Establishing Efficacy in Neonates

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Disclaimer

The views expressed in this presentation are mine and do not necessarily represent the views of the U.S. Food and Drug Administration

Discussions on Drug Development in Pediatrics

- March 7-8, 2016: Second Annual Neonatal Scientific Workshop
  - FDA and International Neonatal Consortium of Critical Path Institute
- April 5, 2016: URGENT: Improving Pediatric Trials in Antibacterial Drug Development: No Sick Child Left Behind
  - Clinical Trials Transformation Initiative (CTTI)
- June 1, 2016: Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in Pediatrics
  - FDA and University of Maryland Center for Excellence in Regulatory Science and Innovation (CERSI)
- September 23, 2016: Pediatric Master Protocols
  - FDA and CERSI

Substantial Evidence

- Federal Food, Drug, and Cosmetic Act established requirement for demonstration of "substantial evidence" of effectiveness through adequate and well-controlled investigations (1962 amendment)

- Pediatric Research Equity Act (2003): for new drugs*, assessments of safety and effectiveness are required for all relevant pediatric subpopulations
  - Adequate and well-controlled studies
  - Extrapolation

  * new active ingredient, new indication, new dosage form, new dosing regimen, new route of administration
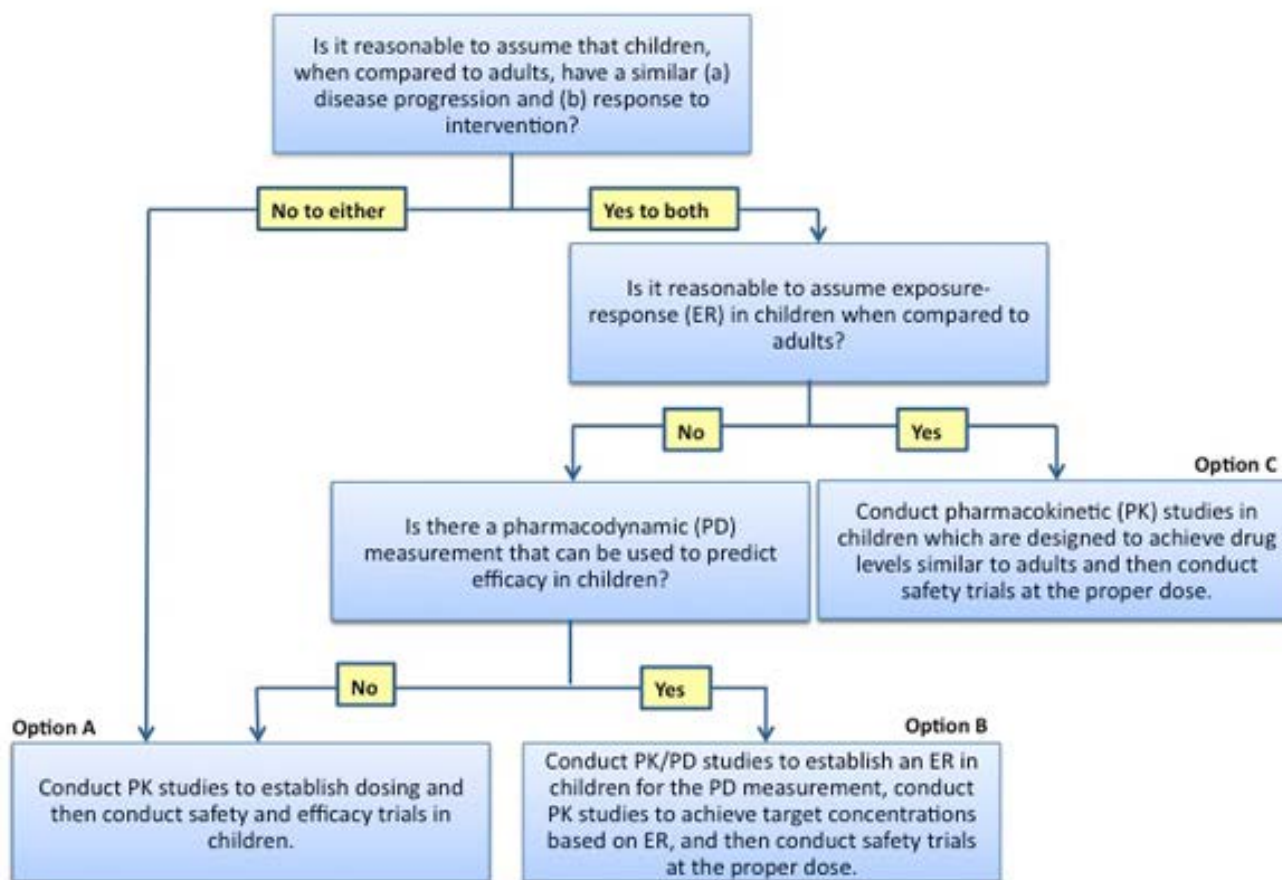
Extrapolation

21 CFR 314.55

Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.

