Pediatric Drug Development: Safety Considerations

Mona Khurana, MD
Pediatric Team Leader
Division of Pediatric and Maternal Health
Center for Drug Evaluation and Research

Disclosure Statement

- I am employed by the US Food and Drug Administration and 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.

Outline

- Pediatric drug development
  - Progress report
  - Ongoing challenges
  - Pediatric-specific safety considerations
  - Potential utility of real world evidence

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Progress Report

Regulatory Definitions: Pediatrics

Prescription drug/biologic labeling regulations

- Birth to 16 years of age inclusive [21 CFR 201.57(c)(9)(iv)]

2007 Pediatric Medical Device Safety and Improvement Act

- Birth to 21 years [Section 303(E)(i)]

Additional Safeguards for Children: 21 CFR 50 Subpart D

- "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(0)]

Pediatric Drug Development: Past

- Drug labeling
  - Pediatric use information uncommon
- Pediatric use
  - Avoid product use in pediatric patients
  - Off-label use in pediatric patients

Pediatric Drug Development: Present

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
- Addendum to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E11 Guidance published September 12, 2017

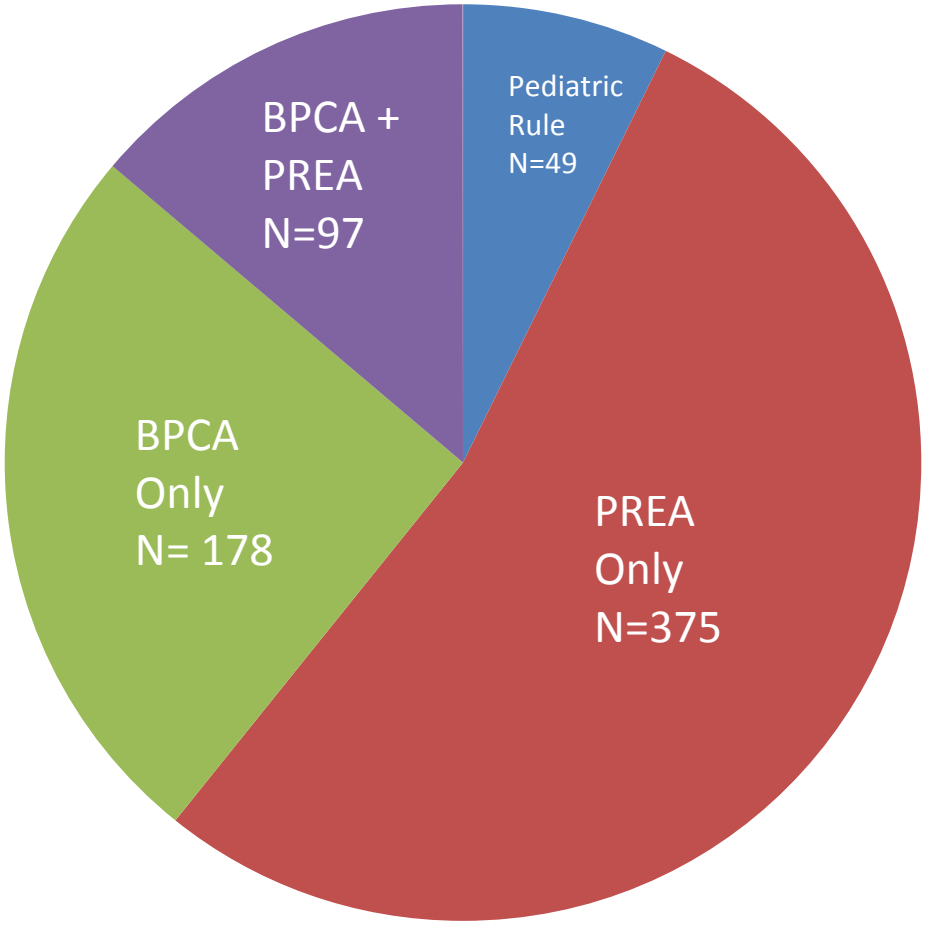
December 2000 FDA Guidance to Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population

Pediatric Drug Legislation

- 2002 Best Pharmaceuticals for Children Act (BPCA)
  - **Voluntary** pediatric assessment for approved and unapproved indications linked to financial incentive
- 2003 Pediatric Research Equity Act (PREA)
  - **Required** pediatric assessment for same indication being developed or approved in adults
- 2012 FDA Safety and Innovation Act (FDASIA)
  - Permanently reauthorized BPCA and PREA

Pediatric Labeling Changes

N=701 as of July 31, 2017



New Pediatric Information Labeling Database accessed 9/1/17:
https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

