Challenges of sensory evaluation (palatability/acceptability) of pharmaceutical products for adults and children

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Today’s snapshot

- Opportunities for sensory analysis during the development of (paediatric) medicines
- The EU paediatric medicine regulation: 9 years down the line

- Acceptability and Palatability of medicines

- Methodological similarity/differences with food sensory research
  a case study: ‘to select or not to select’
- Moving towards non human tools?
Acceptability is an **overall ability** of the patient and caregiver (defined as ‘user’) **to use a medicinal product as intended** (or authorised).

Acceptability of a medicinal product is likely to have a significant impact on the **patient’s adherence** and consequently is likely to have an **impact on safety and efficacy** of the product.
Characteristics of medicinal product

• **Palatability** *(one of the main but not exclusive elements)*
  • appearance (e.g. colour, shape, embossing, etc.)
  • swallowability (size/shape, integrity of dosage form (e.g. coating)
• Required dose (e.g. dosing volume, number of tablets, break marks, etc.)
• Required dosing frequency and duration of treatment
• Actual mode of administration
  • Complexity of modification prior to administration (if required)
  • Selected administration device (if any)
• Container closure system (primary and secondary)

*(physical and behavioural) age appropriate / clinically relevant*
• **Palatability** is defined as the **overall appreciation** of a *(often oral)* medicine by organoleptic properties such as vision *(appearance)*, smell, taste, aftertaste and mouth feel (e.g. texture, cooling, heating, trigeminal response), and possibly also sound *(auditory clues)*.

• It is determined by the characteristics of the components *(Active Substance and Excipients)* and the way the active substance is **formulated into a medicine**.

• **Palatability** is also relevant for **other routes of administration** e.g. buccal, nasal, inhalation use, and whenever the product may contact the taste receptors indirectly e.g. by deposition in the throat, post nasal run off, etc.
Children DO NOT think that the worse a medication taste, the better it works! 

A survey of over 800 paediatricians on barriers to treatment completion for children with acute/chronic illnesses:
Frequency of dosing (96%/91%)
Unpleasant taste (91%/84%)
Side effects of medication (88%/88%)
American Society of Pediatrics; 2000

A survey of 500 parents [Ascent Pediatrics, Inc.] 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.
Is the future bright?
Since January 2007 the **Paediatric Regulation** came into force in EU and obliges pharmaceutical companies to develop paediatric medicines.

A system of **OBLIGATIONS** and **INCENTIVES**
Part D - Paediatric investigation plan

D.1. Existing data and overall strategy proposed for the paediatric development.
D.1.1. Paediatric investigation plan indication
D.1.2. Selected paediatric subset(s)
D.1.3. Information on the existing quality, non-clinical and clinical data
  D.1.3.1 Quality data
  D.1.3.2 Non-clinical data
  D.1.3.2 Clinical data
D.2. Quality aspects
  D.2.1. Strategy in relation to quality aspects
  D.2.2. Outline of each of the planned and/or ongoing, studies and steps in the pharmaceutical development

Early in development (end of phase 1 in adults)
| Acceptability or palatability testing | The acceptability, including palatability, of <*> specify the dosage form, e.g. oral solution, oral suspension, etc. *> should be confirmed during the clinical trial with the target population.  
  or (if relevant)  
  Acceptability of <*> specify the dosage form, e.g. tablets, capsules, etc. *> should be tested during the clinical trial with the target population. | Whenever an oral liquid formulation is proposed, it is advisable to include a request for confirmation of acceptability of this formulation during a trial with the target population. In case of liquid formulations, acceptability includes palatability testing (taste, texture, flavour, etc.).  
  In case of tablets, especially when proposed to the younger subsets of paediatric patients (6 – 8 years of age), or when the tablets size is large, their acceptability should be investigated and confirmed. Usually palatability testing for tablets is not needed.  
  Due dates for acceptability (palatability) testing should be aligned with due dates for clinical studies during which the testing takes place. Having different deadlines may result in submission of the data as part of another application (due to compliance check rule). |
Guideline on pharmaceutical development of medicines for paediatric use

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“It is recommended that taste assessment is conducted hand-in-hand with formulation development”…catch 22!