Extrapolation Algorithm

Figure 1: FDA Pediatric Study Decision Tree

Pediatric Extrapolation

Evidence to support extrapolation

- Common pathophysiology and natural history of the disease in adult and pediatric populations
- Common drug metabolism and similar concentration-response relationships in each population
- Experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions

Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

Pediatric Extrapolation

- Possible for
  - Acute bacterial skin and skin structure infections (ABSSSI)
  - Complicated urinary tract infections (cUTI)
  - Complicated intra-abdominal infections (cIAI)
  - Hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP)
- Not possible for
  - Neonatal sepsis/meningitis
  - Invasive candidiasis

Acute Bacterial Skin and Skin Structure Infections

- ABSSSI
  - Bacterial infection of skin with lesion size of $\geq$75 cm^2
    - Includes cellulitis/erysipelas, wound infection, major cutaneous abscess
  - Predominant pathogens: *Staphylococcus aureus* (methicillin-sensitive and -resistant), *Streptococcus pyogenes*
  - Extrapolation possible; deferred PK and safety studies to age 0

Hospital-Acquired Bacterial Pneumonia/ Ventilator-Associated Bacterial Pneumonia

- HABP: acute infection of pulmonary parenchyma associated with clinical signs and symptoms (e.g., fever, chills, rigors, cough, purulent sputum, chest pain, dyspnea) accompanied by presence of new or progressive infiltrate on CXR in patient hospitalized >48 hr or developing within 7 days after discharge

- VABP: similar findings in a patient receiving mechanical ventilation via an endotracheal tube or nasotracheal tube for a minimum of 48 hr

- Predominant pathogens: Enterobacteriaceae, *Pseudomonas aeruginosa,* MRSA

- Extrapolation possible

Complicated Urinary Tract Infections

- cUTI
  - Pyuria and a documented pathogen from urine or blood accompanied by local and systemic signs and symptoms, including fever, chills, flank pain, back pain, CVA pain or tenderness, occurring in presence of functional or anatomic abnormality of urinary tract or in presence of catheterization
    - Includes pyelonephritis regardless of underlying abnormalities of urinary tract
  - Predominant pathogen: *Escherichia coli*
  - Extrapolation possible; deferred PK and safety studies to age 0

Complicated Intra-Abdominal Infections

- cIAI
    - Intra-abdominal infection extending beyond hollow viscus of origin into peritoneal space, associated with abscess formation or peritonitis
        - Includes intra-abdominal abscess, perforation of stomach or intestine, peritonitis, appendicitis with perforation or periappendiceal abscess, cholecystitis, diverticulitis with perforation, peritonitis, or abscess
        - Generally requires surgical procedure
    - Predominant pathogens: Enterobacteriaceae, anaerobes, Gram-positive; often mixed
    - Extrapolation possible; deferred PK and safety studies to age 0
    - Surgical necrotizing enterocolitis falls into this category; medical NEC requires further discussion (no adult correlate to permit extrapolation)

Neonatal Sepsis and Meningitis

- Each of the preceding infectious syndromes carries risk of CNS infection in a neonate

- No recent antibacterial development in the areas of sepsis or meningitis

- No possibility for extrapolation

- Adequate and well-controlled trials needed

Invasive Candidiasis

- Micafungin
  - Treatment of patients with esophageal candidiasis (2005)
  - Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (2005)
  - Treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses (2008)
- PREA requirement
  - Studies deferred initially
  - 2013: dosing for pediatric patients $\geq$4 months
- Neonatal candidiasis: cannot extrapolate efficacy

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=MYCAMINE

Central Nervous System Issues

- Drug penetration into CSF
  - State of blood-brain barrier
  - Presence of inflammation
  - Physical characteristics of drug
  - PK characteristics
    - Gestational age
    - Postnatal age
    - Renal maturation
    - Hepatic maturation
  - Difficulties in obtaining samples
    - Availability
    - Timing

Possible Solutions

- Animal models

- In vitro models

- Opportunistic sampling

- Master protocols and networks