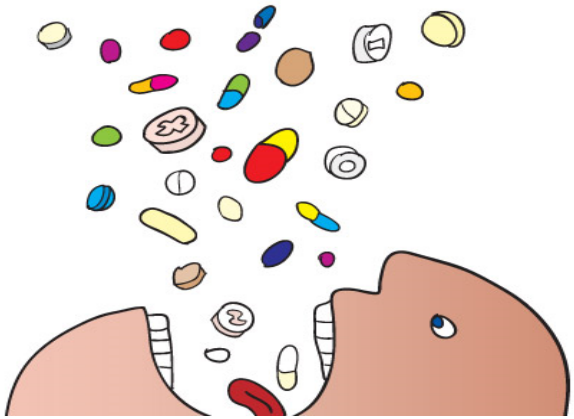
3.9 Acceptability and palatability - methods available for assessment



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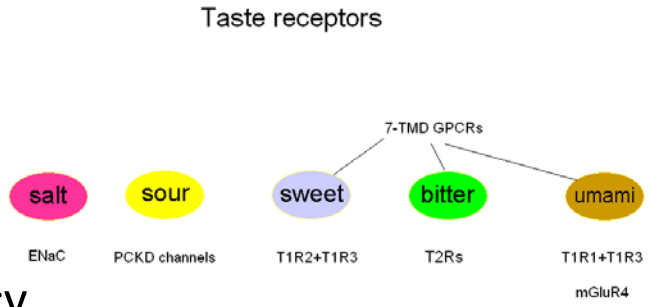
Workshop on Paediatric Formulations II for Assessors in National Regulatory Agencies - 8 November 2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

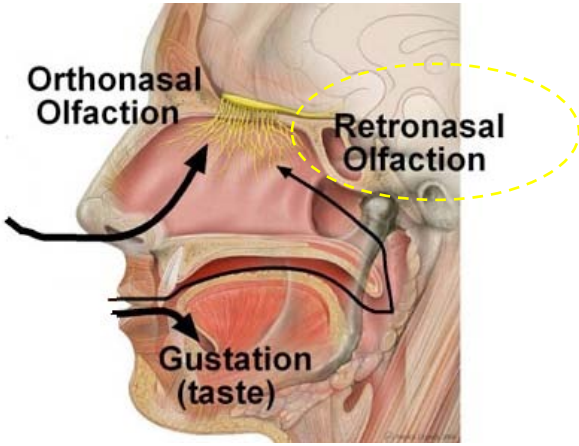
Objectives

- Acceptability & Palatability of children dosage forms
  - *Only oral route*
  - Definitions
  - Relationship with Compliance
  - How to measure it in children?
    - *Excluding in vitro assessment (e tongue)*
    - Including what the Draft GL says (*10. Patient Acceptability*)
- Case examples: recently published and PIPs
- Sharing experience with the audience (discussion)

‘Taste’: Definition



– Overall sensory quality
  - **Taste / After Taste** (gustatory sense)
    - 5 primary tastes + metallic, hot/spicy
  - **Somatosensory modalities** such as
    - touch (**texture)**
      - Grittiness, astringency
    - temperature
      - Cooling effect
    - and appearance **(vision)** even sound
  - and, most importantly, **smell** (olfaction)



– Flavour: small number of primary taste + much larger of odour qualities

Taste maturation in children

Taste

- Human foetus:
  - specialised taste buds by 7-8th week of gestation
  - structured mature taste buds by 13-15th week
- Newborn can detect and tend to reject bitterness
- Early experience with bitter taste predispose to increased acceptance
- Anterior and posterior taste buds composition develop until ~15yo
- Stronger liking for salty, sour, **sweet** until late adolescence

Menella et al. 2008. Clin Ther 30(11): 2120-2132

Smell

- Olfactory bulbs finished by week 11th and function by week 28th
- Sense of smell+++: *maternal odour, guiding to nipple*
- Affective responses to pleasant/unpleasant odours appear later (3-4yo)

Concerns and uncertainties about the age at which *(young)* children can (*safely*) swallow oral (*monolithic*) solids

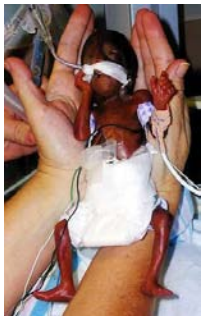
?

- Large age variations reported in the literature: *3yo*...**<u>6yo</u>…**older?