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

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

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**Challenges of developing palatable oral paediatric formulations.**

Cram A¹, Breitkreutz J, Desset-Brêthes S, Nunn T, Tuleu C; European Paediatric Formulation Initiative (EuPFI).
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

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.

Later phase ‘panels’

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>3–12, 37 4–9, 40 5–8, 39 5–9, 38 5–10, 21 5–11, 35 6–11, 33 6–12, 41</td>
</tr>
<tr>
<td>Sex-specific 5-point Hedonic scale</td>
<td>4–6</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>8–17</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>
<tr>
<td>Verbal response</td>
<td></td>
</tr>
<tr>
<td>Taste “good,” “not good,” or “very bad;”</td>
<td></td>
</tr>
<tr>
<td>Converted to 1-3 scores</td>
<td></td>
</tr>
<tr>
<td>Converted to 1-5 scores</td>
<td></td>
</tr>
<tr>
<td>Converted on scale 1 to 10</td>
<td></td>
</tr>
<tr>
<td>No details</td>
<td></td>
</tr>
</tbody>
</table>
Regulatory expectations?

“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...including risks at population level (e.g. emergence of resistance), and should take account of the characteristics of the target age group, the condition relevant to the medicine, incidental and multiple use and co-medication”
Several methods described in the literature 

**BUT** knowledge still fragmented 

- an internationally harmonized method has not yet been developed 

- **iUK** 

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**SPaeDD-UK:** Smart Paediatric Drug Development - UK  
*Accelerating paediatric formulation development*  
*An open innovation R&D project*  
http://www.paediatricscienceuk.com

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Numerous aspects need to be further explored, including: 

- **design of studies** incl. number of subjects involved, questionnaires to patients and/or caregivers, type of scales used etc.  

- **acceptance criteria**  
  - eg 100% 80%? What % is ‘acceptable’?
Design of the acceptability study

Acceptability tests must be considered as clinical studies performed by qualified personnel with Ethical Committee approval and informed consent from parents or guardians.

This acceptability studies should be conducted in communities, in children with acute diarrhoea, who have been prescribed dispersible zinc tablet (one 20-mg tablet per day for 10 days). Blister packs of zinc tablets are given to selected drug-sellers and healthcare providers in the community. A visit to the home of the children prescribed zinc dispersible tablets is arranged 2 weeks after to assess acceptability of and adherence to the instructions for zinc treatment.

The study population should include children aged 3–59 months with an acute diarrhoea episode, whose caretakers sought assistance from one of the selected drug-sellers or healthcare providers and are provided with the zinc blister pack.

Sample size
To identify a ± 7.5% minimal difference in acceptability between children aged over and below 18 months with an anticipated 70% acceptability (p), setting the level of confidence at 95% (z = 1.95), the resulting sample size estimate is 140 children per group. To adjust for potential drop-outs, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age-group).

5.2 Evaluation of acceptability and adherence to treatment

Adherence to the treatment regimen for 10 to 14 days is essential to ensure the full effect of zinc for the prevention and treatment of diarrhoea. However, adherence to treatment can be obtained only if the zinc products promoted for use in the management of diarrhoea are acceptable to infants and young children.

So, it is strongly advised that all zinc products considered for use in the management of diarrhoea be tested for acceptability using a standard methodology. Such a methodology (Annex 8) should allow one to precisely determine the proportion of children receiving zinc for a duration considered satisfactory. As a general guideline, a treatment may be considered to have good acceptability if 80% of the prescribed treatment is taken by at least 70% of the children.
Guideline on the demonstration of palatability of veterinary medicinal products

‘…voluntary full consumption within the maximum offering time…’

7.4. Criteria to grant a palatability claim

To be granted a palatability claim, the overall voluntary acceptance rates should at least reach the threshold of 80% in dogs and 70% in all other species. The threshold should be reached in a group of at least 50 animals if the product is administered only once. The threshold should be reached in a group of at least 25 animals if the product is for at least two administrations.

