M-CERSI Symposium:
Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products

Acceptability of Pediatric Formulations: Palatability and Swallowability
FDA/CDER Office of Pharmaceutical Quality
(Chemistry and Product Performance) Perspective
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Outline

Desired State
• Age-appropriate formulations for all age groups, all patients
• Are supported by methods that are sensitive, reliable and robust for optimizing pediatric formulations

Where we are
(Challenges and Opportunities for Palatability and Swallowability)
• Patient related
• Pediatric drug product attributes
• Methods
• Sharing and leveraging knowledge

Moving Forward
Converging on the next steps to reach the desired state
Drug Product Quality (Drug Product Performance)
Understanding Patient Needs and Understanding and Managing Risk - Utilizing the three principals

1) Critical knowledge for supporting drug product Performance

2) Timely access to critical knowledge for shortening time to decision and action

3) Effective collaboration and leveraging knowledge for supporting safe and efficacious use of drug products

Managed risk based on systems knowledge and understanding

Decreasing risk

Likely risk (not identified but anticipated)
Where we are--
Challenges and Opportunities

Critical knowledge* related to pediatric patients

- Patient needs and characteristics:
  - Growth/maturation stage, acute or chronic indication/treatment, influence of disease states and other factors affecting drug exposure and patient experience
- Patient response and preferences:
  - cultural, age/growth-related, likely to vary over time
- Training
  - child’s ability to learn
  - learned acceptance or rejection

*: not an exhaustive list
Critical knowledge* related to the oral pediatric dosage forms

• Age-appropriateness
• Dose accuracy and flexibility—for low doses and small volumes as well
• Size/shape/thickness appropriate for swallowing
• Drug product attributes for palatability
• Of acceptable taste, smell, texture (mouthfeel) for compliance/adherence
• If given in liquids and/or soft-foods, drug product performance is not compromised
• Formulation attributes (taste masking vs. taste concealing)

*: not an exhaustive list
Flow Chart for Making Oral Dosage Formulations

FDA Expectations for Oral Solid Dosage Forms for Pediatric Patients

• Easy to swallow
• Palatable
• Stable
• Can be dosed accurately (small volumes)
• Age-appropriate excipients (safety considerations)
• If vehicle is used for administration, liquid and/or soft food should be acceptable for use
• Suitable package for good compliance
• Clear identification when several strengths of the same product are presented
• Use/dosing instructions are clear and accessible
FDA Expectations for Liquid Formulations for Pediatric Patients

- Palatable (taste, texture, smell)
- Stable
- Proper Measuring Device
- Suitable Container/Closures
- Age-appropriate excipients (safety considerations)
- Use/dosing instructions are clear and accessible
Mouthfeel
(includes taste, smell, texture, palatability, swallowability assessments—numerous mouthfeel wheels)

Translates the drug product for the patient
- Can be performed by in vitro methods and sensory panels

Develops relationship between the product and the consumer (such as in food science)
Some methods for assessing acceptability

- Quantitative for taste-masking
  - Analytical methods (e.g. measuring drug release for screening (for bitterness), coating efficiency, monitoring stability of taste, etc.)
  - In vitro taste sensors (electronic tongue, e-tongue) and hybrid approaches
- Preference, liking assessments (questionnaires)
  - Sensory assessments in taste panels
  - Facial and/or verbal hedonic scales (various scales, including 5-, 9- or 11-point)
# Sensory Testing and Analysis

<table>
<thead>
<tr>
<th>Test for</th>
<th>Evaluators</th>
<th>Methods</th>
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<tbody>
<tr>
<td>Differences between products</td>
<td>Experienced with test methodology</td>
<td>a) Triangle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Duo-trio</td>
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<tr>
<td></td>
<td></td>
<td>c) Directional</td>
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<tr>
<td>Acceptability</td>
<td>Target consumers</td>
<td>a) Monadic</td>
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<tr>
<td></td>
<td></td>
<td>b) Paired</td>
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<tr>
<td>Preference</td>
<td>Target consumers</td>
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<tr>
<td></td>
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<td>b) Paired</td>
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<tr>
<td></td>
<td></td>
<td>c) Ranking</td>
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<tr>
<td>Descriptive analysis</td>
<td>Highly trained panel calibrated to reference</td>
<td>a) Quantitative</td>
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<tr>
<td></td>
<td>standards</td>
<td>b) Spectrum</td>
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What is the experience with palatability and swallowability studies?
From a 2013 survey on current practices in palatability and swallowability assessments—breakdown of positive responses (n=5) to organoleptic assessments—showing the type of assessments.

(total responses, n=10)

Results of a systematic literature review of assessment of palatability and swallowability of pediatric oral dosage forms

**Purpose:** to identify
1) palatability and swallowability assessment scales in clinical trials
2) any potential relationship between palatability and adherence

**Period covered:** January 2008-March 2013
**Source:** 137 citations were identified (and 102 excluded)

27 articles identified with primary clinical data on palatability (qualified for the final full-text analysis)

LA Squires et al. Ther. Innov & Reg Science. 2013, 47: 533-541
Results of a systematic literature review (continued)

Breakdown of the 27 articles:
Palatability assessment tools, n=2
Palatability only, n=19
Palatability and adherence, n=6

Findings:
• palatability assessed using two visual scales  
  (not suitable for across-study comparisons)
• Limited evidence regarding correlation between palatability and treatment adherence

LA Squires et al. Ther. Innov & Reg Science. 2013, 47: 533-541
Additional information in ClinicalTrials.gov?