Evidence based data !?

Change in ability to cope with dosage forms

ICH E11



Can't

could?

(small)

Can swallow Tablets/Capsules

Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use
19 May 2011 EMA/CHMP/QWP/180157/2011

Acceptable Tablet size?
Nothing on capsules

3-5mm >2yo
5-10mm >6yo
10-15mm >12yo
15mm + >18yo

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Overall Palatability: Definition

- **palatability** - the property of being acceptable to the mouth
  'TASTE'
- **palatability** - acceptability to the mind or feelings
  ACCEPTABILITY

- *important part of compliance/adherence/concordance*

Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use

19 May 2011 EMA/CHMP/QWP/180157/2011
Committee for Medicinal Products for Human Use (CHMP)

10. Patient Acceptability

Patient acceptance can be defined as the overall ability of the patient to use a medicine as intended. Patient acceptability is likely to have a significant impact on the patient's adherence and consequently on the safety and efficacy of the medicine. It is determined by the characteristics of the medicinal product and the user. The product aspects involve the pharmaceutical characteristics of the medicine such as 1) palatability, size and shape; 2) the required dose e.g. the dosing volume, number of tablets etc.; 3) the required dosing frequency; 4) the selected administration device; 5) the primary and secondary container closure system and 6) the actual mode of administration to the child. For paediatric medicines, the user may comprise both the child and its adult caregiver.

Is it important in practice?

- Children DO NOT think that the worse a medication taste, the better it works!

- 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)

- Compliance rates in children range from 11-93%, with major factors attributed **to formulation and palatability**

Matsui. 2007. PPDT 8: 55-60

Is it important in clinical research?

- How much is a table spoon of medicine minus two coughs, a dribble and a bit of gag reflex…? Dose! Bioavailability!

- **Phase II protocol:**

-Administration:

Emptying content of capsules in apple juice or infant formula

-Data analysis:

Apple juice group showed increased presystemic clearance

-Delay + extra costs:

Multi cross-over bioequivalence bridging study in adults

Abdel-Rhahman et al. 2007 Clin Pharm Ther. 81(4): 483-494

Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use

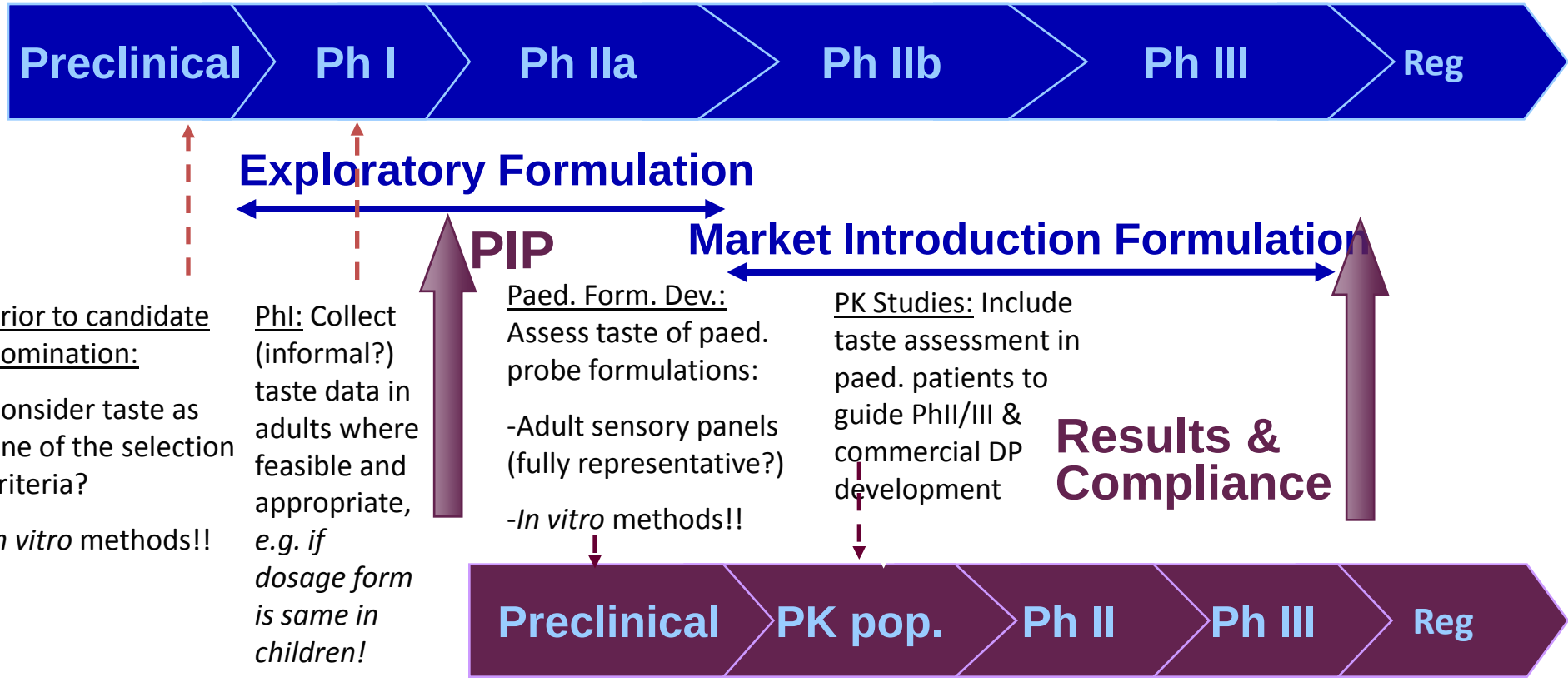
19 May 2011 EMA/CHMP/QWP/180157/2011
Committee for Medicinal Products for Human Use

