U.S. FOOD & DRUG ADMINISTRATION

GENERAL APPROACH TO THE SAFETY REVIEW OF PEDIATRIC EXCIPIENTS

Presented by:
Amrita Ghosh, MD, PhD
Lead Physician

Office of Safety and Clinical Evaluation,
Division of Clinical Review

December 6, 2022

Office of Safety and Clinical Evaluation
Division of Clinical Review

Disclosure Statement

- I have no financial relationships to disclose relating to this presentation
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

General Background

- **Excipient:** Any inactive ingredient *intentionally added* to therapeutic/diagnostic products that are present in the ("to be marketed") drug product
  1) not intended to exert therapeutic effect at intended dosage
  2) may be used to improve product delivery (e.g., enhance absorption or control release of drug substance)

- In general, Applicants must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product. (21 CFR 314.94(a)(9)(ii))

Safety Considerations

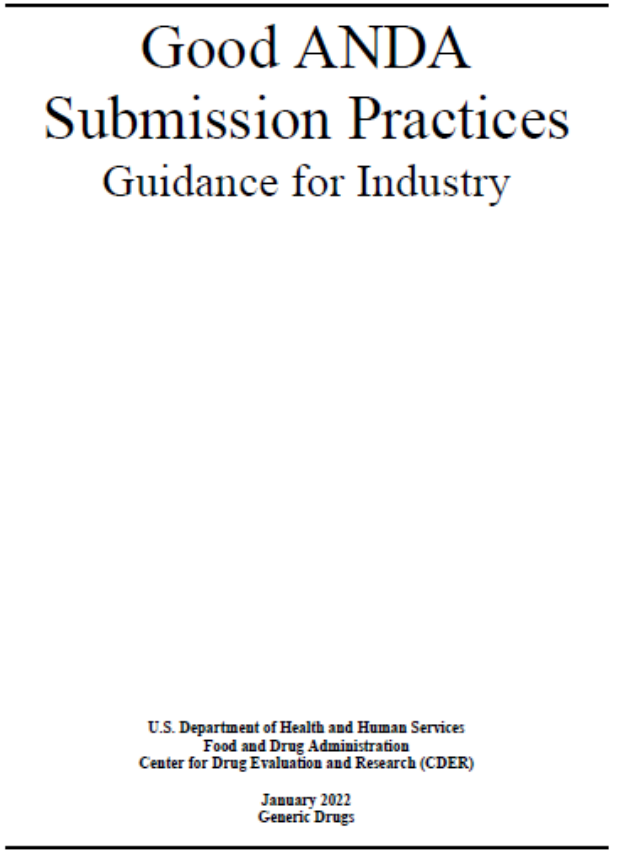
- Commonly used excipients in adults may not be commonly used in pediatric formulations
  - Acceptable levels in adult formulations do not always guarantee acceptable levels for pediatric formulations
  - Maximum daily exposure in pediatric formulations is not always evident in the Inactive Ingredient Database (IID)
- Some excipients that are commonly used in adults have been associated with risks in children
  - Toxicity may vary across pediatric age groups and between pediatric and adult populations (e.g., benzyl alcohol and derivatives, propylene glycol)

Approach to Excipient Safety Review

- *"A generic drug formulation should include inactive ingredients that have a well-defined safety profile for the proposed context of use (i.e., dose, route of administration, duration of use, and patient population) and maintain the same safety profile as the RLD."**

- Risk-based approach, considering the principles of **Context of Use**:
  1. The route of administration and dosage form
  2. Level and duration of exposure
  3. Patient population

- Proposed levels may be acceptable, even if the excipient ***is not present*** or has ***higher*** levels than in the RLD, providing levels are comparable to an approved product with comparable context of use



https://www.fda.gov/media/110689/download

*RLD = Reference Listed Drug

Safety Review of Pediatric Excipients

GENERAL PRINCIPLES

Principle 1: Route of Administration and Dosage Form Should Be Similar

- Compare oral products to FDA-approved oral products, parenteral products to approved parenteral products, etc.
  - Excipients used in an FDA-approved drug product for a particular route of administration can generally be considered safe for use in a similar manner for a similar type of product

- The dosage form (e.g., gum, lozenge, orally disintegrating tablet, sublingual film) should be similar to ensure that the safety assessment is based on appropriate comparisons.
  - Important to consider children's ability to swallow the drug product (i.e., tablet or capsule)

- In some limited instances, a different route of administration or dosage form may be used to establish safety.

