Pediatric Excipient Evaluation: BE Perspective

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SBIA Generic Drug Forum – April 11th, 2024

Learning Objectives

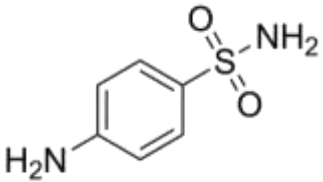
- Understand the rationale and importance of excipient safety evaluation in pediatric populations for generics
- Understand OGD's current approach for excipient evaluation in pediatric populations for generics – ANDA* submissions

*ANDA: Abbreviated New Drug Application

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

Excipient Safety

Excipient Safety



Sulfanilamide

- Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938
- Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident
- At least 107 deaths, mostly children, were linked to Elixir Sulfanilamide in this tragedy [1]

[1] https://www.sciencedirect.com/science/article/pii/B9780123694409500116

Excipient Safety

- Not all excipients are inert substances, some have been shown to have potential toxicity
- In general, applicants must identify and characterize the excipients in the proposed drug product and provide information demonstrating that the excipients (at the proposed levels) do not affect the safety or efficacy of the proposed drug product
- 21 CFR 314.94(a)(9)(ii)

FDA's Consideration for Pediatrics

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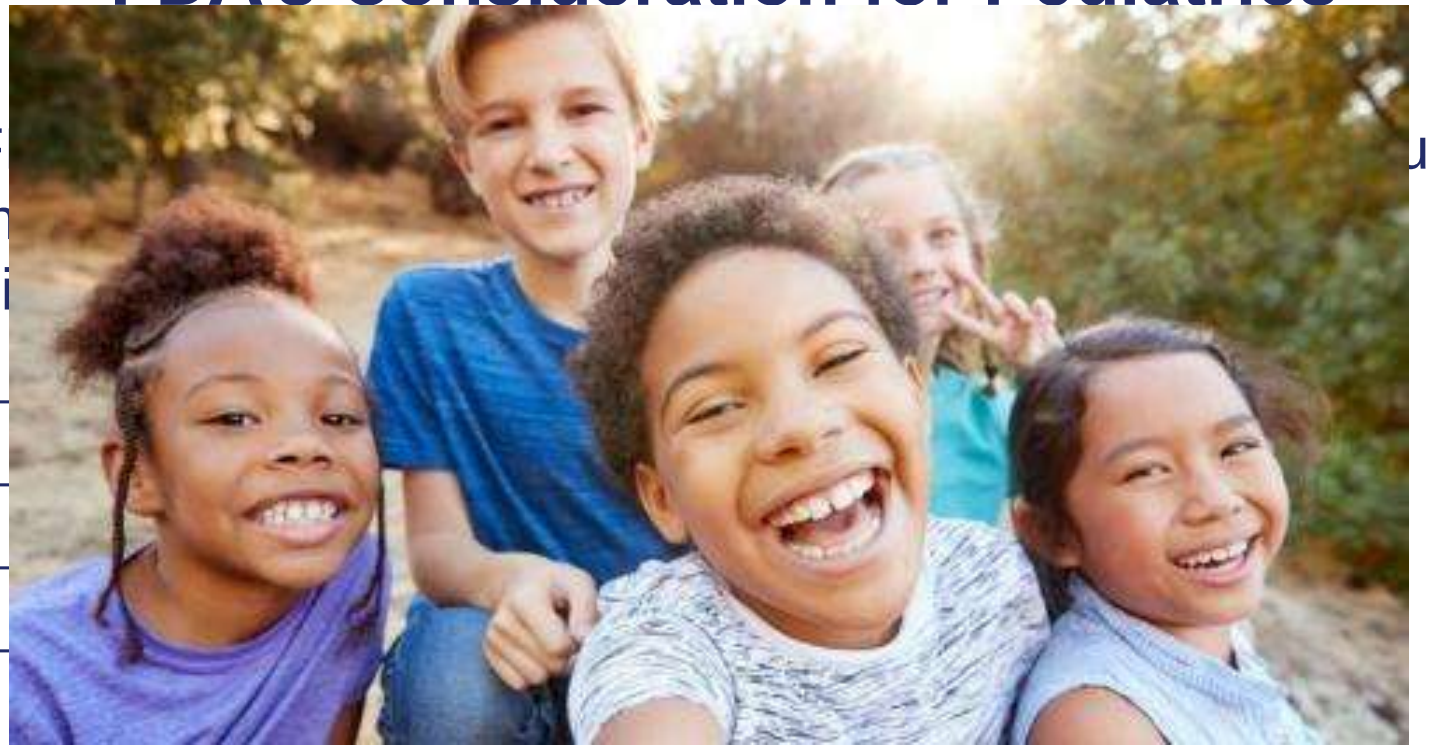

