FDA's Experience and Perspective with Excipients in Regulatory Submissions

Excipient Safety Evaluation for Pediatric Drug Products

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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

Outline

- Brief Definition of Excipient
- Common Excipients of Concern
- The Inactive Ingredient Database (IID) tool for Excipient Safety Determination
- A Framework for Excipient Safety Evaluation
- Illustrative Case Studies
- Summary

What Are Excipients?

- Excipients are substances in the drug product that are not the active pharmaceutical ingredient (API).
- Excipients are not intended to exert therapeutic effects or augment the active pharmaceutical ingredient’s (API's) pharmacological action.
- Despite being 'inactive,' excipients can pose real safety risks

Selected Excipients with Pediatric Safety Concerns

Excipient	Use	Pediatric Toxicity
Benzyl Alcohol	Preservative	Metabolic acidosis, gasping syndrome, cardiovascular collapse
Glycerol	Solvent	GI upset, electrolyte disturbances, osmotic diarrhea
Propylene Glycol and PEG	Solvent	Hypotension, arrhythmia, CNS depression, lactic acidosis
Parabens	Preservative	Hyperbilirubinemia, skin sensitization
Sodium Benzoate	Preservative	Urticaria, atopic dermatitis, jaundice
Ethanol	Solvent	CNS depression, GI upset, hepatorenal dysfunction
Sorbitol	Sweetener	Liver damage, osmotic diarrhea, decreased drug absorption

Belayneh A, et al Int J Gen Med. 13: 2020.

The IID: A Useful — But Limited — Tool

- The Inactive Ingredient Database (IID) lists excipient levels in FDA-approved drug products and is a frequent tool sponsors use to justify excipient safety.
- If an excipient is listed at or above the proposed level for the same route of administration, it is generally recognized as safe (GRAS).
- Key limitation: The IID reflects the maximum excipient exposure per dose — not the maximum daily intake, treatment duration, or the age of the approved patient population.
- The IID is generally understood to reflect adult formulations and does not account for pediatric-specific risks.
- FDA guidance for Industry states that in “certain cases” Sponsors should provide evidence of safety at the proposed level “taking into consideration the context of use.”

Using the Inactive Ingredient Database
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Susan Zuk 240-402-9133.

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245
246 The IID is often used by applicants to help justify the levels of excipients in Investigational New
247 Drug Applications (INDs), NDAs, and ANDAs. An applicant may wish to use an excipient that
248 is found in the IID, but at a higher level or in a different route of administration than listed in the
249 IID. In such cases, the IID alone does not provide sufficient information to determine the safety
250 of the proposed level of the excipient, and the applicant should provide evidence of safety for the
251 excipient at the proposed level or for the proposed route of administration taking into
252 consideration the context of use (e.g., patient population, dosage, and duration of exposure). For
253 additional information on the type of data recommended for review, applicants should refer to
254 the guidance for industry on *Nonclinical Studies for the Safety Evaluation of Pharmaceutical*
255 *Excipients*.

FDA Guidance for Industry: Using the Inactive Ingredient Database 2019

Review Framework for Excipient Safety Evaluation

- FDA evidentiary standard for approval
  - Pediatric product development is held to the same standard as adults
- Products approved in children must:
  - Demonstrate substantial evidence of effectiveness for treatment of proposed indication [Food Drug and Cosmetic Act 505(d)]
  - Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)
- Developers should provide evidence of excipient safety at time of product submission
- DPMH conducts individualized benefit-risk analyses for each excipient of concern, evaluating excipient safety on a case-by-case basis

Review Framework for Excipient Safety Evaluation

- Identify and clearly define the potential safety concern
- Review Available Safety Data: Consult nonclinical and clinical data from the development program and published medical literature.
- Calculate Maximum Daily Dose (MDD): Determine the estimated maximum daily excipient dose at the 95%ile body weight per age, based on the MDD of the API in the proposed product.
- Conduct Benefit-Risk Assessment: Weigh the risks of excipient exposure against the therapeutic benefit of the drug product for the specific pediatric population.
- Assess Monitorability and Reversibility: Determine whether adverse effects can be detected early, managed clinically, and whether they are reversible.
- Monitor in Clinical Trials and Post-Market: Incorporate excipient safety into clinical trial safety assessments and implement enhanced pharmacovigilance where warranted.
- However, developers should conduct a benefit risk assessment early during drug development and prospectively generate needed safety data.