668 Palatability is one of the main elements of the patient acceptance of an oral medicine. It may also be
669 an aspect related to the use of nasal and inhalation medicines. Palatability is defined as the overall
670 appreciation of an (often oral) medicine towards its smell, taste, aftertaste and texture (i.e. feeling in
671 the mouth). It is determined by the characteristics of the active substance and the way the active
672 substance is formulated into a finished medicinal dosage form. Information on the palatability of the
673 active substance should consequently be acquired at an early stage in the development of a medicinal
674 product, e.g. from dedicated adult panels, literature or in-vitro measurements such as the electronic
675 tongue. The palatability of the active substance should contribute to the choice of the selected finished
676 dosage form(s) and route(s) of administration. Unless otherwise justified, the palatability of a
677 paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or
678 beverages).

679 The target quality product profile can be tailored at a paediatric medicinal product with a neutral taste
680 or a paediatric medicinal product with a specific and generally acceptable taste. The choice for either of
681 these profiles should be justified. Normally, development of medicinal products with a neutral taste
682 should be considered, especially for medicines used in the treatment of chronic conditions as strong
683 flavours can become unpalatable with repeated administration. The development of the intended target
684 palatability (neutral or a specific taste) should be clearly described and include information on relevant
685 alternative compositions or dosage forms.

When and how to introduce taste/acceptibility assessment?

Development in adults



Development in pediatrics

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Cram et al. 2009 Int J Pharm. 365:1-3.

Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use

19 May 2011 EMA/CHMP/QWP/180157/2011

653 Evaluation of the patient acceptability of a medicine should be an integral part of the pharmaceutical
654 development studies. For medicines falling under the scope of the Paediatric Regulation, patient
655 acceptability of the medicine should preferably be studied in children themselves as part of the clinical
656 trials. In justified cases where no clinical trials will be conducted or in justified cases where patient
657 acceptability will not be studied in the clinical trials, the adequate patient acceptability of the medicinal
658 product(s) as proposed for marketing should be demonstrated otherwise e.g. by literature references
659 or by studies in dedicated adult panels. It should be thoroughly investigated if drop outs and poor
660 compliance during the clinical trials are due to a bad patient acceptability.

661 For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient
662 acceptability is also encouraged to be tested during paediatric clinical trials if any. If not, adequate
663 palatability should be demonstrated otherwise e.g. by data from literature, studies in dedicated adult
664 panels or feedback from patients who have been using the same or a similar product. In lack of actual
665 data in children, applicants are encouraged to confirm the adequate patient acceptability post
666 marketing by actual studies in children who are already under treatment or by a careful evaluation of
667 voluntary patient feedback.

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717 If possible, the adequate palatability of a medicinal product should be studied as part of the patient
718 acceptability studies. Otherwise, adequate palatability should be demonstrated by other means and
719 confirmed post marketing in real patients. Actual palatability studies may be conducted in several
720 ways. The suitability of the chosen method and the appropriateness of the limits to be applied should
721 be discussed and justified in terms of risk to benefit considerations, including risks at population level
722 (e.g. emergence of resistance), and should take account of the characteristics of the target age group,
723 the condition relevant to the medicine, incidental and multiple use, co-medication and differences
724 between countries.

