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Excipients in Pediatric Formulations: Evolution, Current Use, and Regulatory Considerations

Sandip Tiwari, *Ph.D.*

Head of Technical Services

BASF Pharma Solutions, NA

Disclaimer

Views and opinions expressed are those of the presenter and not necessarily those of BASF

Agenda

- Historical lessons that shaped excipient regulation
- Excipients as drug product components, not just “inactive ingredients”
- Pediatric age groups, dosage forms, and excipient challenges
- Current regulatory expectations for pediatric excipient evaluation
- Closing perspective and future direction

Excipients, FDA & Children: Historical Perspectives

Mrs. Winslow's Soothing Syrup
Medical Trade Card ~ 1886

1906

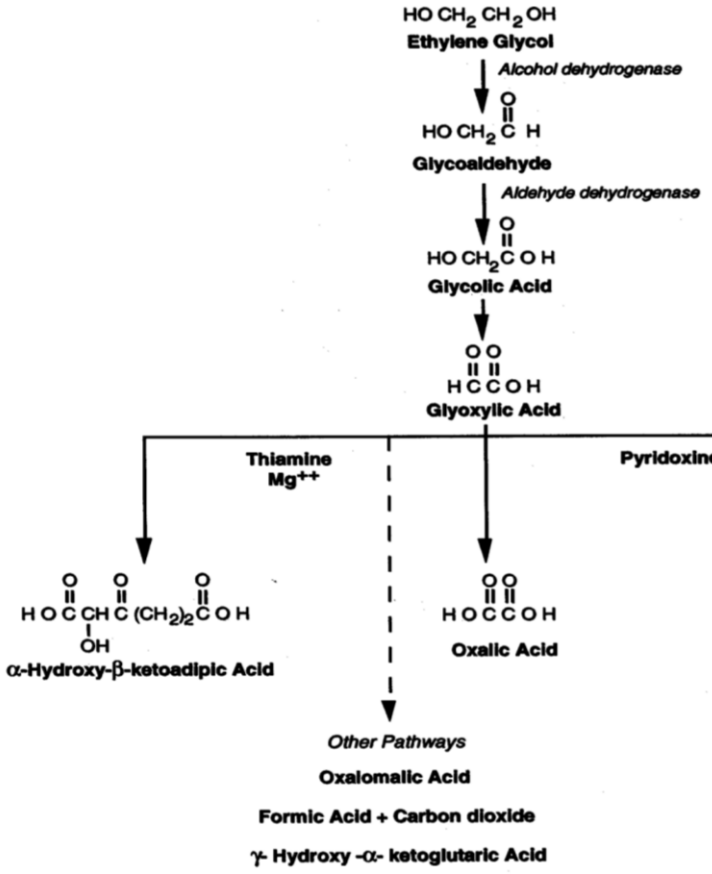
Food and Drugs Act

- Prevent **adulterated** or **misbranded** food or drugs
- Drug products required **labelling** of ingredients.

1912

Sherley Amendment

- Prohibits the labeling of medication with **false therapeutic claims**



solvent was the cause

- Laws **did not require safety** of the drugs marketed

1938

& Cosmetics Act

s shown **to be safe**

ances set for **unavoidable poisonous substances.**

- Conduct factory inspections.

Mrs. Winslow's Soothing Syrup Medical Trade Card. Source: Medical Center Archives of NewYork-Presbyterian/Weill Cornell Medicine, https://library.artstor.org/public/28305419;
Ethylene glycol metabolism pathway, ATSDR
(cdc.gov)

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Excipients, FDA & Children: Historical Perspectives

1962

The Kefauver-Harris Amendments to FD&C act

- **Inspired by the Thalidomide** tragedy in EU ~ 1950's/1960's
- **Thalidomide was not approved in the US**

- Mandated ***efficacy/ safety*** *studies*
- Control for ***clinical trials/ advert.***
- ***180 days*** to FDA

1962-2002

Pediatric Drug Development & Testing

- < 20% of drugs for use
- "Off label" use
  - Market size
  - Challenges in clinical trials
    - Children aren't small adults
    - Technical challenges
    - Ethical issues

2002-2003

1. **The Best Pharmaceuticals for Children Act (BPCA): 2002**
2. **Pediatric Research Equity Act 2003**
   - More studies in last 10 years

Mrs. Winslow's Soothing Syrup Medical Trade Card. Source: Medical Center Archives of NewYork-Presbyterian/Weill Cornell Medicine, https://library.artstor.org/public/28305419; Ethylene glycol metabolism pathway, ATSDR (cdc.gov); photo courtesy of USFDA

Why Excipients Matter More in Children

- Children are not a single population; formulation needs differ across neonates, infants, children, and adolescents.
- In pediatrics, excipients influence not only manufacturability and stability, but also swallowability, palatability, dose flexibility, and safety.
- The same excipient can be acceptable in adults yet problematic in younger pediatric populations because developmental physiology changes exposure and tolerance.