BPCA: Best Pharmaceuticals for Children Act; PREA: Pediatric Research Equity Act

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Ongoing Challenges

Challenges in the 21st Century

- Substantial lag time between adult approval and incorporation of pediatric use information in labeling
- Feasibility of conducting clinical trials for rare, pediatric-onset diseases
  - Neonates and premature infants
  - Cancer and genetic diseases
- Ability to establish long-term safety of drugs in pediatric patients

U.S. Evidentiary Standard for Approval

- Same standard for adults and pediatric patients
- Product is safe and effective for labeled indications under labeled conditions of use
  - Demonstrate substantial evidence of effectiveness/clinical benefit (21 CFR 314.50)
  - Safety assessment is relative to benefits and considered favorable if benefits outweigh risks for labeled use(s)

Pediatric-Specific Safety Considerations during Drug Development Life Cycle

Pediatric-Specific Safety Considerations

- Prior to enrolling pediatric patients in clinical trials
  - Ethics of pediatric enrollment
  - Evidence of sufficient proof of concept
  - Evidence of non-clinical safety
  - Appropriate dose selection
- After completing pediatric enrollment
  - Adequacy of safety database

Ethics of Pediatric Enrollment

- Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
- Maximize applicability of adult human data in informing need for and types of pediatric studies
- Establish prospect of direct clinical benefit before enrollment in studies involving more than minimal risk (21 CFR 50.52)

Evidence of Nonclinical Safety

- Routine part of human risk assessment
- Need for juvenile animal studies determined case-by-case
  - To assess for developmental age-specific toxicities
  - To assess for differences in sensitivity between adult and immature animals
  - When prior adult and pediatric experience are minimal (e.g. rare, pediatric-onset disease)
  - When adverse reactions (ARs) are reported with off-label pediatric use for an indication to be studied

February 2006 Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products

Appropriate Dose Selection

- Target systemic drug exposure found to be safe and effective in adults
- Dedicated pharmacokinetic (PK) studies (intensive PK sampling)
- Alternative PK study designs (sparse PK sampling)
  - Low volume assays
  - PK modeling and simulation
  - Opportunistic study settings
  - Use of biological fluids obtained non-invasively

December 2014 Guidance for Industry General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Clinical Trial Safety Database

- Informed by non-clinical toxicity and adult safety profile
- Ideal database
  - Proposed labeled pediatric dosage
  - Anticipated duration of use
  - Examines more than one dose level to better characterize exposure-toxicity relationship
  - Includes diverse population representative of expected target population

Clinical Trial Safety Database

- Pediatric studies too small to detect rare ARs
- Safety data may not be representative of broader pediatric population that will use product post-approval
- Pediatric studies too short in duration to capture ARs associated with long-term use
- Comparative safety data difficult to obtain when needed
  - Background rate of ARs is high
  - Well-established treatment already exists with effect on survival or irreversible morbidity

Post-Marketing Safety

- FDA required to review product-related adverse event (AE) reports for 18 months after any approved pediatric labeling change
- Present findings to Pediatric Advisory Committee
- This effort provides a window on “real world” pediatric use of products

Post-Marketing Safety Databases

- FDA's Adverse Events Reporting System Database (FAERS)
  - Voluntary reporting database
  - Most suited for identifying new, rare, serious ARs temporally associated with a product which has a low background event rate
- Data mining
- Sentinel System https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm

Post-Marketing Safety Databases

- FAERS Database
  - Unreliable for analyzing ARs with delayed onset or with long latent interval relative to product exposure
  - Can't be used to quantify a risk or calculate an incidence
  - Can't be used to make comparative assessments to identify a differential risk between drugs or biologic
- Sentinel system
  - Issues with data integrity, validity, reliability, reproducibility of results

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Potential Utility of Real World Evidence

Utility:
During Drug Development Life Cycle

- Provide evidence to support acceptability of efficacy extrapolation for a given indication
- Support proof of concept
- Inform need for juvenile toxicity studies
- Identify settings for opportunistic PK studies
- Identify trends in short- and long-term product safety

Utility: Overall Product Safety

- Identify previously unrecognized, unlabeled serious ARs
- Capture product safety
  - Broader population (e.g. wider age range, more co-morbidities, variable disease severity, variety of concomitant drug use)
  - When co-prescribed with other drugs
  - With off-label use
  - With accidental exposures
  - Related to excipient content

Utility: Capturing Long-Term Safety

- Identify trends in safety of products
  - Taken chronically during childhood or over a lifetime
  - Taken for shorter duration but during critical stages of development
- Detect ARs
  - Reversible versus permanent
  - Manifest months to years after product exposure

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