- Taste masking

686 The measures that can be undertaken to improve the palatability of a medicinal product e.g. involve
687 the selection of the excipients including taste maskers, sweeteners and flavouring agents, a change in
688 the particle size of the active substance or excipients, the choice of a different salt form of the active
689 moiety, coating of the active substance, coating of the finished dosage form, the application of a
690 complexing agent or for liquid preparations by any means to lower the amount of free drug in solution
691 such as the choice of a different strength and subsequent change in volume. Any oral paediatric
692 dosage form should by no means become too attractive to children (candy like) as this is known to
693 increase the rate of accidental poisoning.

- Mixing with food

694 Mixing instructions with food or beverages may be recommended in the SmPC and PIL. The
695 instructions can either be intended to mask the unsatisfactory palatability of a medicinal product in
696 cases where it has been demonstrated that the palatability of the medicine cannot be further improved
697 and where it is not an option to select an alternative dosage form. Or mixing recommendations can be
698 applied as a further means to improve the patient acceptability and the ease of swallowing of an
699 otherwise already palatable medicinal product.

700 In cases where mixing instructions are provided to mask the unsatisfactory taste of a medicinal
701 product, it should be discussed which foods mask the original taste best. The applicant should
702 understand whether the medicinal product is likely to dissolve in the food. The applicant should
703 demonstrate that the medicine becomes sufficiently palatable after mixing with the recommended
704 foods or beverages. The patient should be informed that such mixing is not an option, but a necessity.
705 In all other cases, mixing instructions with food or beverages do not need any further justification from
706 the perspective of patient acceptance.

707 However, certain foods of beverages may affect the bio-availability and/or therapeutic action of the
708 medicine. Moreover, the lack of recommendations on mixing with food or beverages will not assure
709 that caregivers will not employ this method in order to administer the medicine. Therefore, the effect
710 of mixing the medicinal product with different types of common food or beverages for children should
711 be discussed and/or studied in the development pharmaceutics targeting at in in-use shelf-life of 30
712 minutes.

713 Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken
714 immediately i.e. within 5 minutes. Positive mixing instructions with common food or beverages are
715 recommended. Appropriate warnings should be added in cases where the medicine can not be mixed
716 with certain food or beverages for even 5 minutes or shorter.

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19 May 2011 EMA/CHMP/QWP/180157/2011

Sensory analysis

ISO 6658:2005 Sensory analysis -- Methodology -- General guidance

- Food/consumer analysis
- Affective testing
  - Subjective/Preference
- **Effective/analytical testing**
  - Objective/facts = discrimination tests
    - Difference testing (triangle, duo-trio, paired and multiple comparisons)
    - Descriptive analysis
    - Ranking

CLEAR END POINT!!!!!

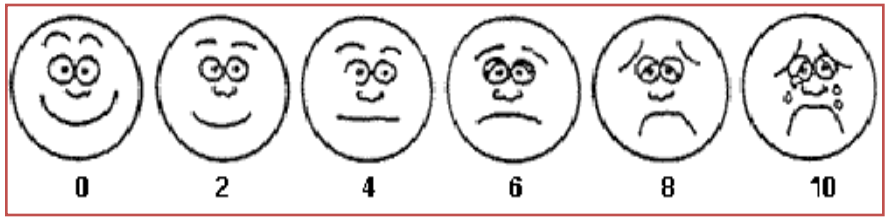
- Basic sensory and statistical analysis techniques when testing **with children** but **special considerations** (physical, emotional, and cognitive levels of development) to develop
  - tasks that are understandable to children
  - alternative modes for children to communicate their opinions or perceptions, such as appropriate scales and measures.