Key Factors in the Benefit–Risk Assessment

- Indication severity: Is the condition life-threatening or associated with major morbidity? Does it represent an unmet medical need?
- Availability of alternatives: Are there FDA-approved treatment options for the target population, or would excluding this product leave patients without therapy?
- Target pediatric age range: Neonates, infants, and young children have immature organ systems (GI tract, kidneys, liver) that alter excipient metabolism and increase vulnerability.
- Disease-excipient interaction: Could the underlying condition amplify known excipient toxicity? (e.g., diarrhea from glycerol leading to fluid and electrolyte abnormalities in a child with chronic kidney disease).
- Ontogeny of metabolizing enzymes: Age-related immaturity of enzymes affects how excipients and their metabolites are processed — a critical consideration for novel or high-risk excipients.

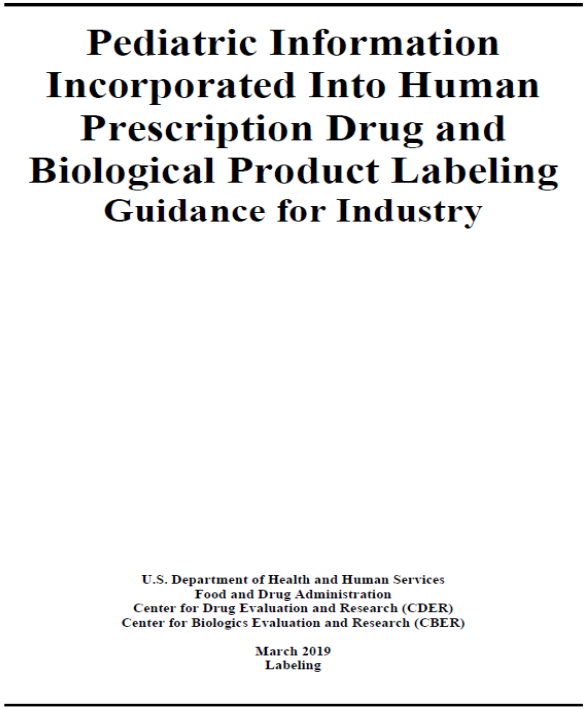
Case Example 1: Single Excipient Safety Evaluation

- **Product:** An oral liquid solution for pediatric patients from birth
- **Rationale:** Provides dosing flexibility
  - Contains a high concentration of glycerol as a dissolving agent
- **Sponsor's justification:** Cites the IID, which listed products with higher glycerol concentrations — without accounting for daily intake, patient age, or pediatric-specific risk.
- **Mechanism of concern:** Glycerol is an osmotic agent in the GI tract and systemically, it acts as an osmolar agent
- **Vulnerable population:** Neonates and infants have immature GI tracts and kidneys, limiting their ability to manage fluid and electrolyte imbalances.
- **MDD analysis:** Maximum daily glycerol dose at the 95%ile weight for age

Case Example 1: Single Excipient Safety Evaluation

- Considerations:
- Severe illness with strict fluid/electrolyte management needs (e.g., adrenal insufficiency, heart failure):
  - **Benefit-risk may NOT favor approval in neonates and infants.**
  - Approval may be recommended for older pediatric patients with more mature metabolic systems.
  - Will need to include warning language in labeling regarding fluid/electrolyte concerns in these patients and pharmacovigilance may still be required.
- **Key point:**
  - Early benefit risk assessment in the drug development cycle would allow for greater accessibility of drug products
  - Disease indication and co-morbidities must always be evaluated in conjunction with excipient exposure
  - Appropriate warning language describing the excipient content and its associated risks must be incorporated into product labeling

FDA Guidance on Labeling Information for Inactive Ingredients used for Pediatric Formulations



IV. INACTIVE INGREDIENTS

"If a drug contains one or more inactive ingredients that may be associated with a significant safety concern in pediatric patients (all pediatric patients, specific pediatric age group(s), or subgroup(s)) (e.g., benzyl alcohol toxicity in neonates or infants), the risk must be described in labeling.* The significant safety risk related to an inactive ingredient generally should be summarized in the BOXED WARNING, CONTRAINDICATIONS, and/or WARNINGS AND PRECAUTIONS section, and should also be described in the *Pediatric Use* subsection"

*21 CFR 201.57(c)(9)(iv)(H).

