PQRI WORKSHOP

MIDD Approaches in Pediatric Formulation Development

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Overview: Challenges in Pediatric Drug Product Development and Potential for Using Biorelevant Dissolution Testing

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A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Content

- **Pediatric drug product development**

  - ➢ Physiological considerations

  - ➢ Formulation considerations

  - ➢ Biopharmaceutical considerations

  - ➢ Regulatory considerations

- **Biorelevant dissolution testing**

- **Current landscape**

Pediatric drug product development

- In previous decades, the development of pediatric drug products was predominantly guided by advancements in adult drug product's development:

  - The process is beneficial for diseases occurring in both adults and children.
  - Concern for pediatric specific diseases.

- Need for drug products appropriate for pediatric administration.

- Prevalent "off-label" use for drug products in pediatric population, particularly among newborns.

Pediatric drug product development Cont..

- Children are not just small size adults; Drug products development should be tailored to pediatric population.

- Drug performance and clinical effects may vary for different pediatric subgroups.

- Lack of or insufficient safety and effectiveness information in the labeling of some drug products indicated for pediatric use.

Pediatric subgroups

Several age classifications for the purpose of drug development:

- **Preterm newborn infants (<27 days)**: *Small blood volume, immature CNS*

- **Newborn (0 to 27 days):** *BBB is not mature, unpredictable oral absorption*

- **Infants and toddlers (28 days to 23 months):** *CNS, immunity, and body development*

- **Children (2 to 11 years):** *Physical growth, onset of puberty, mature drug clearance*

- **Adolescents (12 to 16-18 years):** *Sexual maturation, hormonal changes (male vs female), very rapid growth stages*

Pediatric Drug product development considerations

- Physiological considerations

- Formulation considerations

- Biopharmaceutical considerations

- Regulatory considerations

Physiological considerations

Physiological and anatomical changes throughout childhood:

- Gastric pH and gastric volume

- Gastric emptying and intestinal transit time

- Intestinal surface area and permeability

- Bile secretion

- Drug transporters

Formulation considerations

Developing formulations/dosage forms suitable for different pediatric age groups:

- Solutions

- Suspensions or powders/granules/tablets for suspension

- Chewable tablets/Gummies

- Tablets

- Films

- Effervescent granules

Formulation considerations cont..

Specific considerations related to dosage forms:

- Oral tablets: Ease of swallowing; size and shape

- Oral liquids: Palatability, taste masking

- Chewable tablets: Organoleptic properties

- Reconstituted products: Ease of reconstitution procedure to avoid errors

- Choice of excipients and toxicity

Biopharmaceutical considerations

- **Pediatric biopharmaceutical considerations:**

  - ➢ Dosing and administration - Infants to teens

  - ➢ Age-appropriate gastric volume, fluid content, etc.

  - ➢ Development of biorelevant and routine-QC dissolution testing

  - ➢ Bridging throughout pediatric drug product's development

  - ➢ Biowaiver requests for pediatric drug products

- **In Silico Modeling:**

  - ➢ PBPK models to predict in vivo drug product behavior considering age, weight, and physiological changes.

  - ➢ PBBM to support pediatric drug development, formulation selection, dissolution method development & acceptance criteria selection, product's quality throughout life-cycle, etc.

Regulatory considerations

- Pediatric Research Equity Act (PREA): **Requires** assessment of safety and efficacy of new drugs/biologics in pediatric patients.

- Best Pharmaceuticals for Children Act (BPCA): Provides a financial incentive to **voluntarily** conduct pediatric studies.

- Title V of FDA Safety and Innovation Act (FDASIA)

- Creating Hope Act (CHA): Priority review vouchers (**PRVs**) for developing drug products for rare pediatric disease.

Biorelevant dissolution testing

- Dissolution is a powerful tool to predict oral absorption and for decades has been a cornerstone test in ensuring the quality of drug products.

- The dissolution test has emerged as a pivotal screening tool for formulations in the early stages of development.

- Plethora of biorelevant dissolution tests has surfaced to support the development and approval of drug products for adults.

Biorelevant dissolution testing for Pediatrics

- The concept of biorelevant dissolution tests for pediatric dosage forms is emerging.

- Continuous physiological and anatomical changes throughout childhood underscore the challenge of relying on a single test as a truly biorelevant dissolution test.

- There is a crucial need for the development of age-appropriate biorelevant dissolution methods that also can be used for QC dissolution testing.

In Vitro Biopharmaceutical factors for In Silico modeling

- Maturation changes significantly impact pediatric gastrointestinal fluids, particularly in newborns and young infants.

- Age-related changes in media composition influence drug solubility and dissolution; particularly for poorly water-soluble drugs.

- The use of age-appropriate biorelevant media in dissolution experiments can enhance predictive accuracy.

- Dissolution medium: Milk (newborns, infants) or buffer, Pepsin concentrations, pH, bile salt concentration.

In Vivo Biopharmaceutical factors for In Silico modeling

- The disintegration and dissolution of a dosage form are influenced by **GI volume.**

- The absorption window for the drug is determined by **GI transit times and motility.**

- The extent of drug absorption relies on the **intestinal surface area and permeability.**

- Patient age influences the variability in drug **metabolism and elimination.**

- Pediatric subgroups exhibit variations in both the type of food and feeding schedules.

Case Study: Carbamazepine (CBZ)[1]

Purpose: To investigate impact of GI volume and bile salt concentration on dissolution profiles of CBZ IR tablets and their integration in PBPK models.

- Dissolution profiles in 50-900 mL adult FaSSGF and FaSSIF and 200 mL pediatric FaSSGF and FaSSIF were generated.

- PBPK models: 500 mL of adult FaSSGF and FaSSIF and 200 mL pediatric FaSSGF and FaSSIF resulted in most predictive outcomes.

- Study demonstrated that biorelevant dissolution testing can predict the PK profile of a poorly soluble drug in adults and pediatric population.

[1]Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: A Carbamazepine Case Study, The AAPS journal, 2023

Current Landscape

- Pediatric drug product development is crucial to address the unique needs and characteristics of children; Special considerations are required to develop pediatric drug products.

- Regulators have provided framework and incentives to encourage pediatric drug product development.

- Examples of age-appropriate biorelevant dissolution testing are beginning to surface in the literature.

Current Landscape cont..

- Biorelevant dissolution testing in pediatric drug development shows promise and can be a valuable tool in PBPK/PBBM simulations and QC testing.

- Developing dependable methodologies to forecast the performance of pediatric drug products can provide substantial benefits.

- The development of predictive biorelevant dissolution tests for pediatrics is still a work in progress.

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Thank you !

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