationale for studies and study design
  - Detailed study design
  - Appropriate formulations for each age group
- FDA may issue a WR without a PPSR
- Sponsors who submit studies to fulfill a WR may be eligible to receive pediatric exclusivity

BPCA: Pediatric Exclusivity, continued

- If the terms of the WR have been met and studies were conducted using good scientific principles, the company is awarded an additional 6 months of exclusivity
  - Exclusivity attaches to all existing marketing exclusivities and patents for the drug moiety (initial WR)
  - Pediatric exclusivity does not require positive pediatric studies (initial WR)
- Granting of exclusivity is reviewed by the FDA Pediatric Exclusivity Board

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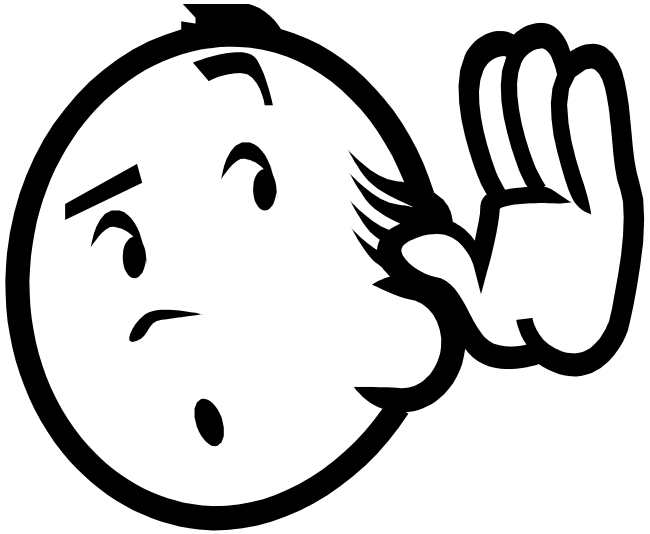
FDASIA: Selected Changes

- Permanently reauthorized PREA & BPCA
- Changes to PREA
  - New ability to provide extensions for the submission of deferred studies
  - Issuance and publication of non-compliance letters
  - Requirement to submit Pediatric Study Plans
- Changes to BPCA
  - Neonates must be addressed in Written Requests

Question 1

How do I learn more about these pediatric drug development laws?

Stay Tuned…



Questions?

I wonder if PREA is triggered.