Pediatric Drug Development: Successes and Challenges

Lynne Yao, M.D.
Director, Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U.S. FDA
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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
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
Special Considerations for Pediatric Product Development

• Ethical considerations
  – 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)
  – Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low”
  – Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care

• Feasibility considerations
  – The prevalence and/or incidence of a condition is often much lower compared to adult populations
Pediatric Drug Development Laws

• **Best Pharmaceuticals for Children Act (BPCA)**
  – Section 505A of the Federal Food, Drug, and Cosmetic Act
  – Provides a financial incentive to companies to voluntarily conduct pediatric studies
  – FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)

• **Pediatric Research Equity Act (PREA)**
  – Section 505B of the Federal Food, Drug, and Cosmetic Act
  – **Requires** companies to assess safety and effectiveness of certain products in pediatric patients
## PREA vs. BPCA

<table>
<thead>
<tr>
<th>PREA</th>
<th>BPCA</th>
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</thead>
<tbody>
<tr>
<td>• Drugs and biologics</td>
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</tr>
<tr>
<td>• <strong>Required</strong> studies</td>
<td>• <strong>Voluntary</strong> studies</td>
</tr>
<tr>
<td>• Studies may only be required for approved indication(s)</td>
<td>• Studies relate to entire moiety and <strong>may expand indications</strong></td>
</tr>
<tr>
<td>• Products with orphan designation are exempt from requirements</td>
<td>• Studies may be requested for products with orphan designation</td>
</tr>
<tr>
<td>• Pediatric studies must be labeled</td>
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- **PREA** is for **Drugs and biologics** and requires studies for approved indications.
- **BPCA** is for **Voluntary** studies that may expand indications.

**BPCA** allows for voluntary studies and includes pediatric studies which must be labeled.

**PREA** is more stringent with required studies and products with orphan designation are exempt from requirements. **BPCA** is more flexible with voluntary studies and includes products with orphan designation.
Pediatric Review Committee Activities
Written Requests Issued 1998-2015
Written Requests issued 2015

Number

- Rheumatology
- Psychiatry
- Nephrology
- Oncology
- Ophthalmology
- GI/Inborn Errors of Metabolism
- Endocrinology/Metabolism
- Dermatology
- Cardiovascular
- Anti-Viral
Pediatric Labeling Changes 2005-2015

![Bar chart showing the number of labeling changes by year from 2005 to 2015.](chart.png)

- **2005**: Number of labeling changes
- **2007**: Number of labeling changes
- **2009**: Number of labeling changes
- **2011**: Number of labeling changes
- **2013**: Number of labeling changes
- **2015**: Number of labeling changes

**Legend**:
- **Number of labeling changes**
Pediatric Product Development in 2016

• Pediatric Product Development matured
  – Over 600 products now labeled with pediatric-specific information

• Increased experience and understanding of
  – Pediatric clinical trial design
  – Pediatric extrapolation
Pediatric Extrapolation

• Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  – The course of the disease is sufficiently similar
  – The response to therapy is sufficiently similar

• Dosing cannot be fully extrapolated

• Safety cannot be fully extrapolated
Summary of Approaches to Extrapolation 1998-2008

<table>
<thead>
<tr>
<th>Extrapolation</th>
<th>Supportive Evidence Requested From Pediatric Studies</th>
<th>Products n/N (%)</th>
<th>New or Expanded Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two adequate, well-controlled, efficacy and safety trials plus PK data.</td>
<td>19/166 (11)</td>
<td>7/19 (37)</td>
</tr>
<tr>
<td></td>
<td>Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.</td>
<td>10/166 (6)</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Partial</td>
<td>Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.</td>
<td>67/166 (40)</td>
<td>35/67 (52)</td>
</tr>
<tr>
<td></td>
<td>Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.</td>
<td>20/166 (12)</td>
<td>15/20 (75)</td>
</tr>
<tr>
<td></td>
<td>Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.</td>
<td>26/166 (16)</td>
<td>19/26 (73)</td>
</tr>
<tr>
<td>Complete</td>
<td>PK and safety data.</td>
<td>10/166 (6)</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td></td>
<td>Safety data only.</td>
<td>14/166 (8)</td>
<td>6/14 (43)</td>
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Review of Extrapolation

• First published review in 2011 based on 166 products with submitted pediatric studies between 1998-2008
• Recent review (just completed in 2016) based on 157 products with submitted pediatric studies between 2009-2014
  – Partial extrapolation decreased from 68% to 29%
  – Both Complete and “No” Extrapolation increased
• Changes in extrapolation based on:
  – Evolving science and knowledge from the pediatric trials that allow one to be more confident in assumptions
  – Failed pediatric trials and better understanding of the differences between adults and children
  – New science in the area of molecular or genetic biology
Challenges in the 21st Century

• Pediatric-specific diseases
  – Neonates and pre-term infants
  – Rare diseases, including pediatric cancers
• Long-term safety
  – Chronically administered drugs
  – Drugs administered during specific developmental periods
• Improving efficiency in pediatric product development
  – Coordinated global development programs
  – External and International collaborations
  – Clinical research networks
  – Innovate clinical trial designs
Pediatric Specific Diseases

• Pediatric Cancer
  – Traditionally understudied because PREA does not apply to many adult-only cancers

• Neonatal population
  – Only 35% of commonly used drugs in NICU are FDA approved*
  – Of 409 drugs with pediatric-specific labeling changes between 1997-2010, only 28 included information for use in neonates

Long-term Safety

• Pediatric long-term safety questions persist
• Many issues related to long-term safety of drugs used in children are unknown and not well studied
• Advancing Development of Pediatric Therapeutics (ADEPT)
  – ADEPT 1 held in June, 2014 discussed long-term bone health issues
  – ADEPT 2 held in April 2015 discussed evaluation of long-term neurocognitive and behavioral outcomes
  – ADEPT 3 held in April 2016 discussed long-term safety of drugs used in infants and children
Strategies to Address Challenges
International Collaborations

• Monthly Pediatric Cluster Conference
  – European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada (HC); Australia Therapeutic Goods Administration (TGA)

• ICH E11 (pediatrics) addendum
  – Updates on several topics including extrapolation, modeling and simulation, ethics
Pediatric Research Initiatives and Networks

• Critical path launched two pediatric network initiatives in 2014
  – International Neonatal Consortium (INC)
  – Pediatric Trials Consortium (PTC)—plan to advance to an independent non-profit (Institute for Advanced Clinical Trails for Children)

• European Research Network initiatives
  – European Network of Pediatric Research at EMA (Enpr-EMA)
  – GriP (Global Research in Paediatrics)
  – Consortium for Innovative Therapies for Children with Cancer (ITCC)
  – Paediatric European Network for Treatment of AIDS (PENTA)
  – UK Clinical Research Network (UK CRN)
Innovative Clinical Trial Designs

• Bayesian Modeling Applied to Pediatric Trials
  – Make use of, or borrow, prior information in pediatric trials
  – Provides a formal approach for incorporating prior information into the planning and the analysis of the next study
  – Bayesian statistical modeling is NOT the same as Pharmacometric modeling
Master Protocols

• One overarching protocol that includes one or more of the following:
  – Multiple diseases
  – Multiple treatments
  – Multiple molecular markers

• Master Protocols can increase efficiency of clinical trials

• Requires collaboration between academic investigators and/or industry sponsors with input from regulatory authorities
Pediatric Product Development in the 21st Century

- Children are protected THROUGH research, not from it
  - BPCA and PREA have led to incorporation of pediatric-specific labeling in over 600 products
- Commitment and collaboration to increase availability of safe and effective treatments for pediatric patients
- FDA committed to working with external stakeholders to improve efficiency of pediatric clinical trials
  - Extrapolation
  - Innovative clinical trial designs
  - Clinical trial networks