General Considerations for Age-Appropriate Formulations: FDA Clinical Perspective

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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

Overview

- Past problems with Pediatric Drug Development
- Current FDA Legislation
  - Best Pharmaceuticals for Children Act (BPCA)
  - Pediatric Research Equity Act (PREA)
  - FDA Safety and Innovation Act (FDASIA)
- FDA Clinical Perspective

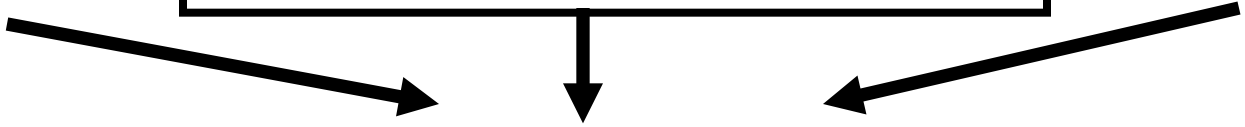
Pediatric Product Development: The Historical Problem

Acknowledged different drug responses, toxicity, and metabolism in adults versus children

Discouraged the study of drugs in children

- Concerns related to ethical issues
- Fears of harming children
- Perceived increased liability of testing drugs in children

Lacked an incentive for drug companies to conduct pediatric trials



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)

Pediatric Drug Development General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

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

Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Provides a financial incentive to companies to **voluntarily** conduct pediatric studies
- Pediatric Research Equity Act (PREA)
  - **requires** companies to assess safety and effectiveness of certain products in pediatric patients
- Title V of FDA Safety and Innovation Act (FDASIA)
  - Permanently reauthorized PREA & BPCA

BPCA and the Written Request

- Proposed Pediatric Study Request and Written Request should contain:
  - Rationale for studies and study design
  - Detailed study design
  - **Appropriate formulations for each age group**

BPCA and Formulation Development

- If there is not an age-appropriate formulation available, the Sponsor must develop and test one
- If the formulation is found to be safe and effective in the population, the Sponsor must seek marketing approval for the formulation
  - Notice of Pediatric Formulations Not Marketed or Not Introduced into the Market within 1 year of the Publication of Notice that Pediatric Exclusivity was Granted: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM203653.pdf
- If formulation development fails, the Sponsor must document attempts to develop and reasons for failure of formulation

PREA

- Sponsors are required to provide a pediatric assessment (**using an age-appropriate formulation**) to support dosing, safety, and effectiveness for the claimed indication for all pediatric ages, unless this requirement is waived, deferred or inapplicable.
  - Studies may be deferred or waived for part or all of the pediatric population only if criteria are met
- Not applicable to drugs with indications that have been granted orphan designation

PREA: Waiver and Deferral Criteria

- 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)**
    - ***If partial waiver is granted for this reason, the documentation from the applicant will be posted on the FDA Web site***
- Deferral criteria:
  - Drug or biologic is ready for approval 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

Goal of PREA and BPCA

PREA

BPCA

Approved Pediatric Labeling

Based on sufficient evidence to support the safe and effective use of medications to treat pediatric patients

FDASIA: Selected Changes

- 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**
    - **An initial Pediatric Study Plan (iPSP) must be submitted shortly after End of Phase 2 meeting**
- Changes to BPCA
  - Neonates must be addressed in Written Requests

Pediatric Study Plan: Contents

1) Overview - Disease Condition
2) Overview - Drug/Biologic Product
3) Plan for Extrapolation
4) Plan to Request Waiver(s)
5) Summary of Planned Nonclinical and Clinical Studies
6) **Pediatric Formulation Development**
7) Nonclinical Studies
8) Clinical Data to Support Design and/or Initiation of Studies
9) Planned Pediatric Clinical Studies
10) Timeline of the Pediatric Development Plan
11) Plan to Request Deferral
12) Agreements with Other Regulatory Authorities

Pediatric Formulation Development: iPSP Content

- Details about pediatric-specific formulations being developed and the applicable populations
- If the current formulation is not suitable for all proposed age groups, provide the plan for development of an age-appropriate formulation
  - Type (capsules, tablet, infusion, device)
  - Excipients (safety)
  - Use Pattern (e.g., relative to meals, chronic use)
  - Acceptability relative to age (e.g., size, swallowability, palatability, strength, etc.)
  - Ease of administration
  - Measurement
  - Stability

Pediatric Formulation Development: FDA input

- Multidisciplinary evaluation
  - includes reviewers in Pharmacology/Toxicology, Clinical Pharmacology, Clinical and Chemistry, Manufacturing and Control.
- Potential Questions
  - Is the formulation acceptable based on the type (e.g., tablet size, volume of liquid) and intended use?
  - Does the strength or concentration make sense for the anticipated dose range needed?
  - Any issues for absorption/delivery or safety based on route?
  - For oral formulations, are there any palatability or swallowability issues (e.g., bitter taste, choking risk)
  - For devices, are there any potential issues
  - For injectables, will there be significant wastage?
  - Ensure bridging studies not performed in healthy children

Pediatric Formulations

- Of the 635 products with pediatric labeling changes through June 2016, 45 have included new pediatric formulations including:
  - Oral suspensions/syrup
  - Lower strength tablets/solution
  - Oral disintegrating tablets
  - Chewable tablets
  - 3-D printed tablets
  - Nasal spray/inhaler
  - Oral powder
  - Oral granules
  - Delayed and extended release tablets and capsules

Thank you

Acknowledgements

Thanks to Alyson Karesh, M.D., Hari
Cheryl Sachs, M.D., and Lynne Yao,
M.D. for their assistance in
preparation for this presentation