FDA Pediatrics

Pediatric Excipient Safety Evaluation

- Excipients that are commonly used in adult medications could be associated with high toxicological risks in pediatric populations

- FDA Draft Guidance for Industry, Using the Inactive Ingredient Database (IID), July 2019
  - The IID, however, does not currently provide information regarding the different exposure models, including safety in pediatric populations

Pediatric Excipient Safety Evaluation

Excipients	Major Use	Toxicity	References
Parabens [propyl, methyl]	Preservative	Hyperbilirubinemia, skin sensitization and cross-sensitization	[21,31]
Benzyl alcohol	Preservative	Respiratory spasm, hemorrhage, metabolic acidosis, cerebral palsy, hypotension, bradycardia, cardiovascular collapse, convulsions and paralysis	[4,24,35]
Benzalkonium chloride	Preservative	Bronchospasm	[5]
Sodium benzoate	Preservative	Urticaria, atopic dermatitis and jaundice	[21,33,37]
Thiomersal	Preservative	Childhood autism and hypersensitivity	[38]
Ethanol	Solvent	CNS depression, confusion, GI upset and hepatorenal dysfunction	[4,24,34,39]
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	[4,23,37,41]
Glycerol	Solvent	Mucositis, diarrhea, electrolyte disturbances, headache and stomach upset and decrease drug absorption	[42]
Peanut Oil	Solvent	Hypersensitivity	[4,36]
Sulfites	Antioxidant	Dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhea to life-threatening anaphylactic and asthmatic reactions	[21,47]
Propyl gallate	Antioxidant	Pruritus and rythema	[4,24]
Sucrose	Sweetener	Tooth decay cariogenicity, increased degradation of active drug, and allergic reactions	[47,48]
Aspartame	Sweetener	Phenylketonuria and cross-reactivity with sulfonamides	[49]
Saccharin	Sweetener	Cariogenetic and irritability, insomnia, opisthotonus and strabismus, cross-sensitivity with sulfonamides	[12]
Sucralose	Sweetener	Diabetes and cariogenic	[21,47]
Sorbitol	Sweetener	Damage of the liver, coma, abdominal pain, decreased absorption of active drug, flatulence, osmotic diarrhea	[50,24,47]
Fructose	Sweetener	Elevation in blood glucose, cause laxative effects	[4,24]
Peppermint oil	Sweetener	Atrial fibrillation, muscle pain, burning sensations	[51]
Coloring agents and dyes	Colorant	Hypersensitivity, anaphylactic reactions, angioedema, asthma, urticaria, hyperkinesis, bronchoconstriction, skin rash, photosensitization and carcinogenicity	[52,61,65]
Lactose	Filler	Severe abdominal pain, flatulence, distention or bloating, and diarrhea, joint pain and eczema, dehydration, jaundice, bacterial proliferation, and metabolic acidosis	[4,35,70]
Mannitol	Filler	Diarrhoea	[29]
Polysorbates	Surfactant	Hypersensitivity, thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis	[66,68]

Belayneh, A. et al., International Journal of General Medicine, 2020 Nov., 13, 1051–1066

Excipients with known/reported pediatric safety issues/concerns

List is not exhaustive

Pediatric Excipient Safety

- In generic drug applications (ANDAs), the recommended BE studies usually enroll adult subjects although the product may be indicated to pediatric patients
- Excipient safety evaluation in pediatrics considering safety and ethical factors for study conduct of generics
- Pediatric excipient safety evaluation is an important consideration in ANDA reviews

Challenge Question #1

If the maximum daily intake level of an excipient in the proposed generic formulation is within the 'limit' for the same excipient per FDA's Inactive Ingredient Database (IID), it will be deemed safe and acceptable for all ages (adult and pediatrics)?