Principle 2: Level and Duration of Exposure Should Be Similar

- Levels of excipients established for adult use may affect children differently
  - Knowledge of age-related differences in absorption, distribution, metabolism, and elimination may inform the acceptability of excipient levels.

- Duration of treatment is defined as:
  - Acute: treatment consisting of a single dose or lasting for a few days (short-term)
  - Intermediate: clinical use of more than 2 weeks but less than or equal to 3 months
  - Chronic: repeated intermittent use lasting longer than 6 months (long-term)

https://www.fda.gov/media/72260/download
https://www.fda.gov/media/71650/download

Principle 3: Patient Population Should Be Similar

- Children should not be considered little adults, nor should they be evaluated as a single group.
  - Due to physiological and pharmacokinetic differences, toxicities may be different in pediatric patients as compared to adults, as well as within pediatric subpopulations (neonates, infants, children, and adolescents)
- Population at risk should be similar
  - Consider whether the intended patient population is at increased risk for the known adverse events (e.g., premature and newborn infants have delayed liver maturation and may be at increased risk of toxicity when exposed to high levels of benzyl alcohol)

Principle 3: Patient Population Should Be Similar

- The conditions treated by each product should be similar
  - common pediatric conditions vs. rare or life-threatening illnesses
- Must consider the disease or condition the drug will treat, prevent, cure, or mitigate
- Example:
  - A drug used for the treatment of a rare or life-threatening infection where few other treatment options exist may not be an appropriate drug to justify a product intended for the treatment of a more common infection.

APPROACH TO PEDIATRIC EXCIPIENTS

Excipients With Known Toxicities

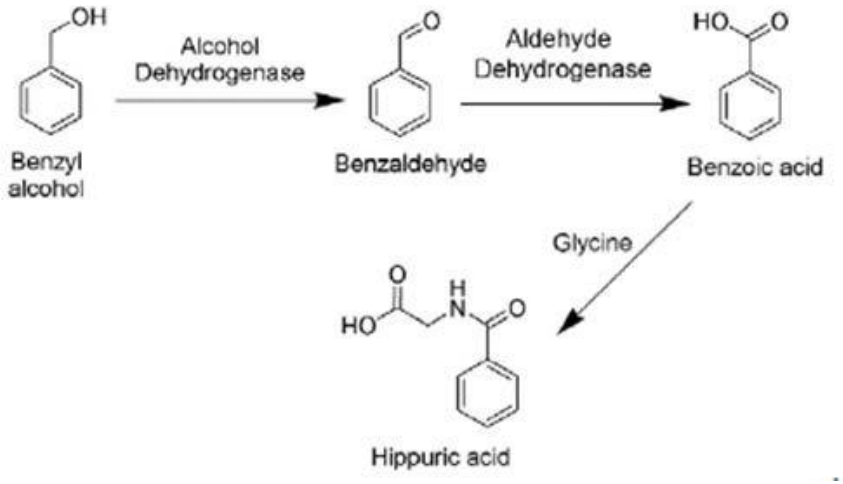
Excipients	Major Use	Toxicity	References
Parabens (propyl, methyl)	Preservative	Hyperbilirubinemia, skin sensitization and cross-sensitization	[31,33]
Benzyl alcohol	Preservative	Respiratory spasm, hemorrhage, metabolic acidosis, cerebral palsy, hypotension, bradycardia, cardiovascular collapse, convulsions and paralysis	[2,24,35]
Benzalkonium chloride	Preservative	Bronchospasm	[4]
Sodium benzoate	Preservative	Urticarial, atopic dermatitis and jaundice	[24,33,37]
Thiomersal	Preservative	Childhood autism and hypersensitivity	[36]
Ethanol	Solvent	CNS depression, confusion, GI upset and hepatorenal dysfunction	[2,24,34,39]
Propylene glycol and PEG	Solvent	Hypotension, arrhythmia, hemolysis, lactic acidosis depression of the central nervous system, laxative effects, contact dermatitis, serum hyperosmolality and decreased whole gut transit time	[2,23,27,31]
Glycerol	Solvent	Mucositis, diarrhea, electrolyte disturbances, headache and stomach upset and decrease drug absorption	[33]
Peanut Oil	Solvent	Hypersensitivity	[2,36]
Sulfites	Antioxidant	Dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhea to life-threatening anaphylactic and asthmatic reactions	[33,47]

Belayneh, A., Tadese, E., & Molla, F. (2020). Safety and Biopharmaceutical Challenges of Excipients in Off-Label Pediatric Formulations. International journal of general medicine, 13, 1051–1066.

List is not exhaustive

Benzyl Alcohol and Derivatives

- Metabolic enzymes are immature in neonates and infants
- Metabolites may displace bilirubin from albumin leading to hyperbilirubinemia, bilirubin encephalopathy, and kernicterus
- Benzyl alcohol metabolite build up has been linked to “gasping baby syndrome” and death in preterm neonates and low birth weight infants
  - Adverse events reported in children up to age 6
- FDA has not established a safe level for pediatric populations



Assessment of Benzyl Alcohol and Benzyl derivates

- Benzyl alcohol (BA) may be acceptable if the levels are similar to an FDA-approved product with similar context of use

- Each benzyl derivative should be assessed individually

- If the RLD was reformulated to a benzyl alcohol-free formulation, the proposed generic product may contain benzyl alcohol if the reformulation was NOT for product-specific safety issues.

Case Study

- Illustrating concepts of risk-based approach to Context of use
- Proposed generic Drug A oral solution
  - Is indicated in pediatric population in common illnesses
  - Has benzoic acid as an excipient AND benzyl alcohol in the flavoring
- RLD (withdrawn not for S/E) has less benzoic acid and it is not clear if the RLD flavor contains benzyl alcohol

Case Study

- During review,
  - FDA-approved Drug B and Drug C are indicated in pediatrics
  - Drug B has a higher level of benzyl alcohol. Can proposed level of benzyl alcohol be justified using Drug B?
  - Drug C has a higher level of benzoic acid. Can proposed level of benzoic acid be justified using Drug C?
  - Let's explore these justifications

Context of Use: Similar Safety Profile

For **benzyl alcohol:**

- Drug B is indicated for common illnesses and has 1-3 in common with Drug A:
  - (1) route of administration is oral
  - (2) duration of exposure is acute
  - (3) used in pediatric patients
    - Similar conditions treated

Context of Use: Similar Safety Profile

For **benzoic acid:**

- In *adults*, Drug C has 1-3 in common with Drug A
  - (1) route of administration is oral, (2) duration of exposure is acute, and (3) similar population and conditions treated
- In *pediatrics*, Drug C has 1-2 in common with Drug A
  - (1) route of administration is oral, (2) duration of exposure is acute
  - Indications for Drug C in pediatric population are rare, serious, life-threatening infections with few treatment options
    - Different than conditions treated with Drug A

Context of Use: Similar Safety Profile

- FDA searched and found another drug, Drug D, indicated in infants, children, and adolescents for common illnesses
- Drug D has all three in common:
  - (1) route of administration is oral
  - (2) duration of exposure is acute
  - (3) used in pediatric patients for common conditions
- Drug D has *similar context of use* to the RLD
- Drug D has a higher MDE of benzoic acid; therefore, this product supports the proposed levels of benzoic acid

Context of Use: Similar Safety Profile

- Can level of benzyl alcohol be justified using Drug B and level of benzoic acid be justified using Drug C?
  - **Answer:** benzyl alcohol can be justified using Drug B but **benzoic acid cannot be justified for entire population using Drug C**
  - In pediatric population, Drug C indicated for rare, life-threatening infection with few treatment options
    - Different from Drug A
  - Alternative products (e.g., Drug D) may be able to justify level of benzoic acid

Key Takeaways

- Excipients commonly used in adults may have different risk and/or safety concerns in children
- It's important to consider the pediatric population who have safety concerns that are unlike those of adults
- Consider a risk-based approach to your excipient safety evaluation using the three principles of context of use
- Consider early communication through controlled correspondences to determine whether excipient levels may be appropriate for your proposed drug product

Thank you!