Pediatric formulation success depends not only on the API, but also on age-appropriate excipient selection.

Excipients Are Drug Product Components — Not Just "Inactive" Ingredients

- Definition from IPEC:
  - "Pharmaceutical excipients are substances other than the pharmacologically active drug or product.

- In FDA nomenclature, an excipient is also known as an "inactive ingredient" means any component other than an active ingredient."

- But more importantly, FDA considers both active ingredients and excipients/ inactive ingredients to be drug "components"- "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."

In pediatrics, this matters because excipients affect formulation performance, administration, palatability, exposure, and sometimes toxicity.

Reference: www.fda.gov

Pediatric Age Groups, Dosage Forms & Excipient Considerations

Dosage form	Preterm newborn infants	Term newborn infants (0d – 28d)	Infants and toddlers (1m-2y)	Children (pre-school) (2-5y)	Children (school) (6-11y)	Adolescents (12-16/18y)
Solution/drops	○	◒	●	●	◒	◒
Emulsion/suspension	○	◒	◒	●	◒	◒
Effervescent dosage forms	○	◒	●	●	◒	◒
Powders/multiparticulates/ mini-tablets	○	○	○	◒	◒	●
Orodispersable form	○	○	◒	◒	●	●
Chewable tablets	○	○	○	◒	●	●
Tablets	○	○	○	◒	◒	●
Capsules	○	○	○	○	◒	●

○ Not applicable or applicable with problems
◒ Acceptable/preferred
● Dosage form of choice

Source: European Medicines Agency: Reflection paper: formulations of choice for the pediatric population 28 July 2006
Strickley, R.G. et al. Pediatric Drugs – a Review of Commercially available Oral Formulations J. Pharm. Sci. 97(5) 2008 pp. 1731-1774

Key formulation considerations

- Dosage-form suitability changes with developmental stage and swallowing ability.
- Liquids are often preferred in the youngest patients, while multiparticulates, ODTs, chewables, tablets, and capsules become increasingly feasible as children mature.
- Excipient choice must support palatability, dose flexibility, administration volume, and age-appropriate safety.

Age-appropriate dosage forms require age-appropriate excipient choices.

Excipients of Concern in Pediatrics: Common Examples

- **Ethanol:** can contribute to neurotoxicity, hypoglycemia, metabolic disturbances, and should be tightly limited, especially in younger children.
- **Propylene glycol:** may accumulate in neonates and young infants because of immature metabolism and clearance.
- **Benzyl alcohol:** is associated with serious neonatal toxicity and remains a major excipient of concern in neonates and young infants.
- **Polysorbates, benzoates/preservatives, and selected sweeteners/polyols:** can also raise age-specific tolerability or exposure concerns depending on route and context.

How Pediatric Excipient Risk Is Evaluated Today

- IID alone does not establish pediatric safety
- Assessment depends on route, age group, exposure, duration, disease context, and comparator products.
- The youngest relevant subgroup often becomes the most conservative benchmark

Pediatric excipient acceptability is not binary — it must be justified by age, exposure, route, and clinical context.

Structured Pediatric Excipient Risk Assessment

- **The STEP database** was developed to compile safety and toxicity information on excipients in pediatric populations and provide easier access to relevant evidence.
- **The PERA framework and tool** provide a structured way to compare excipient options by considering patient age, product attributes, route, prior use, exposure, safety, and data gaps.
- Together, these tools reflect the field's movement toward more transparent, exposure-based, and age-specific decision-making.

These tools do not replace judgment — they make excipient selection more transparent, consistent, and defensible

Closing Perspective

- The history shows, hidden formulation risk leads to harm, harm leads to scrutiny, and scrutiny leads to stronger science and standards.
- In pediatrics, excipient selection must be justified by age, exposure, formulation need, and benefit-risk context.
- The goal now is proactive design: safer, age-appropriate formulations supported by better evidence, better tools, and better judgment.

Excipient selection in pediatrics is not a secondary detail — it is a design decision.

Thank You

Questions/ Discussion

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