



PQRI WORKSHOP
MIDD Approaches in Pediatric Formulation
Development



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ADMINISTRATION

Current Trends and Experience with the Development of New Pediatric Drugs after the Implementation of Regulations: Regulatory Perspective

Lynne Yao, M.D.

Director, Division of Pediatrics and Maternal Health

Office of New Drugs

Center for Drug Evaluation and Research

U.S. FDA



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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

Incorporation of regulatory standards into pediatric clinical research strengthens the quality of the research

From FDA guidance to industry titled *E11(R1)- Clinical Investigation of Medicinal Products in the Pediatric Population*, December 2017

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 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

PREA

- Drugs and biologics
- Required studies
- Studies may only be required for approved indication(s)
- Products with orphan designation are exempt from requirements except molecular targets relevant to pediatric cancers
- 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

Formulation Development under PREA and BPCA



PREA

BPCA

Must conduct necessary studies using an age-appropriate formulation for each proposed age group

If there is not an age-appropriate formulation available, the Sponsor must develop and test one

Partial waiver available if reasonable attempts to produce a pediatric formulation have failed; documentation from the applicant will be posted on the FDA website

If formulation development fails, the sponsor must document attempts to develop and reasons for failure

An initial Pediatric Study Plan must be submitted by End of Phase 2, including a section outlining pediatric formulation development

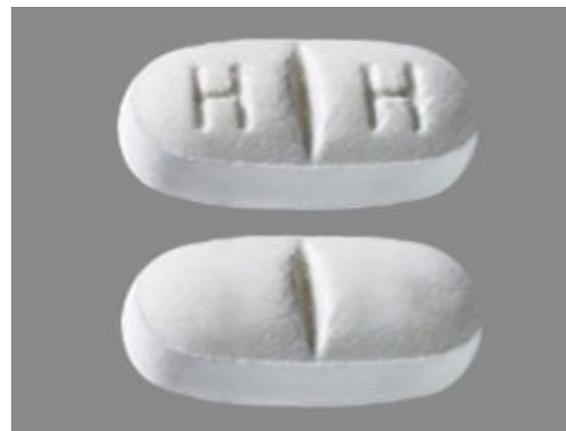
If approved, the pediatric formulation must be marketed within 1 year of approval

Pediatric Formulations: Realities

- Meropenem 500mg Vial (Single-dose vials)
 - Dose for premature neonate born at 32 weeks and post natal age less than 2 weeks (3kg):
 $20\text{mg/kg} = 60\text{ mg}$



- Hydroxurea 100 and 1000 mg film coated tablets
 - For patients who are not able to swallow the tablets, these can be dispersed immediately before use in a small quantity of water in a teaspoon
 - Dose for 2 year old with sickle-cell anemia (11 kg): $20\text{mg/kg} = 220\text{ mg}$



Pediatric Formulation Development

- Safety of Excipients
- Patient acceptability
 - Can lead to compliance issues that may have clinical consequences
- Pediatric-specific considerations

Excipients: Pediatric Safety Considerations

- Similar to safety concerns of the active ingredient
- Excipients may have differential safety compared to adults
- Considerations for choice of excipients in pediatric formulations
 - Dosage form
 - Age of patient
 - Development and maturation of metabolic pathways
 - Expected duration of treatment
 - Allergies and sensitization

Excipient Safety

- Safety and Toxicity of Excipients for Paediatrics (STEP) Database
 - Created in cooperation with European and US Pediatric Formulation Initiatives
 - Free and publicly accessible evidence base for safety and toxicity of excipients
 - <https://step-db.ucl.ac.uk/eupfi/appDirectLink.do?appFlag=login>

Patient Acceptability

- Many factors affect patient acceptability
 - palatability, swallowability (e.g. size, shape, texture)
 - complexity of the modification to be conducted by the child or its caregivers prior to administration
 - the required dose (e.g. the dosing volume, number of tablets, etc.)
 - the required dosing frequency and duration of treatment
 - the selected administration device
 - the primary and secondary container closure system
 - the actual mode of administration to the child and any related pain or discomfort
- No harmonized standards to evaluate acceptability
- EMA has issued guidance: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/paediatric-medicines-research-and-development/paediatric-investigation-plans/paediatric-formulations>
- FDA does not have specific guidance

Formulation Considerations: initial Pediatric Study Plan (iPSP)