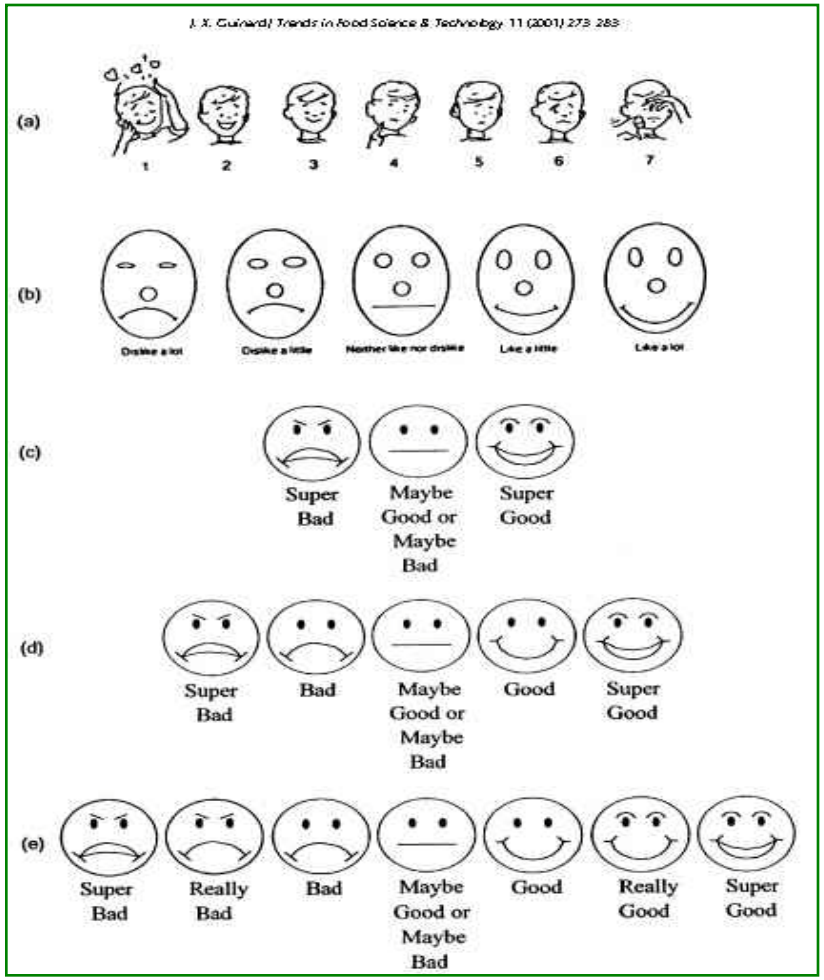
(Age) appropriate Methodology!

Pain scale

3yo+, self report

Wong & Baker, 1988





Guinard FX. Sensory and consumer testing with children
Trends in Food Science & Technology 11 (2001) 273–283

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

Measurement tool	Age group (years)
2-point Hedonic scale	3-5[34]
3-point hedonic scale	4-7[45]
4-point Hedonic scale	5-13[34]
5-point Hedonic scale	3-12,[37] 4-9,[40] 5-8,[39] 5-9,[38] 5-10,[21] 5-11,[35] 6-11,[33] 6-12[41]
Sex-specific 5-point Hedonic scale	4-8[18]
Sex-specific 5-point Hedonic scale	4-8[19]
10-point Hedonic scale	3-8[28]
10-cm VAS (very bad to very good)	15-19[24]
10-cm VAS (really good to really bad)	8-17,[28] 5-9,[27] 4.2-11,[29] 4-7,[25]
Rank order in between 2 products	4-8[31]
Rank order in between 3 products	Not specified[17]
Verbal response	
Taste "good," "not good," or "very bad:"	
Converted to 1-3 scores	Old enough for verbal assessment (>1)-7[44]
Converted to 1-5 scores	3-10,[36] 3-12[37]
Converted on scale 1 to 10	8-17[45]
No details	5-10[26]

Davies & Tuleu. 2008 Journal of Pediatrics. 153, 599-604.