In cases where palatability is evaluated as part of clinical studies with similar testing conditions, none of which have 25 or 50 animals treated with the investigational VMP, the results obtained could be pooled to accumulate the required number of animals in the studies.
Formulation development - earlier phase and panels of healthy adult volunteers.

What to learn from the modern sensory and consumer science of food industry?
The market
- Pharma (small) vs Food (Big)
- Global
- Development geared towards more developed countries where there is less kids
- Rx market not driven by competitive sales (excl. OTC)

- Soft food to administer medicines (as administration vehicle/taste masking effect)?
- Flavouring? Level of sweetness acceptance…
Pharma vs Food

• Start point….Endpoint

• Product attribute
  – limited
  – can’t be attractive (Rx)

• Product quality for testing:
  – GMP

BAD (bitter, metallic… AVERSIVE) OK
Socio-demographics
Age (direct vs proxy measurement)
Environment (parents) influence gender, genetics...

Panel healthy (sick) volunteers

Methodology
- Swallow / swirl-spit
- 5ml? -> 15ml?
- 5sec? -> 15sec?
- Single vs repeated exposure (compliance)

End point
Product development
Benchmarking – generics!

Degree of liking (preference) = many naïve subjects
Vs
Degree of tolerance (acceptability) = few trained subject (patients?)

Methodology
Questionnaires / Scale used
Stats
Setting
is it a CT?

Pain scale
3yo+, self report
Wong & Baker, 1988

Aversiveness scale
n=6

P.R.O. iUK 2016

n=5
**IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?**

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A CLINICAL TRIAL OF A MEDICINAL PRODUCT?</strong></td>
<td><strong>B</strong></td>
<td><strong>C</strong></td>
<td><strong>D</strong></td>
<td><strong>E</strong></td>
</tr>
<tr>
<td>Is it a medicinal product (MP)?</td>
<td>Is it not a medicinal product?</td>
<td>What effects of the medicine are you looking for?</td>
<td>Why are you looking for those effects?</td>
<td>How are you looking for those effects?</td>
</tr>
<tr>
<td>If you answer no to all the questions in column A, the activity is not a clinical trial on a MP.</td>
<td>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</td>
<td>If you answer no to all the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.</td>
<td>If you answer no to all the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.</td>
<td>If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A, B, C &amp; D brought you to column E and you answer no to any of these questions the activity is a clinical trial within the scope of the Directive.</td>
</tr>
<tr>
<td>If you answer yes to any of the questions below go to column B.</td>
<td>If you answer no to this question below go to column C.</td>
<td>If you answer yes to any of the questions below go to column D.</td>
<td>If you answer yes to any of the questions below go to column E.</td>
<td></td>
</tr>
<tr>
<td>A.1 Is it a substance or combination of substances presented as having</td>
<td>B.1</td>
<td>C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.3 Is it an active substance in a pharmaceutical form?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**YES (Phase 1 study)**

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**NO**
ISO guideline on participant training (selection?) methodology

Retrospective analysis of 3 studies selection on quinine

<table>
<thead>
<tr>
<th></th>
<th>Sample</th>
<th>APIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>N=21 males and females</td>
<td>Quinine hydrochloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caffeine citrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sildenafil citrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Study 2</td>
<td>n=48 males and females</td>
<td>Quinine hydrochloride</td>
</tr>
<tr>
<td>Study 3</td>
<td>n=48 males</td>
<td>Quinine hydrochloride</td>
</tr>
</tbody>
</table>

Intra-individual Variability
To select or not to select…

inter-individual variability

Rationale for selecting participants:

- For lowest [quinine] all ratings <25
- For highest [quinine] all >75
- Range between two ratings of the same concentration no greater than 50

6 participants “sensitive” (the first 6)
the remaining 15 as “non-sensitive”
To select or not to select...

