M-CERSI Pediatric Workshop Session 2 and 3 Breakout Pre-work

Proposed Topics for Discussion by Session 2 Swallowability and Session 3 Palatability
Co-chairs and Presenters

Purpose

- In order to help organize and facilitate the Session 2 Swallowability and 3 Palatability Breakout Sessions for the upcoming M-CERSI Pediatric Workshop, the following topics and questions are being provided to participants for their consideration prior to the workshop
- The topics here are not intended to constrain the discussion but rather to provide some insight and opportunity for participants to consider these or similar questions related to the topics of Swallowability and Palatability. Participants are encouraged to share any comments, perspectives or potential solutions in their respective breakout discussions.
- The workshop participants will be split into smaller discussion groups and "seeded" with topics and questions. The sessions will be led by the co-chairs and designated facilitator/participants. Key discussion points will be captured for synthesis and readout post workshop and shared with registered participants. These notes will also be used by the co-chairs in creating a post workshop publication strategy.

Request to Participants

- Please come prepared to share your ideas and opinions on the topics of palatability, swallowability and the overall acceptability assessment for drug products in pediatric patients. In addition to our discussions, we plan to provide a mechanism for you to contribute your written thoughts during the workshop as well.
- Please refer to the publication reference lists. Please familiarize yourself with the content of the highlighted/bolded articles. They are provided to form a baseline level of understanding across the participants.

Swallowability Breakout Discussion Topics

- **Developing Risk-Based Strategic Approaches**
  - **What are some best approaches/practices for incorporating the following elements into a Risk Based Development Strategy and Drug Product Design?**
    - **e.g., patient age, disease state, product**
  - **What is the acceptability of using dose form manipulation in instances where the drug product may not address all potential patient needs?**
  - **Criteria for demonstrating swallowability, or any attribute that affects the acceptability of the product, will need to be established.**

Swallowability Breakout Discussion Topics

- **Product Attributes**
  - **Dose Form (Tablet) Attributes**
  - **Use of Dosing Vehicles and the effect on swallowability of solid oral dose forms**
  - **If a generally accepted correlation between a product attribute and SW can be established, does that minimize or eliminate the need to conduct additional research for a similar product?**

Note: for the breakout discussion we are using solid oral tablets as an example dose form for swallowability assessment

Swallowability
Breakout Discussion Topics

- **Methodology**
  - **Definition of Swallowable**
  - **Consistent and/or Standard approaches and tools to assessing swallowability in children**
  - **Population to be assessed**

Palatability
Breakout Discussion Topics

- **Risk-Based Strategic Approaches**
  - **What are best approaches/practices for incorporating the following elements into a Risk Based Development Strategy and Drug Product Design?**
    - **e.g., patient age, disease state, product**
  - **What is our current understanding of palatability issues and impact on adherence?**
  - **How can we leverage other tools – in vitro, e-tongue, animal data – to predict the acceptability in human population?**

Palatability
Breakout Discussion Topics

- **Product Attributes**
  - **Use of Excipients to improve palatability**
  - **Use of "After Market" Products (e.g., commercially available reconstitution media, FlavoRx system in the US)**
  - **Pediatric drug product strategies to address Palatability**
    - **e.g., taste-masking, "taste neutral", meeting heterogeneous population needs**

Palatability
Breakout Discussion Topics

- **Methodology**
  - **Definition of Palatable**
  - **Consistent and/or standard approaches and tools to evaluating Taste/Palatability in children**
  - **Population to be assessed**

Optional Detail Supporting Breakout Discussion Topics

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The following slides provide additional detail that the co-chairs and presenters for Session 2 Swallowability and Session 3 Palatability discussed in preparation for the workshop.

