# Considerations for Age-Appropriate Pediatric Formulations Industry Perspective

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FDA-University of Maryland CERSI Public Workshop

July 15th – 16th, 2026

# General Aspects

## Requirements

- Pediatric Investigation Plans (PIPs) in EU and Pediatric Study Plans (iPSP) in the US
- Medicines for use in children are **High quality, ethically researched and authorized appropriately.**
  - **Include taste masking**
  - **Compatibility with administration systems e.g. medical devices & stability in the presence of relevant common food and drinks.**
- Deliver a safe product that meet the pediatric demand and low environmental impact
- Pediatric Products are made available commercially

Pediatric drug development

The pediatric drug development landscape has experienced major shifts, largely in response to legislative and regulatory initiatives.

~50 to 75% rare disease affect in children

Without pediatric formulations, there is limited assurance that medicines can be safely and accurately ad ministered to children.

## Industry Perspective

- Develop medicines faster and shorter supply
- To **develop Safer, Stable and Quality products**
  - Reduce cycle approval time (below 9 years average in US)
- Patients benefits – reach every patient faster. Improve patient's quality of life

# Age-Appropriate Pediatric Formulation Design for Commercial Manufacturing

**Integrated Strategy approach** – combination of science based, risk-based approach with the aim to identify the Critical Quality Attributes (CQAs) and Control Strategy

- Define product **critical quality attributes (CQAs)**that ensure robust product and packaging
- Establish the **Quality Target Product Profile** is key focusing on route of administration, dosage form and delivery systems.

Stability, Manufacturability, Bioperformance, **Patient Acceptability,** Regulatory Compliance

# Pediatrics Patient Population needs and challenges

- Age-appropriateness medicine considerations for all age groups
  - Good mouth feel, ability of patients to take/swallow dosage form
- Provides taste masking
- Flexible and Accurate Dose and methods of administration
- Stability: chemical and physical
- Excipients
- Enhance Patient compliance


# Age-Appropriate Formulation Considerations

**Can** children take it?

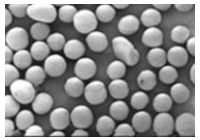
**Will** children take it?

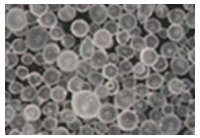
**Extra Considerations**

**Platform Technologies**

- **Dose flexibility**
- **Dose accuracy**
- **Swallowability**


Mini-tabs

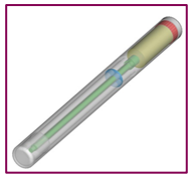

Pellets


LMPs

Others, disintegrating tablet, etc.