“sensitivity selection” to quinine did not necessarily result in participants being significantly more sensitive to other APIs.
Need for screening tools for taste assessment at different stages of the drug development process

**EARLY PHASE**

- Pre-candidate stage?
- Selection of salt?
- Formulation?
Thanks to my group for their hard work! …And still smiling…
Thank you.
Back up slides
Obligation: data in children agreed as per binding Paediatric Investigation Plan (PIP)

- End of phase I
- Or Waiver from the requirement
- Or Deferral of the timing of the studies
- Discuss all subsets

Paediatric Committee (PDCO) at the EMA

- FORMULATION WORKING GROUP

Reward (incentives) for paediatric studies conducted if information included in the product information (SPC)

- even if clinical trial do not show efficacy
### Solid dosage forms = smaller is nicer?

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Swallow-ability</th>
<th>Dosing flexibility</th>
<th>Taste masking</th>
<th>Modified release</th>
<th>Chemical stability</th>
<th>Excipients tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquids</td>
<td>✅</td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Solids</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Multi-particulates</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
</tbody>
</table>

**Powder**
- Granules
- Pellets
- Minitablets
- 1 to <4mm

**Ready to use**
*(mono, multidose Packaging -Device)*

**Require manipulation**
*(reconstitution, sprinkle)*

**Intermediate for SODF**
*(compaction, API combination)*
Mouthfeel of dispersible tablets excipients (coprocessed or not)

- Tribology
- BATA model
- Texture aids?
- Swallowability models
- Gastrointestinal transit of non disintegrating MP

**INTRODUCTION**

Evaluation of patient acceptability of multiparticulate formulations should be an integral part of the pharmaceutical development [1]. Multiparticulates, in the form of pellets or beads, offer benefits over conventional solid and liquid formulations (Figure 1) [1]. However, grittiness or rough mouthfeel could be a barrier to the patient acceptability of multiparticulates [3].

**AIM**

To evaluate overall palatability of multiparticulates and its influence on the willingness to take the formulation by young adults.

**EXPERIMENTAL METHODS**

- Microcrystalline cellulose pellets (Cellets®; Pharmatran Samas, Switzerland) were used as model multiparticulates (Figure 2).
- Samples were composed of 250 or 500 mg of Cellets of either of two particle size distributions (Table 1). Dry samples administered directly in the mouth followed by water (dry) were compared to samples pre-dispersed in 10 ml of water (wet administration).

**RESULTS AND DISCUSSION**

Grittiness perception increased with increasing amount and size of the multiparticulates (Figure 3). For the majority of the formulations (6/8) at least 50% of the volunteers scored grittiness 4 and above. Volunteers comments are provided in Figure 4.

**Willingness to take multiparticulates:** For 7 out of 8 samples at least half of the volunteers would be willing to take the formulation every day (Figure 5). A correlation was found between grittiness and willingness to take multiparticulates (Rho = 0.85), i.e. grittier formulations were less often accepted.

**CONCLUSIONS AND FUTURE WORK**

Oral grittiness is an outcome of multiparticulates which hinders palatability and reduces the willingness of the patient to take the product. Increasing the amount and size of multiparticulates exaggerates the issue whilst pre-dispersion in water slightly improves acceptance. Future work involves sensory evaluation of multiparticulates in children and investigation of formulation strategies to improve palatability.

**REFERENCES**

Acceptability of mouthfeel of Multiparticulate study

1. Please rate the grittiness of the sample.
   *(Grittiness means that you can feel ‘bits’ in the sample)*

   Not Gritty *(No bits)*

   Very Gritty *(Lots of bits)*

2. What did you think of the overall volume of the sample?
   *(Volume means the amount you had to take)*

3. What did you think of the overall mouthfeel of the sample?
   *(Mouthfeel means how the sample felt in your mouth)*

4. What did you think of the overall taste of the sample?

5. Can you still feel any of the ‘bits’ in your mouth?

   Yes  

   No  

Any other comments about this sample: