Pediatric Product Development in the 21st Century

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

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

BPCA NIH Program

- Many older drugs used in pediatrics are not labeled for use in the pediatric population
- Under BPCA, NIH administers a program to develop products for use in pediatric patients that sponsors do not wish to develop
  - Mostly for “off-patent” products
  - NIH may award funds for conduct of pediatric studies intended to provide pediatric-specific product labeling
- The NIH submission process is unique
  - The process includes access to all data submitted through a public docket

PREA vs. BPCA

PREA

- Drugs and biologics
- **Required** studies
- Studies may only be required **for approved indication(s)**
- Products with orphan designation are exempt from requirements
- 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 products with orphan designation
- Pediatric studies must be labeled

Evidentiary Standard for Approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease

Substantial evidence

- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling

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 generally much lower compared to adult populations

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

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

Challenges in the 21st Century

- Pediatric-specific diseases
  - Neonates and pre-term infants
  - Rare diseases
- 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

Product Development in Neonates

- 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
- International Neonatal Consortium (INC)
  - Critical Path funded global collaboration including FDA, EMA, NIH, Neonatal Advocacy Groups, Industry, Academic researchers and Neonatal Nurses
  - Mission is to accelerate the development of safe and effective therapies for neonates

*Hsieh EM et al., Medication Use in the Neonatal Intensive Care Unit,Am J Perinatol 2014;31:811–822.

Long-term Safety

- Pediatric long-term safety questions persist
- 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 Long-term safety workshop scheduled for April 13-14, 2016, DoubleTree Hilton, Bethesda, MD

International Collaborations

- Monthly Pediatric Cluster Conference
  - European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Cananda (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

- Clinical Trials Transformation Initiative
  - Pediatric Antibiotic Trials
- Critical path launched two pediatric network initiatives last year
  - International Neonatal Consortium (INC)
  - Pediatric Trials Consortium (PTC)
- EU-funded Global Research in Pediatrics (GRiP) Network
  - Link existing pediatric research networks

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
  - Global Pediatric Networks and Initiatives
  - Academic researchers and community practitioners
  - Patients and patient organizations
- FDA committed to working with external stakeholders to improve efficiency of pediatric clinical trials