Taste testing *in vivo*

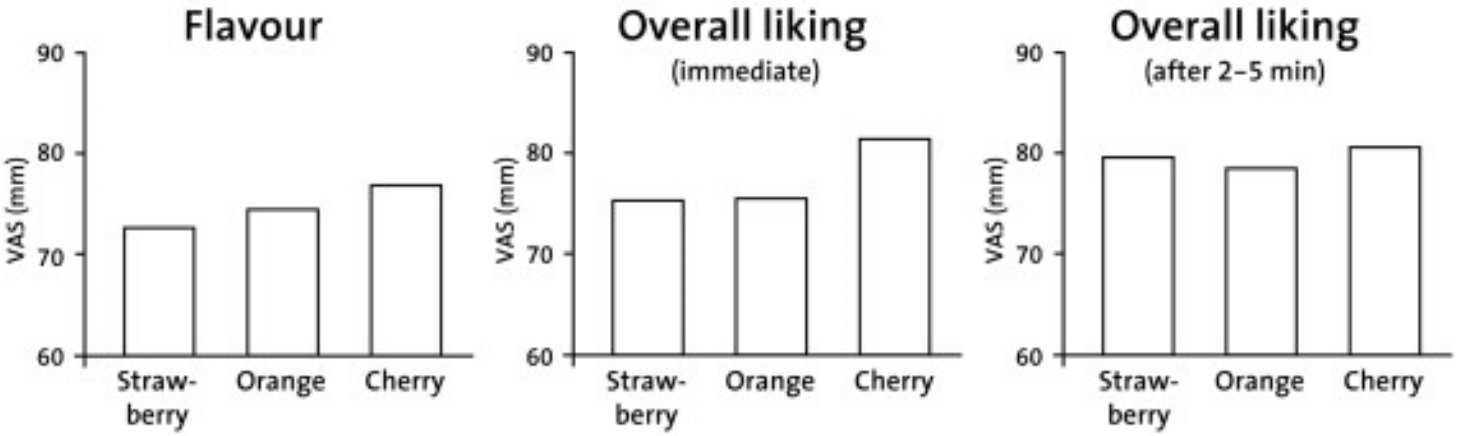
- In **Adults**?
  - Extrapolation/Validation of results for children palatability?
- In children
  - **Healthy children** may participate ; 'swill and spit' eg. new flavoured medicine
  - **Sick children** can be enrolled but preferably if palatability test embedded within CT (& multiple dosing)
- ethical, safe, (and valid) testing methods. GCP!
  - randomisation, blinding, placebo controlled, power calculation, minimisation, incl-excl criteria, stats
- ***In Davies & Tuleu. 2008 Journal of Pediatrics. 153, 599-604***
  - systematic retrieval of peer-review articles (30) on palatability of medicines (not food) in children
  - Healthy/sick Kids & Sex: 50/50; N= 15 – 500
  - 1 to 5 products tested! (mode = 2)
  - mainly monodose, few multidose studies (7-10 days…90days)

Early clinical development of Artemether-Lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects

Malar J. 2010 Sep 3;9:253

- Randomized, single-blind, crossover study (schoolchildren in Tanzania)
- **Immediately** after each test dose [**orange- and cherry-flavoured oral A-L suspension for 10 seconds (without swallowing],** the child was asked to separately rate the flavour, smell, sweetness and overall liking of the medicine using a modified 100 mm visual analogue scale (VAS)
- The rating for overall liking was repeated **after 2-5 minutes**
- **15-20 minutes after** the last administration children were asked which of the three administrations they thought tasted best (ranking from 1 to 3)
- Any AE were recorded + final assessment (after last drug administration)
- VAS scores were analysed to determine whether a significant difference exists between flavours, using a SAS PROC MIXED procedure (e.g. using linear mixed effects modelling). The ranked data were analysed by Friedman's non-parametric procedure. ($p<0.05$)

- **Mean VAS palatability scores**
- **24 girls**, **24 boys**
- 8.6 ± 0.7 years. All participants were of black ethnicity.
- As no significant gender difference was observed, data from girls and boys were pooled.



- There was no significant difference in pooled VAS scores between the three flavours for any rating (data not shown for **smell and sweetness**).

(Age) appropriate Methodology!

- Indirect 'proxi' measurement

Table IV. Measurement scale used for parents/carer interpretation in relation to cohort age

Measurement tool	Age group (years)
4-point Hedonic scale	2-15 days; 2-5 months[23]
5-point Hedonic scale	4-16[42]
Scale ranging from 1 (good), 2 (indifferent), to 3 (bitter, unpleasant)	1-6.5[22]
Scale ranging from 1 (disliked) to 3 (liked a lot)	0.5-12[16]
Scale ranging from 1 (refusal) to 4 (child liked the drug)	0.2-8.1[20]
Acceptability on a 1 (pleasure) to 4 (refused) scale; willingness to swallow on a 1 (no problem) to 3 (vomits) scale	<4[43]
10-cm VAS ranging from 1 (nice taste) to 10 (foul taste)	0.25-8[30]
Same, better, or worse than other medicine	0.25-4.9[32]
Evaluation of administration (very easy/easy/difficult)	1: Too young for verbal evaluation (<7)[44]

Davies & Tuleu. 2008 Journal of Pediatrics. 153, 599-604.