Swallowability Breakout Discussion Topics

- **Developing Risk-Based Strategic Approaches**
  - **What are some best approaches/practices for incorporating the following elements into a Risk Based Development Strategy and Drug Product Design?**
    - **Patient Considerations (e.g. Age, Developmental Status, Functional Limitations…)**
    - **Disease State and/or Unmet Medical Need (e.g. Severity, Duration of treatment….)**
    - **Dose Form/Product Considerations – dose form design**
  - **What is the acceptability of using dose form manipulation in instances where the drug product may not address all potential patient needs?**
    - **When is this mitigation approach acceptable?**
    - **What data are required to support these mitigations?**
    - **How does patient training and education fit into risk mitigation strategies?**
  - **Criteria for demonstrating swallowability, or any attribute that affects the acceptability of the product, will need to be established.**
    - **Should the criteria for establishing appropriate swallowability vary based on the risk assessment for individual products?**
    - **Is criteria based on ability to swallow, or on the inability to swallow or both?**

Swallowability Breakout Discussion Topics

- **Product Attributes**
  - **Dose Form (Tablet) Attributes**
    - **Which attributes of a tablet should be assessed and why?**
      - **Physical Attributes (size of tablets, shape of tablets, volume)**
      - **How would these attributes be different from minitablets / multiparticulates? (mass or volume)**
    - **Should/could a correlation between tablet size and swallowability be established as a function of patient age?**
  - **Use of Dosing Vehicles and the effect on swallowability of solid oral dose forms**
    - **How are the vehicles provided or identified and assessed?**
    - **Stability Considerations**
    - **Swallowing aides – is this acceptable as a part of the product?**
  - **If a generally accepted correlation between a product attribute and SW can be established, does that minimize or eliminate the need to conduct additional research for a similar product?**
  - **Note: for the breakout discussion we are using solid oral tablets as an example dose form for swallowability assessment**

Swallowability Breakout Discussion Topics

- **Methodology**
  - **Definition of Swallowable –**
    - **What constitutes a successful swallowing occurrence**
      - **For example - if a patient chews and swallows is that acceptable?**
    - **Is swallowability defined by how the product is designed? (e.g. IR tablet versus Chewable tablet)**
    - **Is there a time component?**
  - **Consistent and/or Standard approaches and tools to assessing swallowability in children**
    - **How can consistent methodology be created and shared?**
    - **How can foundational studies be leveraged to create or support specific criteria?**
    - **How might consistency/standardization be leveraged to create a common public database?**
  - **Population to be assessed**
    - **Size of the population to be assessed?**
    - **Leveraging data from other similar patient populations**
    - **Is use of volunteers appropriate and if so when?**
    - **Use of patients and assessing as a part of the clinical trial – is this a primary or secondary outcome of the trial?**

Other Swallowability Considerations

- **Developing Risk-Based Strategic Approaches**
  - Data Collection, Analysis and Extrapolation
    - Can data collected on swallowability from one product (or series of products) be extrapolated to create justification of acceptable swallowability for future products?
  - Timing and interaction for creating and getting feedback from regulators on these risk based strategies
    - PIP process, process in US?
  - Format for communication of risk based strategies
    - Consistent and holistic versus a string of individual elements
  - How prescriptive should sponsors be in the method of administration and how does Real World Evidence factor into that risk?
- **Product Attributes**
  - For younger children how do we assess or address the interaction between SW and PA (or other factor) that may interfere with ingestion
  - NG tube administration
- **Methodology**
  - Are healthy volunteers suitable surrogates to assess swallowability and when (or not)?
  - When do we assess patients directly versus caregiver/parent?
  - The use of Placebo products for SW
  - What are the in-vitro approaches that could be developed or used?
  - How to assess SW of a dose form in Children less than 30d old (Neonates)?
  - Potential application of animal models
  - In the clinic is this part of the CT protocol (as a primary or secondary endpoint) or is the data gathered outside the clinical protocol?
  - Can the dose be split to facilitate swallowability (e.g. take a portion of the total dose and follow with the remainder for minitablets)
    - Can scoring for IR tablets be a mitigation?