FDA Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products_2019

Case Example 2: Multiple Excipient Safety Evaluation

- **Product:** An oral liquid solution for pediatric patients from birth
  - Provides dosing flexibility
  - Contains propylene glycol (PG), polyethylene glycol 400 (PEG 400) and benzyl alcohol (BA)
- **Mechanism of concern:**
  - PG, PEG 400, and BA are all metabolized by alcohol dehydrogenase (ADH)
  - Saturation of ADH may result in accumulation of each excipient
    - PG toxicity includes lactic acidosis, hypoglycemia, cardiac arrhythmias, seizures, and kidney injury
    - PEG 400 toxicity may include metabolic acidosis and kidney failure
    - BA is associated with gasping syndrome in neonates
- Co-administration within the same product creates competitive metabolic interaction, raising additional safety concern when a combination of these excipients are present together.
- Likewise, concomitant administration with other products containing the same excipients compound the risk of excipient accumulation due to competition for the same metabolic pathway

Case Example 2: Multiple Excipient Safety Evaluation

- **Vulnerable population:** Neonates and young children (theoretically up to 5 years of age)
- **Benefit/Risk evaluation does not favor approval down to birth as is**
- Premarket Evaluation should address
  - Remaining knowledge gaps such as potential for systemic accumulation of PEG 400, PG, and BA in specific pediatric age range with immature metabolic systems
- Recommendation:
  - Limit product approval to >5 years of age in absence of safety data because ADH maturity close to adult activity, reducing risk of potential accumulation of metabolites
  - Include excipient information and warning language in labeling
  - Consider enhance pharmacovigilance program to monitor for systemic toxicity.
- Encourage drug developer to develop a formulation without these excipient combination at this amount and or generate prospective data to address safety concerns to avoid limiting approval in specific pediatric age range because of excipient-related safety concerns

Key Point: When a product contains multiple excipients that share the same metabolic pathway, the combined risk may be greater than the risk of any single excipient alone. Reviewers should consider excipient-excipient interactions, particularly in young children with immature enzyme systems.

Benzyl Alcohol (BA) — Background

- Benzyl alcohol (BA) is a widely used antimicrobial preservative
- In 1982, reports linked 16 neonatal deaths in neonatal intensive care units (NICU) to repeated intravenous exposure to BA-preserved bacteriostatic flush solutions
  - the 'gasping syndrome': metabolic acidosis, compensatory gasping respirations, and hemodynamic collapse.
- Root cause: Immature neonatal liver unable to metabolize BA,
- Affected infants - low birth weight (<2,500g) and moderately pre-term (<34 weeks), receiving 99–405 mg/kg/day IV.
- No comparable cases were reported in older infants, children, or adults, or by any non-IV route of administration.
- Industry and regulatory response: IV products were labeled 'not for use in newborns.'
  - BA-containing products became broadly avoided beyond the neonatal period— even when potential exposures were far below reported exposures associated with toxicity

Benzyl Alcohol — Updated Assessment

- **DPMH and Multidisciplinary Team-** Updated literature review and available evidence (2019–2022):
- **Group's conclusion:** The broad population-wide restriction on BA was not supported by available evidence and was preventing pediatric patients from accessing needed therapies.
- **Monitorability:** early signs of BA toxicity consist of new-onset or worsening metabolic acidosis. This is a monitorable risk that can be incorporated into a pediatric clinical development program.
- DPMH suggested revised approach:
  - Labeling should precisely identify the at-risk neonatal subgroup (Sections 5 and 8.4).
  - Developers should evaluate pediatric patients outside the neonatal period, with safety monitoring — focusing on evidence of safety and not blanket exclusion.

Summary and General Principles for Excipient Safety

- Excipients require pediatric-specific safety evaluation
  - Excipients are not inherently safe across all patient populations.
- The IID is a starting point, not a safety determination
  - Sponsors must independently calculate the patient-level Maximum Daily Dose (MDD), accounting for age-related vulnerabilities, treatment duration, and route of administration.
- Evidence, not assumption, should be the standard
  - Developers should strive to collect evidence of safety during drug develoment
- Excipient evaluation should be conducted on a case-by-case benefit-risk framework
- Benefit may justify proceeding when alternatives are absent
- Labeling and pharmacovigilance are risk management tools
  - Well-designed pre-market clinical trials, targeted labeling, and post-market surveillance can address residual excipient safety uncertainty
- The regulatory goal is to provide access with appropriate safeguards

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