- Details about pediatric-specific formulation development
- Plan must include development of age-appropriate formulations for all pediatric age groups studied
 - Type of formulation
 - Type and quantity of excipients
 - Acceptability (e.g., swallowability, palatability, etc.)
 - Ease of administration
 - Stability

General Approach to Development of Age-Appropriate Formulations

- Questions to be addressed
 - Is the formulation based on its intended use in the pediatric population?
 - Is the strength or concentration of the formulation appropriate for doses needed in all pediatric populations?
 - Are there any safety issues related to delivery or route of administration for all pediatric populations?
 - For oral formulations, are there palatability or swallowability issues?
 - For devices, is there a need for human factors validations testing?
 - For injectables, are there issues related to single or multi-dose presentations?
Are there needle-size or infusion rate issues?
- Often requires multidisciplinary input

Trends in Pediatric Oral Formulation Development

- Ideal Oral Dosage Form
 - Tasteless/taste-masked
 - Minimal excipients
 - Flexible dosage increments
 - Orally dissolvable/easy to swallow/dissolvable in small amounts of liquid
 - Heat, humidity, and light stable

Traditional Pediatric Dosage Forms

Powders/granules/capsules	<ul style="list-style-type: none"> • are usually given with semisolid food or beverage • risk of aspiration and choking • administration may require a measuring device • poor palatability
Orodispersible tablets	<ul style="list-style-type: none"> • risk of direct swallowing • may be dispersed in food and beverage • no dose flexibility • less stable than normal tablets
Suspensions	<ul style="list-style-type: none"> • critical product quality attributes • easy re-suspension with moderate shaking is required
Syrups	<ul style="list-style-type: none"> • need to be preserved • measuring device needed • taste masking requirements
Oral drops	<ul style="list-style-type: none"> • risk of counting the incorrect number of drops • alternative measuring devices are needed when the dose comprises more than 10 drops
Cutaneous/transdermal preparations	<ul style="list-style-type: none"> • developmental changes in barrier function should be taken into consideration • use of penetration enhancer potentially harmful • the size and shape of transdermal patches and medicated plasters should be tailored to the child body
Suppositories	<ul style="list-style-type: none"> • limited bioavailability • accidental expulsion by defecation • lower compliance

Novel Oral Dosage Forms

- Orodispersible tablets
 - No dose flexibility; less stable than normal tablets; risk of direct swallowing
- Oro-dispersible mini-tablets
 - Generally considered ≤ 3 mm
 - Allows for flexible dosing and improved stability
 - Improved reproducibility compared to granules and pellets
 - Successfully administered in young infants (≤ 2 mm)
- Micro-tablets
 - 1.2-1.5 mm
- Orodispersible Films
 - No Dose flexibility
 - Acceptability assessed down to neonates
 - Rapid dissolution times



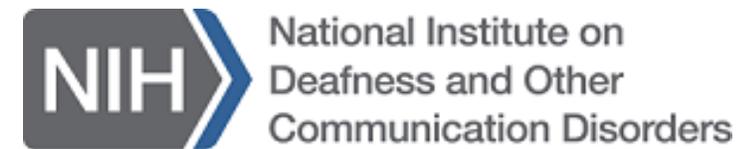
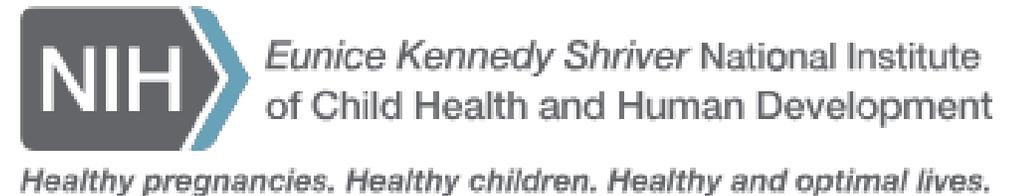
Sundarkumar V, et al.,
<https://doi.org/10.1016/j.ijpharm.2023.123355>



Klingmann V, et al.,
<https://doi.org/10.1016/j.ejpb.2020.03.018>

Global Collaborations and Consortia

- European Paediatric Formulation Initiative (EuPFI)
- WHO Global Accelerator for Paediatric Formulations Network (GAP-f)
- NIH
- IQ Consortium
- And Many Others



Summary

- Pediatric patients deserve to have medicines that have been appropriately evaluated, and that can be safely and accurately administered
- Formulation development should be considered early in overall product development to avoid delays in pediatric product development
- Novel oral dosage forms may offer advantages
- Global collaborations are important to consider needs of children throughout the world

Thank you