A. True

B. False

Pediatric Excipient Evaluation - BE Perspective

Pediatric Excipient Evaluation

- Identical target patient population, route of administration, and recommended dose, etc.
- All excipients in proposed generic formulation are evaluated in pediatric populations if the reference listed drug (RLD) can be indicated to pediatric patients
- Excipient levels are compared with RLD formulation and approved generics for the same product

Pediatric Excipient Evaluation

- If a proposed excipient level is not justified by the RLD or approved generics, it will be compared with other approved product for the same route of administration
- Applicants' submission of supporting evidence for excipient safety will be evaluated
- Multi-disciplinary review (e.g., bioequivalence team, clinical team, toxicity team, quality team, etc.)
- The evaluation is based on maximum daily intake (MDI)
- Pediatric drugs usually have recommended doses for different age groups

Risk-Based Approach

- Evaluate safety of excipient in the youngest age group per RLD label might be acceptable
- Physiological immaturity in the youngest age group, e.g., metabolic system, gastrointestinal development, etc.
- Potentially higher risk in younger pediatrics for the same excipient comparing to adult and older pediatrics
- Swallowability consideration for solid oral dosage forms (age < 6 years old)

Case Example

The RLD is an oral tablet for chronic use in adults and pediatrics (neonates to younger than 17 years of age)

Excipient Name	Proposed unit level (mg)	Highest per unit level in RLD and approved generics (mg)	Comparison
Microcrystalline Cellulose	32.5	120	Below
Mannitol	93	60	Exceed
Magnesium Stearate	1.3	5	Below
Butylated Hydroxytoluene (BHT)	0.4	-	Exceed

Case Example (continued)

Excipient Name	Proposed MDI in Neonates (mg)	MDI Limit in Neonates (mg)	Comparison
Mannitol	233	400	Below
Butylated Hydroxytoluene (BHT)	1	-	Exceed

- BHT was not used in approved products for the same context of use (e.g., neonate group)
- The proposed BHT level was justified in pediatrics at least one month of age
- Very limited information regarding BHT safety in neonates
- Per literature, BHT may increased risk of methemoglobinemia in neonates and infants, a potentially life-threatening condition
- Collaborative review by the OB assessment team and the OSCE* clinical team

*OSCE: Office of Safety and Clinical Evaluation

Challenge Question #2

Which of the following statements is true?

A. OGD only evaluates the safety of the “riskiest” excipients in pediatric populations

B. OGD evaluates the acceptability of an excipient based on its maximum daily intake (MDI) in pediatric population(s)

C. The excipient levels in proposed generic formulation is evaluated by comparing to the RLD formulation

Considerations in Pediatric Excipient Evaluation

Note: For excipients that the proposed levels exceed the RLD or approved generics for the same product

- The excipient limit product can be given to same or younger age than the proposed generic drug
- The excipient limit product should be ‘Rx’ or ‘Discontinued not due to safety and effectiveness reasons’
- Context of use of the excipient limit product should be similar to the proposed generic drug

Considerations in Pediatric Excipient Evaluation

- Context of use
  - Route of administration
  - Duration of treatment: excipient limit in an acute treatment drug can’t be used to support proposed level of the same excipient for a long-term treatment product
  - Example: a positron emission tomography (PET) imaging agent vs a supplemental hormone medication
  - Considerations for potential risk due to long term intake

Considerations in Pediatric Excipient Evaluation

- Severity of the indicated diseases
- Example: an anti-coughing syrup vs a chemotherapy
- Swallowability of solid oral dose form if the RLD label specifies ‘do not chew or crush’

Picture cited from OB internal training: Creator: Bruce Lerman, Team Leader, OB/DBI

Challenge Question #3

The proposed generic drug in a newly submitted ANDA is an orally dosed anti-infectious drug (adult and pediatric patients 2 years and older, recommended 4-week treatment). Which of the following previously approved product may best justify the proposed excipient levels?

A. An anti-inflammatory drug indicated for colitis in adult patients (3 months treatment period recommended)

B. A supplemental medication indicated to adult and pediatric patients (birth to younger than 17 years of age)

C. An anticonvulsant indicated to treat seizure in adult and pediatric patients (1 year of age and old) with a ‘boxed warning’ for toxicity in the RLD label

Acknowledgement

- Special thanks to Dr. Patha Roy, OB Director
- Special thanks to Dr. April C. Braddy, DBIII Director (OB)
- Special thanks to Dr. Lisa Faulcon, DCR Director (OSCE)
- Dr. Ke Ren, DBIII Deputy Director (OB)
- OB Pediatric Excipient Evaluation Working Group
- OB Pediatric Excipient Database (internal) Working Group
- OGD, OB, and OSCE management and staff

Thank You!

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