Efficacy and Palatability of meloxicam 0.5mg/ml oral suspension compared to ketoprofen tablets in cats suffering from painful acute locomotor disorders

Clinical evaluation of meloxicam versus ketoprofen in cats suffering from painful acute locomotor disorders. J Feline Med Surg. 2011 Apr;13(4):237-43.

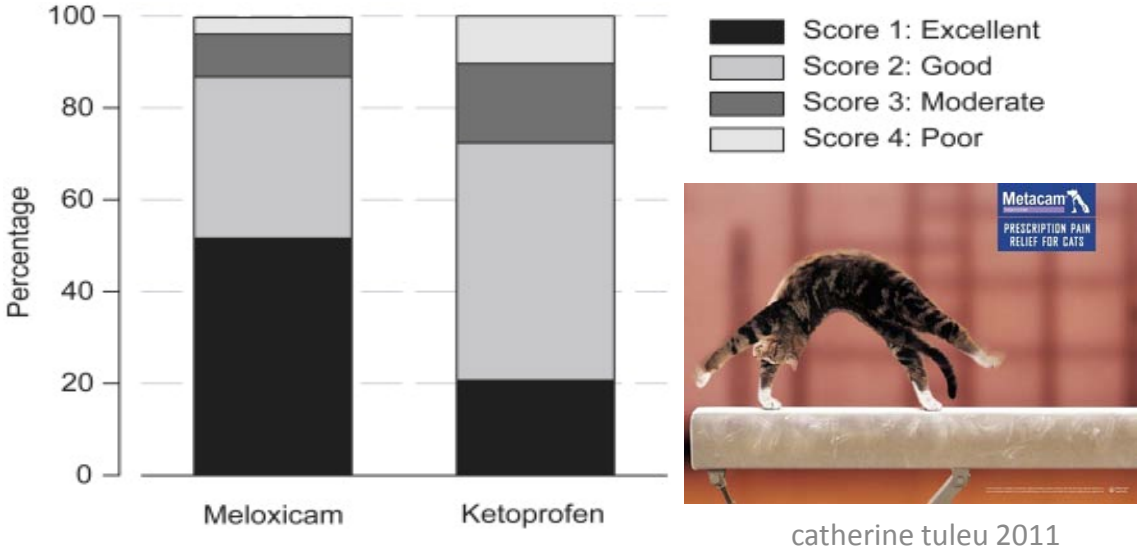
- Palatability

1 – Excellent Immediate voluntary reception

2 – Good Hesitating voluntary reception

3 – Moderate Occasional reluctant reception

4 – Poor Permanent reluctant reception



Meloxicam (Metacam) may be associated with superior compliance in clinical practice due to the higher palatability, which results in better ease of administration.

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15 November 2010
EMA/CVMP/EWP/81987/2010
Committee for Medicinal Products for Veterinary use (CVMP)

Concept paper for a guideline on the demonstration of palatability of veterinary medicinal products

Agreed by Efficacy Working party (EWP)	October 2010
Adoption by CVMP for release for consultation	9 November 2010
End of consultation (deadline for comments)	28 February 2011

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

-'Acceptance': smell taste shape texture and other characteristics

-incl. when administered via food or drinking water

-may differ between animal under experimental and field conditions

Evidence based information ?

- Recent study to assess the efficacy, **palatability (ease of swallowing)** and safety of 4 dose levels of **2mm pancrelipase e/c microtablets** (Pancrease MT®,Jansen Cilag) in 16 subjects, **6 to 30 months of age**
- Indirectly daily assessed by parents "**How easy to swallow do you feel the study medication is?"** (0 poor, 1 fair, 2 good, 3 excellent)
- It was scored fair to good by the parents in each of the treatment groups.

- *Van de Vijver et al Treatment of Infants and Toddlers With Cystic Fibrosis-related Pancreatic Insufficiency and Fat Malabsorption With Pancrelipase MT J Pediatr Gastroenterol Nutr. 2011 53(1):61-64*.

