Assessment of Palatability of Pediatric Drug Products:

*Literature Review*

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Yuet Mei Khong is an employee of AbbVie and may own AbbVie stock. The design, study conduct, and financial support for the research was provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.
Definition of Palatability

Palatability

**Palatability** is one of the main elements of the patient acceptability of an oral paediatric medicinal product. It may also be an aspect related to the use of a product for nasal administration or inhalation. Palatability is defined as the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth). It is determined by the characteristics of taste, smell, aftertaste and texture.


**Palatability** is the overall acceptance of the taste, flavour, smell, dose volume or size and texture of a medicine to be administered to the mouth or to be swallowed. Palatability can be

**WHY does it MATTER?**

*Good medicine tastes bitter.*
*Chinese Proverb*

*A bitter medicine helps patients.*

“A survey of 500 parents conducted by Ascent Pediatrics, Inc. (Wilmington, Massachusetts) indicated that ~50% of children refuse to take their medication at some time and that, for the 75% of those who were noncompliant, the reason reported was related to a drug's taste.”

C.-P. Milne et al, Clin Ther 2008 30 (11) 2133-2145

“Taste was the most commonly reported barrier to medicines administration affecting 35% (188/542) of all prescribed oral formulations, and associated with 64% (54/85) of formulations that were refused.”


Palatability remains one of the key reasons for rejection of medication in young children.

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Tools for palatability assessment
It is recommended that taste assessment is conducted hand-in-hand with formulation development.

**Adult Program**
- Taste as criteria for compound selection.
- Phase I studies – adult.

**Pediatric Program**
- In vitro methods
- Adult volunteers.
- Part of the pediatric clinical studies.
- Other means and confirm post marketing.

**Adults vs Children**

**Taste Test in Adults**
Adult perception of taste is different from children

Data transferable to pediatrics / consider bridging studies

**Taste Test in Children**
Targeted age group and disease state.

Reliability of method

Ethics

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15. **Trials with healthy children**

In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable like children with a disease or condition. Studies should not be performed in children when they can be performed in adults. Exceptions could be where healthy children participate in palatability testing such as swill and spit taste testing for a new flavoured medicine.

*EMA, Ethical considerations for clinical trials on medicinal products conducted in pediatric population, 2008.*

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Study Methodology: Recommendation

**REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION**


**Recommendations for performing taste trials in children**

- **Short**
- **Fun**
- **Simple**
- **Max of 4**

**Evaluation principles**

- **2 principles for taste evaluation:** verbal judgement + facial hedonic scale
- **Children <5-6 years:**
  - Recommend: verbal judgement + control question + parents/caregiver
  - Include a concluding question

“The choice of the method and the acceptance criteria, as proposed by the applicant, should be described and justified for the intended aim. The suitability of the chosen method and the appropriateness of the limits to be applied should be discussed and justified in terms of benefit-risk considerations”

Study Methodology: Assessment Methods

Facial reactions were videotaped and analysed using the Facial Action Coding System (FACS)


Hedonic Scales to determine preference in pre-school children


Forced-Choice Tracking Procedure


Visual Analogue Scale

Study Methodology: Scale vs age group

- Hedonic scale and VAS are the most commonly used scale
- Scale for ranking + additional question (concluding)
- For younger children (<4-5), inputs from parents / caregivers

- Reliability of child to rank

**Table III: Measurement scale used with children in relation to cohort age**

<table>
<thead>
<tr>
<th>Measurement tool</th>
<th>Age group (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-point Hedonic scale</td>
<td>3-5</td>
</tr>
<tr>
<td>3-point Hedonic scale</td>
<td>4-7</td>
</tr>
<tr>
<td>4-point Hedonic scale</td>
<td>5-13</td>
</tr>
<tr>
<td>5-point Hedonic scale</td>
<td>8 studies: 3-12, 4-9, 5-8, 5-9, 5-10, 5-11, 6-11</td>
</tr>
<tr>
<td>Sex-specific 5-point Hedonic scale</td>
<td>4-8</td>
</tr>
<tr>
<td>Sex-specific 5-point Hedonic scale</td>
<td>4-8</td>
</tr>
<tr>
<td>10-point Hedonic scale</td>
<td>3-8</td>
</tr>
<tr>
<td>10 cm VAS (very bad to very good)</td>
<td>15-19</td>
</tr>
<tr>
<td>10-cm VAS (really good to really bad)</td>
<td>4 studies: 8-17, 5-9, 4.2-11, 4-7</td>
</tr>
<tr>
<td>Rank order in between 2 products</td>
<td>4-8</td>
</tr>
<tr>
<td>Rank order in between 3 products</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

**Verbal response**

<table>
<thead>
<tr>
<th>Taste “good”, “not good”, or “very bad”</th>
<th>Old enough for verbal assessment (&gt;1)-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Converted to 1-3 scores</td>
<td></td>
</tr>
<tr>
<td>Converted to 1-5 scores</td>
<td>Old enough for verbal assessment (&gt;1)-7</td>
</tr>
<tr>
<td>Converted on scale 1 to 10</td>
<td>8-17</td>
</tr>
<tr>
<td>No details</td>
<td>5-10</td>
</tr>
</tbody>
</table>


Study Methodology: Sample size

- No standardized statistical method
- Only few literature demonstrated sample size determined by power calculations.
- Parametric vs non-parametric inferential statistics.

**Recommendations:**
- Power analysis for sample size estimation
- Selection of appropriate statistical model


- 2-sided t-test (significance of 0.05)
- SAS software
- 50 subjects
- Forest Plot

*C. Thopmson et al, TIRS, 2015 49 (5) 647-658.*
**Novel Ideas**

**TaStation – High Throughput Taste evaluation through a game**

Image not available due to copyright

[http://www.opertechbio.com/#It-station/oer2w](http://www.opertechbio.com/#It-station/oer2w); Assessed 11 May 2016.

**Automated Assessment of Children’s Postoperative Pain Using Computer Vision**

Image not available due to copyright

K Sikka et al, Pediatrics, 136 (1) 2015.

**Face tracking to monitor emotions and preference**

Image not available due to copyright

Other considerations in palatability assessment

Taste is experienced through a “sensory window” that changes with age and experience and is partially affected by genetics.

Summary

“There is a strong need for a concept paper for a guideline on the demonstration of ‘palatability’ of paediatric medicinal products to support assessment of PIPs in respect to palatability.”

Report - Workshop on Paediatric Formulations for Assessors in National Regulatory Agencies EMA/432389/2011

Many challenges remaining in assessment of palatability of drug product in pediatric population.

- Lack of validated scale of assessment
- Definition of “acceptability”
- Difficulty in interpretation of data
- Ethical issues in palatability assessment in children
- Differences in taste acuity and preference across different cultures
- Number of test subjects

Food for Thought

Can a risk-based approach be implemented to guide palatability assessment strategy?

What are the attributes in this risk-based approach?

![Human Factor Risk Analysis Diagram](image)

QbD Risk Assessment

A benefit/risk approach

Food for Thought

- Palatability Assessment
- Pediatric Workshop
- June 2016
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Leverage on available techniques/data

- Patient profile
  - Formulation
  - In vitro release
    - Electronic tongue
  - Animal studies
  - Adult studies
  - Screen
  - Bridging/Correlation

Risk Assessment
- Risk/benefit model
- QbD RA
- HF RA

Methodology

Palatability Assessment Strategy
References

- D.A. van Riet-Nales et al, Arch Dis Child, 2013, 98:725-731
- Illustrations and art courtesy of Microsoft clipart and Microsoft.com clip art image gallery
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