Pediatric Formulation Development: Pediatric Global Regulatory Overview, Challenges, and Opportunities

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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
• Sulfanilamide is an antibiotic (drug used to treat infections) and saved many lives

• Only available in pill or powder

• Mixed with an untested chemical, diethylene glycol, to make it easier to give to children

• Elixir of Sulfanilamide introduced in September 1937

• Turns out diethylene glycol is highly toxic

• Cause 107 deaths in 15 states
Sulfanilamide Tragedy

- Congress passed the Food, Drug and Cosmetic Act on June 25, 1938
- Signed into law by Franklin D. Roosevelt
- A manufacturer of a drug must prove to FDA that their drug is safe before it can be sold
U.S. Pediatric Drug Development Laws

• **Best Pharmaceuticals for Children Act (BPCA)**
  – 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)**
  – Requires companies to assess safety and effectiveness of certain products in pediatric patients

• **Studies are completed using appropriate formulations**
EU Paediatric Regulation

- Includes similar provisions for incentives and requirements to conduct pediatric studies
- Article 15 requires any measures to adapt the formulation of the medicinal product to be age-appropriate in different subsets of the paediatric populations in the paediatric investigation plan (PIP)
General Approach to Pediatric Product Development

• Evaluate all possible indications based on the mechanism of action of product
  – Literature review, data from other development programs, proof of concept studies, etc.

• Consultation with pediatric experts to assess each indication

• Determine what data would be needed to initiate studies in pediatrics
  – Is there a potential for developmental toxicities that may require juvenile animal studies?
  – Are there additional adult human data?
  – Will a different formulation for use in pediatrics be needed?
General Considerations in Pediatric Formulation Development

- **Route of administration**
  - Oral and Intravenous
  - Oromucosal, nasal, Inhaled, rectal, transdermal

- **Efficacy and Safety**
  - Dosage forms are bioavailable
  - Dose allows for accuracy for all pediatric age groups
  - Dose can be easily or readily administered
  - Amount and number of excipients safe for all pediatric age groups
  - Dosage forms are stable

- **Acceptability**
  - Palatability
  - Swallowability

- **Affordability**
Newer Approaches to Oral Formulations

- **Multiparticulate drug delivery systems**
  - Granules, pellets, minitablets
  - Reduced size intended to improve ease of swallowing and increased dose flexibility
  - Stability and transportation advantages

- **Orodispersible tablets and films**
  - Swallowing of dose not required

- **Chewable formulations**
  - Swallowing aided by ability to chew

- **Use of these formulations still problematic for youngest patients**
Recent Pediatric Approvals for Novel Dosage Form

- **Adenzys XR-ODT (Amphetamine extended-release orally disintegrating tablets)**
  - Indicated for treatment of ADHD
  - Approved 1/27/2016
  - Demonstrated comparable plasma concentration profiles to amphetamine extended-release capsules
  - May be taken with or without food. Allow tablet to disintegrate in saliva then swallow

- **Narcan nasal spray**
  - Indicated for emergency treatment of known or suspected opioid overdose
  - Approved November 18, 2015
  - Instructions for use similar for adults and pediatric patients
  - Consider alternate naloxone-containing products in neonates with known or suspected exposure to maternal opioid use to avoid precipitation of opioid withdrawal symptoms
Ongoing Global Efforts

- NIH/FDA
- Inter-Agency Agreement for Pediatric Formulations Platform in 2009
  - Assessment of pediatric product formulations
  - Open-source, publicly available approach to pediatric oral formulations manufacturing
Ongoing Global Efforts

- **World Health Organization** "Make medicines child size"
  - Development of paediatric medicines: points to consider in pharmaceutical formulation, 2012
  - Inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Its focus is on the conditions and needs in developing countries.
    

- **International Conference on Harmonization (ICH)**
  - Addendum to E11 guideline: Clinical Investigation of Medicinal Products in the Pediatric Population
  - Includes update on considerations related to development of pediatric formulations
Challenges and Opportunities

- **Neonates**
  - Special considerations include limitations on volume, compatibility, excipients

- **Novel technologies for improving solubility and permeability with safe excipients**
  - Requires efforts from chemists, clinical pharmacologists, toxicologists, engineers, and patients/caregivers
Challenges and Opportunities

• **Long-term safety**
  – Additional data on long-term safety not limited to the active ingredients but also on excipients

• **Evidence-based acceptability and adherence**
  – Patient and prescriber feedback on performance of novel formulations

• **Sharing of information/Collaboration**
  – Clinical trial networks and pre-market collaboration may also improve speed/efficiency of development of age-appropriate formulations
Thank you