Effects of the abrupt switch from solution to modified-release granule formulation of valproate

MR granules were judged more palatable and easier to administer ($p<0.05$)

- MR small, off-white to slightly yellow, waxy microgranules in stick pack *(50-100-250-500-750-1000mg) administered in mouth or in liquid/soft food (not hot – not baby bottle)*
- Palatability directly assessed in **children >4yo** *[6.7+/-3.6 yo]*, able to comply with the instruction of the test.
- Children scores **'how much did you like the taste of this medication?'** (facial hedonic scale: 5 = really good; 4 = good; 3 = not sure; 2 = bad; and 1 = really bad)
- Indirectly assessed in parents '**On the basis of reaction / facial expression of your child, do you think that the medication is:** pleasant = 3; not sure = 2; or unpleasant = 1**?'**
- Ease of administration asking parents **'Do you sometimes have problems in giving the medication to your child because he refuses to take it or throws it up?** (Yes /No)
- *Compliance*

Verrotti et al . Acta Neurol Scand. 2011 Jun 28. doi: 10.1111/j.1600-0404.2011.01568.x. [Epub ahead of print]

PIPS

- Examples: from basic to sophisticated

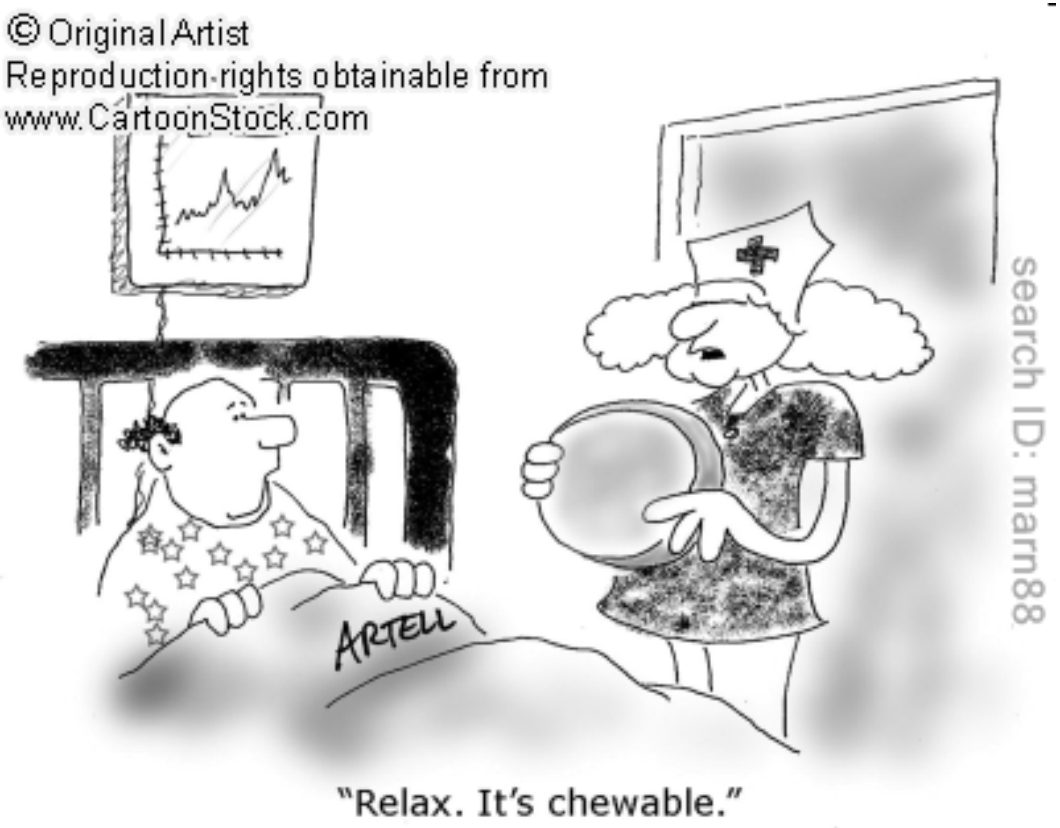
- Still many PIPs state:
- '*Palatability will be assessed*'…how?

To conclude

- **Acceptable palatability** is **essential** but a major and **complex** challenge
- **Formal studies examining role of palatability and factors involved** in medication compliance, adherence, concordance relationship is lacking
- Many **taste masking strategies** are available and should be chosen concomitantly to the dosage form *(age appropriate, non toxic excipients, ease of administration etc)*
- It is important to **assess taste early** on during development
- **Valid and reliable pre-clinical taste assessment method** are needed
- **Human palatability assessment** is inevitable - methodology is important
- **Need for a Concept paper for a Guideline on the demonstration of 'palatability' of a peadiatric medicinal products**

Thank you for your attention

- catherine tuleu 2011



Happy paedia-tricks!

Workshop on Paediatric Formulations II for Assessors in National Regulatory Agencies - 8 November 2011

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