Pediatric studies: 7259

Studies with results: 874

Completed pediatric & palatability study with results: 2 suspension studies

(None completed pediatric and swallowability study with results)
Study 1

Study design: Twice a day and given multiple days
Total n <20, two age groups (< 5 years old and 5-18 years of age)

Taste assessment by the older patient group (Primary outcome):
Taste scores: 5 (very good taste)--1 (very bad taste).
Results (last dose): Median (range): 4.0 (2.0 to 5.0)

Acceptability grading by parents for the younger patient group (primary outcome):
Acceptability scores: 5 (very well)--1 (very badly).
Results: Median (range) 5.0 (4.0 to 5.0)
Study 1 (Continued)

Palatability assessment by the older patient group (secondary outcome):
Palatability scores: 5 (very good), 4 (good), 3 (neither good nor bad), 2 (bad) and 1 (very bad)

Results: Median (range)
Day 1: 4.0 (3.0 to 5.0),
Day 2: 4.0 (2.0 to 5.0),
Day 3: 4.0 (2.0 to 5.0)
Study 2

- Two age cohorts (different than in Study 1)
- Patients in the older age group directly responded to the questionnaire, and the caregiver/parents responded for the younger group
- Extended dosing

Palatability Questionnaire
Q1) How Does This Medicine Taste? (5 options, 5: very good, 1: very bad)
Q2) How Does This Medicine Smell? (5 options, 5: very good, 1: very bad)
Q3) Based on Its Taste, Smell, and How it Felt in the Mouth, How Easy or Difficult Was it for You / Your Child to Take This Medicine Every Day (5 Options: very easy, easy, neither easy or difficult, difficult and very difficult)
Q4) Would You/Your Child Have Preferred This Medicine to Have Been Flavored, e.g. Fruity (3 Options: yes, no and don't mind)
Observations:

- Not many palatability and swallowability studies with methods and results are published
- Developing/making standardized methods and tools may help sharing and building on learnings, and may facilitate leveraging published acceptability (palatability, swallowability) studies.

Leveraging Opportunities

1) Mouthfeel from food science?
2) What would evidence-based palatability, swallowability assessment methods look like for pediatric oral dosage forms?
What is oral processing and mouthfeel?
Oral processing

**Rheology/tribology**
- Particle size and shape (gritty, grainy, coarse)
- Particle shape and orientation (fibrous, crystalline)
- Juiciness
- Fat content (greasy, oily)
- Creaminess
- Slipperiness (slippery, smooth, rough)
- Smoothness (smooth, rough)

**Tribology**
- Astringency

“Mouth process model” for understanding mouthfeel

Things that need to happen before swallowing:
1) degree of structure of food must be reduced below the level of plane ABCD and 2) Its degree of lubrication must have crossed planed EFGH

1: Tender juicy steak, 2: tough dry meat, 3: dry sponge cake, 4: oyster, 5: liquids

Mapping of oral breakdown

With permission from Stefan K. Baier, Ph.D. PepsiCo Research

(Modified from Hutchings & Lillford 1988)
Reducing oil, sugar, and salt

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<th>30-40%</th>
<th>&gt;70%</th>
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<td>Oil</td>
<td><img src="image1" alt="Lays Classic" /></td>
<td><img src="image2" alt="Kettle Cooked" /></td>
<td><img src="image3" alt="Baked!" /></td>
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<table>
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<th></th>
<th>Regular</th>
<th>Mid-cal 50%</th>
<th>Zero-cal</th>
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<tbody>
<tr>
<td>Sugar</td>
<td><img src="image4" alt="Pepsi" /></td>
<td><img src="image5" alt="Pepsi Next" /></td>
<td><img src="image6" alt="Pepsi O" /></td>
</tr>
</tbody>
</table>

From Stefan K. Baier, Ph.D. PepsiCo Research

Regular 25%

... while maintaining the same eating experience!

PepsiCo Proprietary
Ideas for standardizing methods and for identifying Critical Quality Attributes?

What if we could develop a “mouth process model” by age groups (taking into account various vehicles that may be used for dosing) and establish a texture target (as the red line in Slide #26) that can serve as a reference point for the study and across-study comparisons?

(Can we leverage from the food science and engineering?)
Moving Forward
(Converging for the Next Steps)

• Explore and create possibilities for developing learning and confirmatory methods and tools for palatability and swallowability assessments.

• Identify critical quality attributes for achieving the intended drug product performance (e.g. mouthfeel) and support development of best practices for age-appropriate formulations.

• Create a learning and collaborative environment for advancing pediatric formulations.
Additional References

Additional References