Palatability
Breakout Discussion Topics

- **Risk-Based Strategic Approaches**
  - **What are best approaches/practices for incorporating the following elements into a Risk Based Development Strategy and Drug Product Design?**
    - **Patient Considerations (e.g. Age, Developmental Status, Functional Limitations…)**
    - **Disease State and/or Unmet Medical Need (e.g. Severity, Duration of treatment….)**
    - **Dose Form/Product Considerations – dose form design**
  - **What is our current understanding of palatability issues vs adherence?**
    - **i.e. The child may not like the taste but they still take it, is that acceptable?**
  - **How can we leverage other tools – in vitro, e-tongue, animal data – to predict the acceptability in human population?**
    - **How can we use the information to guide palatability assessment design?**
    - **Can we use the information as a basis for risk assessment?**
    - **Learning Tools versus Confirmation of Palatability**

Palatability
Breakout Discussion Topics

- **Product Attributes**
  - **Use of Excipients**
    - **Regulatory acceptance of excipients, sweeteners, flavor agents to improve palatability**
      - **e.g. STEP database - a global approach?**
    - **Thoughts on using commercially available reconstitution media?**
    - **Use of "after market" products (e.g. FlavoRx in the US)**
      - **Stability of product**
  - **Pediatric Drug Products Strategies to address Palatability**
    - **How might we "remove" palatability from the problem statement?**
      - **Development of a low cost, flexible, "taste masking" technology**
      - **Effective amongst a series of compounds with varying physiochemical properties**
      - **Maintains required product performance.**
    - **What is the definition of "taste neutral"?**
      - **Is this the proper target and why or why not?**
    - **Meeting heterogeneous populations needs**
      - **How many different drug products are required to span the entire pediatric subgroups?**

Palatability
Breakout Discussion Topics

- **Methodology**
  - **Defining Palatable**
    - **What constitutes a "successful" drug product administration event?**
      - **e.g. Resistance v. Rejection v. Emesis**
    - **What is the relationship between good, preferred and palatable?**
    - **How is palatability correlated to compliance and overall acceptability?**
      - **Should we assess the long term palatability for chronic meds?**
  - **Taste/Palatability Evaluation**
    - **Can standard approaches be used to evaluate the palatability of new compounds?**
      - **How to validate the scaling method utilized with different age groups?**
      - **Role of Parent or Caregiver in assessment**
      - **Could it be done in a blinded or precompetitive fashion?**
    - **How do we differentiate the different elements of palatability – taste vs smell vs mouthfeel? Do we need to? Which is more important?**
    - **How might we utilize new facial recognition tools into palatability assessment?**

Other Palatability Topic Considerations

- **Product Attributes**
  - How do we leverage the in vitro / e-tongue / animal data to facilitate filing? How relevant is this data from a regulatory perspective?
  - Pediatric Drug Products to overcome these issues
    - Cost of developing and utilizing such a technology would need to be understood. Would forming a consortium with a specific focus on accomplishing this goal benefit all? Are there other models to achieve this?
    - A better agreement/understanding on what drug product platforms can be used for what pediatric subgroups
  - How do we address differences in cultural preferences?
  - Do we have strategy for selecting dosing vehicles? Is it possible to develop a universal dosing vehicle / reconstitution media – e.g. citrus vs mint vs chocolate to mask particular types of adverse taste such as astringency, basic bitterness, aromatics?
  - Mouthfeel is an important element of palatability – at what particle size (in conjunction with viscosity) is mouthfeel considered acceptable?
- **Methodology**
  - What preclinical and clinical tools are available and how predicative are they? For example, can trained adult taste panels be predictive of pediatric formulation selection (across multiple pediatric subgroups and regional dependent)? What is the current "gold standard" approach, and what is the 5 year vision of what this could look like?
    - How can we design taste assessment in adults to bridge / correlate to pediatrics? Can a model be developed?
  - What is the state of art in both preclinical and clinical taste evaluation?
  - What is the state of the art in taste masking and taste modifying?
  - It is known that taste is influenced by genetics. How can we account for this? How can we leverage on this?