**And how do we package that?**

- **Dose flexibility**
- **Ease of use**
- **Supply chain considerations**


**What are the biopharm implications?**

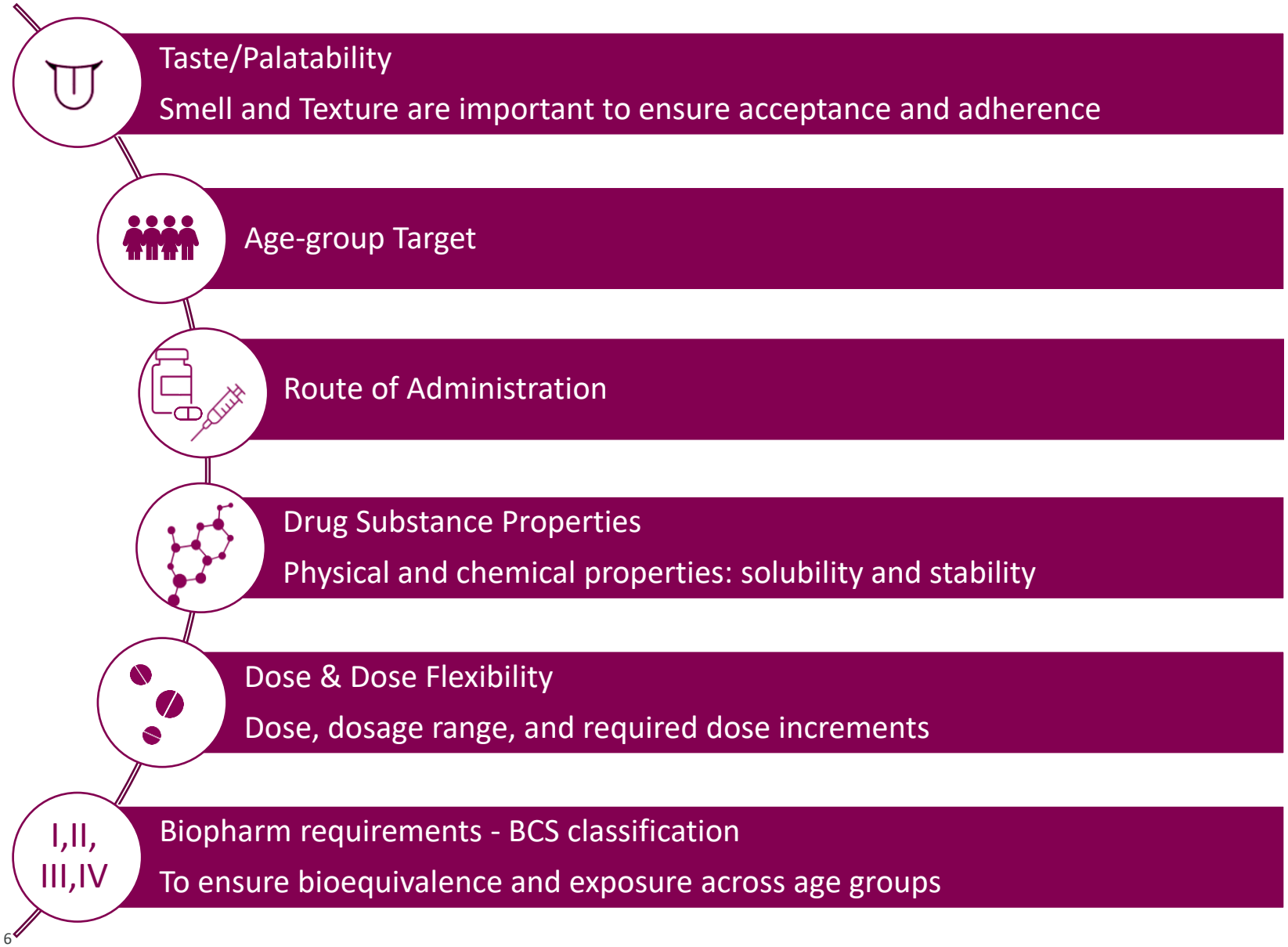
- **Paediatric in silico models**
- **Bio-relevant dissolution**
- **Impact of dosage form manipulation**

**Children are not just small adults!!**

**Is it acceptable/ palatable?**

- **Taste/mouth feel**
- **Are sweeteners and flavours allowed**
- **Compatibility with food/drink**

# Pediatric Formulation Selection Strategy

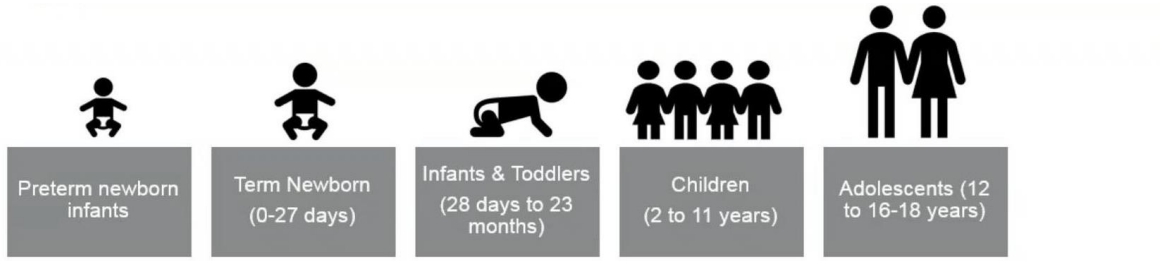



- Minimize the need for manipulation by end user
- Prevent severe dosing inaccuracies
- Minimize excipients used
- Commercially viable

# Additional Considerations

- Nasogastric and Nasojejunal tube administration - compatibility
- Ability of dosage form performance to be unaffected by variable physiology (e.g. GIT pH, transit, etc)
- **Market specific requirements, e.g. developing countries**
  - Need of potable water for constitution may be an issue
  - Reduce/Eliminate need for cold-chain storage
  - Stable in all zone 4 – all zones
  - Eliminate the need for preservatives
  - Can we utilize packaging currently available?

# Defining Pediatric Demographics: Children are a diverse population




E11 Clinical Investigation of Medicinal Products in the Pediatric Population. FDA Dec.2000

## Populations are not homogeneous miniature adults

- ICH E11 defined phases: neonates, infants, children, and adolescents
- Rapid change in body weight & body surface area
  - Size weight increases > 20-fold from birth to adulthood
  - Each stage requires specific dose adjustments and formulation strategies
- Must account for changes in swallowing ability, body surface area

## Age Related to changes in metabolism

- Delayed metabolism in the newborns e.g. trigger unexpected adverse reactions
- Need of clinical data to establish accurate dosing regimens
- Heavy reliance on advanced predictive modeling (e.g., PBPK modeling)

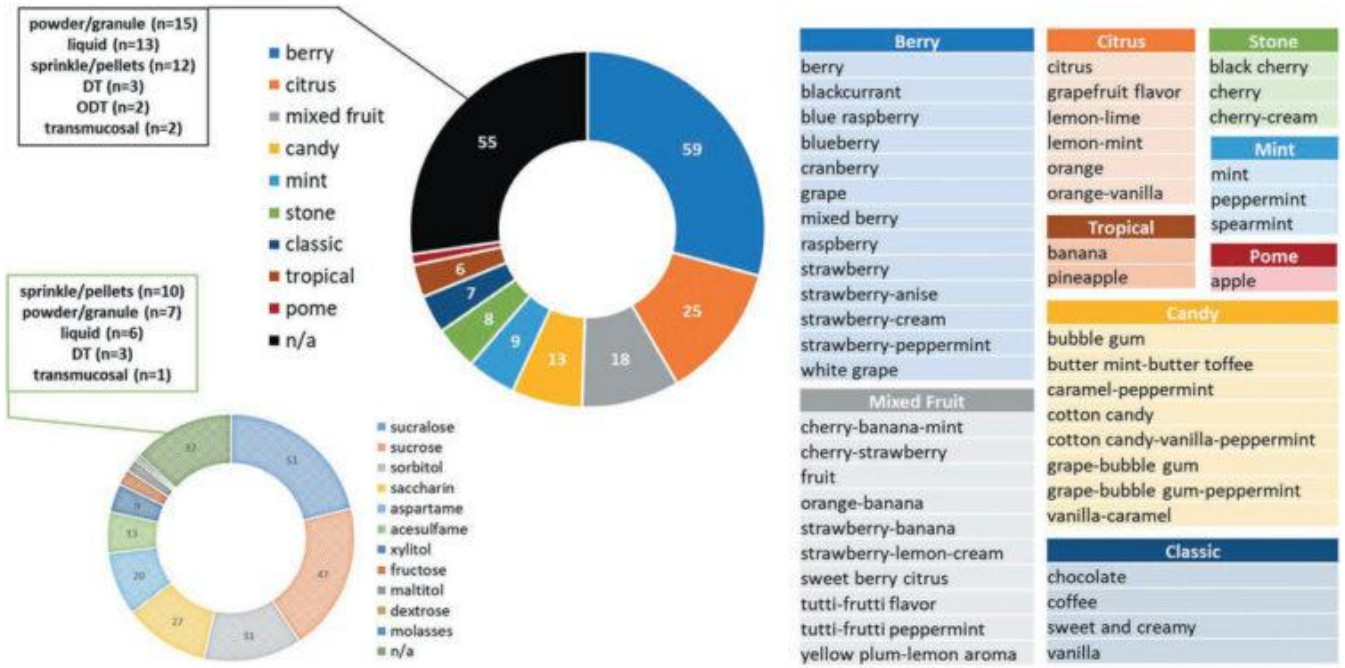
# Dosage Forms Suitable for Paediatrics

## Route of administration and dosage form vs age ranges [1]

| Route | Dosage Form | Preterm newborn infants | Term newborn infants (0-28d) | Infants and toddlers (1m-2y) | Children (pre school (2-5y) | Children (school) (6-11y) | Adolescents (12-16/18y) |
|---|---|---|---|---|---|---|---|
| PERORAL | Solution/ Drops | 2 | 4 | 5 | 5 | 4 | 4 |
| | Emulsion/ Suspension | 2 | 3 | 4 | 5 | 4 | 4 |
| | Effervescent | 2 | 4 | 5 | 5 | 4 | 4 |
| | Powders/ Multiparticulates | 1 | 2 | 2 | 4 | 4 | 5 |
| | Tablets | 1 | 1 | 1 | 3 | 4 | 5 |
| | Capsules | 1 | 1 | 1 | 2 | 4 | 5 |
| | Orodispersibles | 1 | 2 | 3 | 4 | 5 | 5 |
| | Chewable tablets | 1 | 1 | 1 | 3 | 5 | 5 |
| NASAL | Solution | 3 | 4 | 4 | 4 | 4 | 4 |
| | Semisolid | 2 | 3 | 3 | 4 | 4 | 4 |
| RECTAL | Suppositories | 4 | 5 | 5 | 4 | 3 | 2 |
| | Rectal Enema | 5 | 4 | 4 | 3 | 3 | 2 |
| | Rectal capsules | 2 | 3 | 4 | 4 | 4 | 3 |
| TOPICAL | Ointment, cream, gel | 4 | 4 | 4 | 5 | 5 | 5 |
| | Liquid | 4 | 4 | 4 | 5 | 4 | 4 |
| | Transdermal patch | 1 | 2 | 2 | 4 | 4 | 5 |
| PARENTERAL | IV solution | 5 | 4 | 4 | 4 | 4 | 3 |
| | IM | 3 | 3 | 3 | 4 | 4 | 3 |
| | SC | 4 | 4 | 4 | 4 | 4 | 3 |
| | Pump system | 5 | 4 | 4 | 4 | 4 | 3 |
| PULMONARY | Nebuliser | 2 | 3 | 4 | 5 | 4 | 3 |
| | MDI/ Spacer | 1 | 3 | 4 | 5 | 4 | 4 |
| | DPI | 1 | 1 | 3 | 4 | 5 | 5 |
| OCULAR | Eye drops | 3 | 4 | 4 | 4 | 5 | 5 |
| | Semisolid | 2 | 3 | 4 | 4 | 4 | 4 |

1 Not applicable/ not accepted; 2 Applicable with problems/ accepted under reserve; 3 Probably applicable/ acceptable; 4 Good applicability/ preferred acceptability; 5 Best and preferred applicability/ dosage form of choice (With increasing age, the preference of children becomes more important)

## Oral Formulations review 2026 [2]




**Liquid, Solid, Powder/granule across ages groups**




1. EMA Refl Paper Formulations of choice FINAL to CHMP EMAGuideline on pharmaceutical development of medicines for paediatric use
2. 2. Suitability of Oral Formulations Available to Children at the Time of Pediatric Labeling, Susan M. Abdel-Rahman, PharmD; Debbie A. Avant, BS; and Gilbert J. Burckart, PharmD, JPPT | Exploratory Evaluation of Public Databases

# Pediatric Oral dosage forms

## Oral solutions/suspensions

High dosing flexibility but might face stability and taste issues

- Dosed using a syringe/dosing cup/spoon
- Provides dosing flexibility
- No manipulations
- NG tube compatibility

**Considerations:**

- Stability
- Excipients (preservatives, sweeteners, flavours)
- Taste, large dose volumes

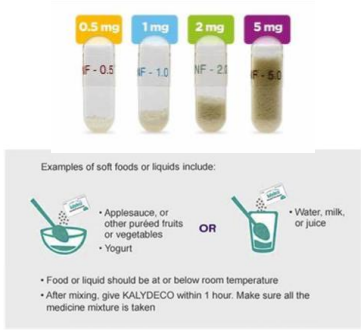

## Solid oral dosage forms

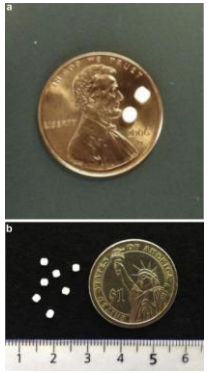
Powder blend, granules, mini-tablets, pellets (sprinkles). High stability

- Presented in capsule, stick pack or sachet.
- Dosed directly to mouth/ onto soft food or intact capsule.
- Minimal excipients: lactose, sucrose
- Reduce/eliminate need for refrigerated storage

**Considerations:**

- Dose administration and manipulation
- Devices under development* to achieve full dose flexibility





Images: https://doi.org/10.1016/j.xphs.2018.11.013

# Toxicology: Drug and Excipient Safety

- Excipients are not inherently inert in children
- High risk of excipient toxicity due to immature metabolism/organs (renal and hepatic clearance)
  - Common adult excipients (propylene glycol, ethanol, preservatives) can be accumulated dangerously
  - Excipients “taste, bitterness” considerations
- Rigorous justification required for every inactive ingredient:
  - STEP database
  - TOXNET
- Justify that excipients and levels are safe excipients and demographic acceptability and formulation is suitable for children




*Pharmaceutical Excipients in Paediatric Formulations, L. Contreras, et al. Handbook of Pharmaceutical excipients*
*Selecting appropriate excipients for paediatric dosage form – Paediatric excipients risk assessment (PERA) framework –Part 1, Smita Salunke, et al. https://doi.org/10.1016/j.ejpb.2024.114458.*

# Acceptability/Palatability

## Requirements

- Acceptability according with guideline[1] is determined by the characteristics of product and the user. Products aspects:
- Palatability, swallowability, (e.g. size, shape, texture), appearance
- Dose frequency, volume, number of tablets
- Palatability is defined "as the quality of the drug product that make it pleasant or acceptable in terms of taste, after taste, smell and texture being critical factors in determining patient acceptance"

## Challenge: How to measure it?

- Key question: How bitter is the compound?
- GAP reliable in vivo and invitro techniques:
- API sensory attributes, taste panel approach, provide some indication of a palatability issue
- Taste and preference in different regions too
- Use of questionnaires in adult clinical studies however can not be directly translated to a pediatric population.

*Patient acceptability*[1]
"The overall ability and willingness of the patient to use and its care giver to administer the medicine as intended"





[1]EMA Guideline on pharmaceutical development of medicines for paediatric use

# Taste masking and Co-Administration

## Taste Masking approaches

- Palatability drives medication adherence in pediatrics
- APIs are often inherently bitter, requiring taste-masking technologies

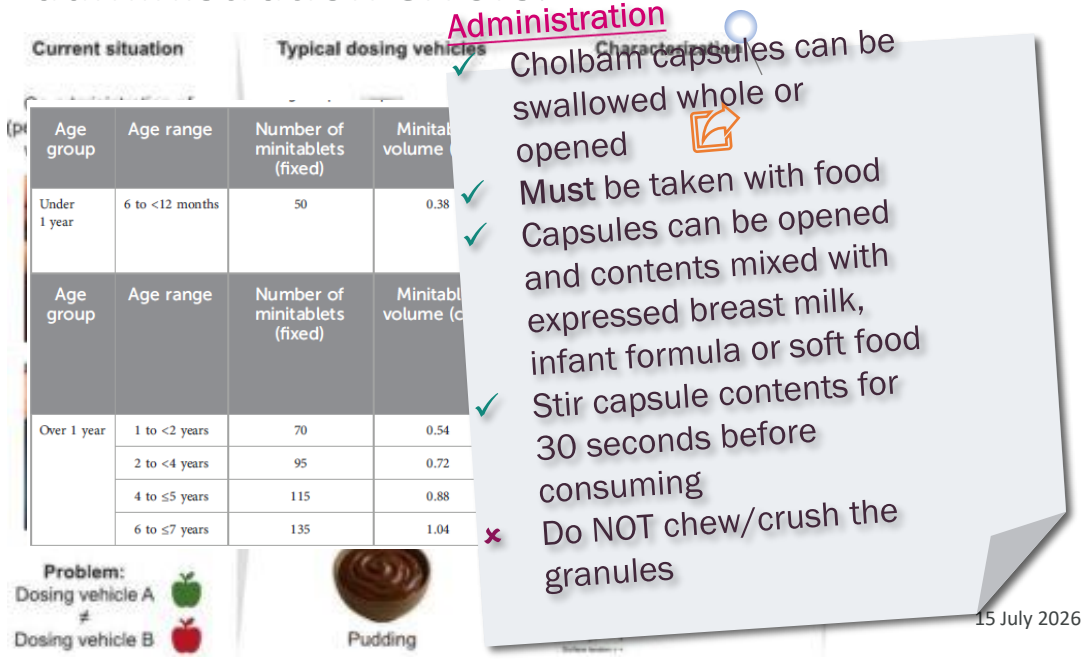
  - Many excipients are known to be bitter or have other aversive sensory attributes including aromatic and or irritation (tongue and mouth or throat burn).

  Traditional methods: Sweeteners and Flavors

- Advanced techniques: Microencapsulation and ion-exchange resins, more complex development times and supply chains

## Co-Administration: Soft foods and vehicles

- Ensure comprehensive stability studies across food types and temperatures.
- Establish clear guidelines for food compatibly in labelling to avoid administration errors.



# Commercial Viability Challenges

- Appropriate delivery systems for various age groups & flexible for multiple dosing strengths
- **Low volume products**
  - Manufacturing scale is relatively small, 5-20 kg batch sizes required for specialized formulations
  - 1-4 batches per year
- Requires manufacturing equipment and extensive validation to ensure operational
- Complex supply chain due to multiple required dosage strengths
- Implementation of robust in-process controls and equipment checks
  - Must demonstrate content uniformity and accurate dosing capabilities e.g. count accuracy- IPCs fill count in individual sachets
  - Final IPCS
- Test on bulk granules and packaged product should be collected during development

# Final Considerations

Health Authorities expectations for Pediatric Marketing Applications are as high as for an adult product and so is the level of details to be provided in the application.

Age-appropriate formulations are a legal, ethical, and scientific necessity. Appropriateness of the drug product for pediatric population, with a focus on:

- Requires balancing dosing flexibility, excipient safety and acceptability
- Risk towards nitrosamines and elemental impurities formation
- Manufacturing and process control strategy
- Compatibility soft food & vehicles for administration, syringe or any other devices to support the method of administration of the product
- Acceptability of the product in pediatric population
- Technological innovations continue to bridge the gap toward accessible pediatric medicines

# Thank you