

Assessment of Palatability of Pediatric Drug Products:

Literature Review

Yuet Mei Khong

AbbVie Pte Ltd



Illustrations and art courtesy of Microsoft clipart and Microsoft.com clip art image gallery

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

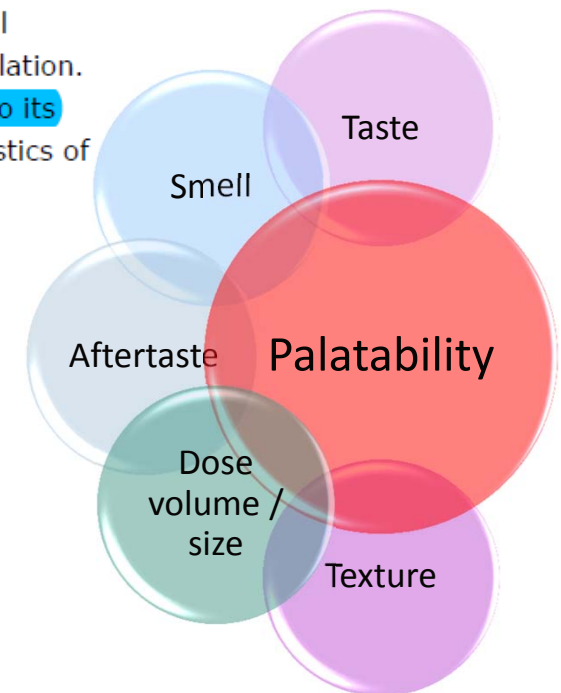
Palatability

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

Guideline on pharmaceutical development of medicines for pediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2, 1 Aug 2013.

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

Development of Paediatric Medicines: Points to consider in Pharmaceutical Development, Working Document AS/08.257/Rev.3 August 2011.



WHY does it MATTER?

Good medicine
tastes bitter.

Chinese Proverb

A bitter medicine

helps patients.



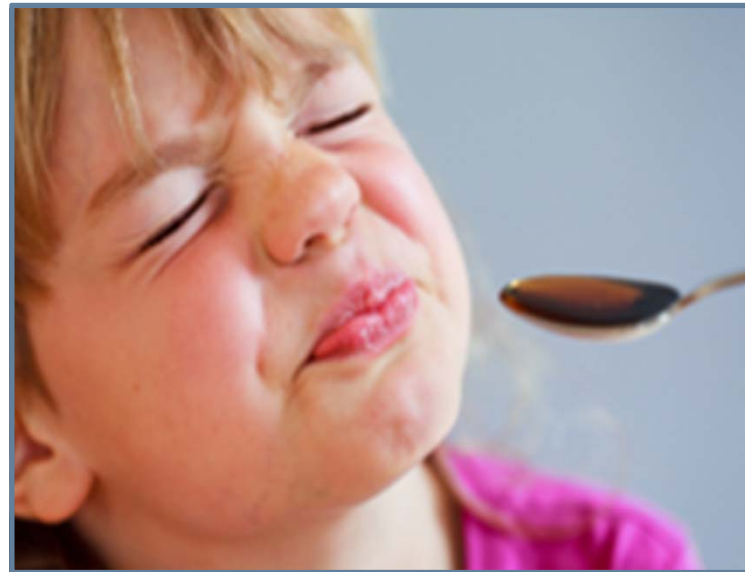
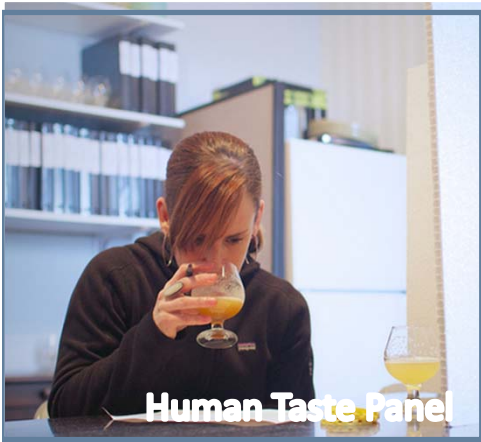
“A survey of 500 parents conducted by Ascent Pediatrics, Inc. (Wilmington, Massachusetts) indicated that ~50% of children refuse to take their medication at some time and that, for the **75% of those who were noncompliant, the reason reported was related to a drug's taste.**”

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

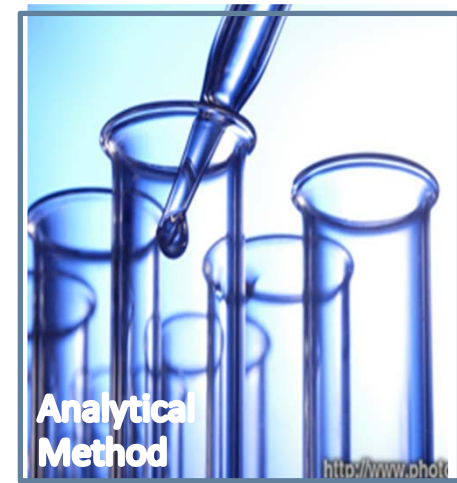
“**Taste was the most commonly reported barrier** to medicines administration affecting 35% (188/542) of all prescribed oral formulations, and associated with 64% (54/85) of formulations that were refused.”

Venables, R., Int J Pharm, 480 (2015) 55-62.

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



**Tools for
palatability assessment**





Start evaluation **AS EARLY AS POSSIBLE**

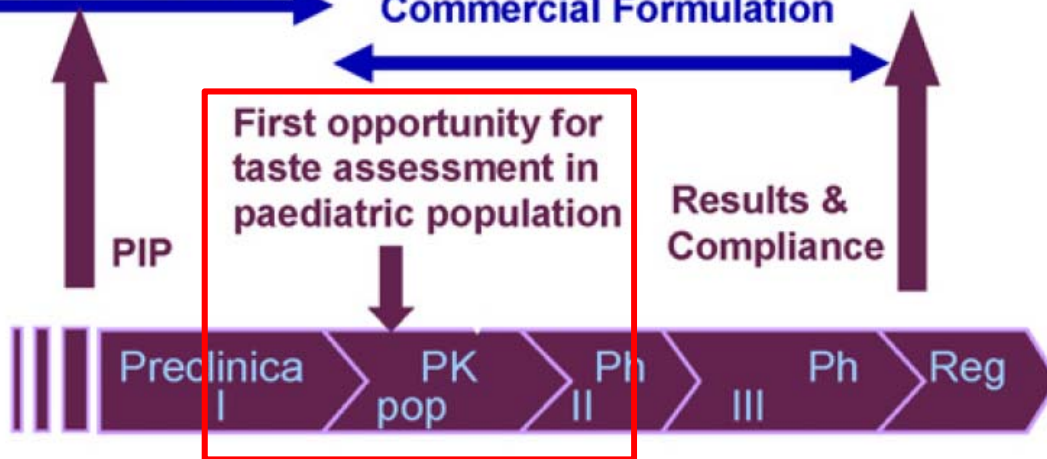
It is recommended that taste assessment is conducted hand-in-hand with formulation development

Development of adult dosage form



Exploratory Formulation

Commercial Formulation



Development of paediatric dosage form

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

A. Cram et al, *Int J Pharm*, 365 (2009) 1-3.; P. Kozarewicz, *Int J Pharm*, 469 (2014) 245-248.

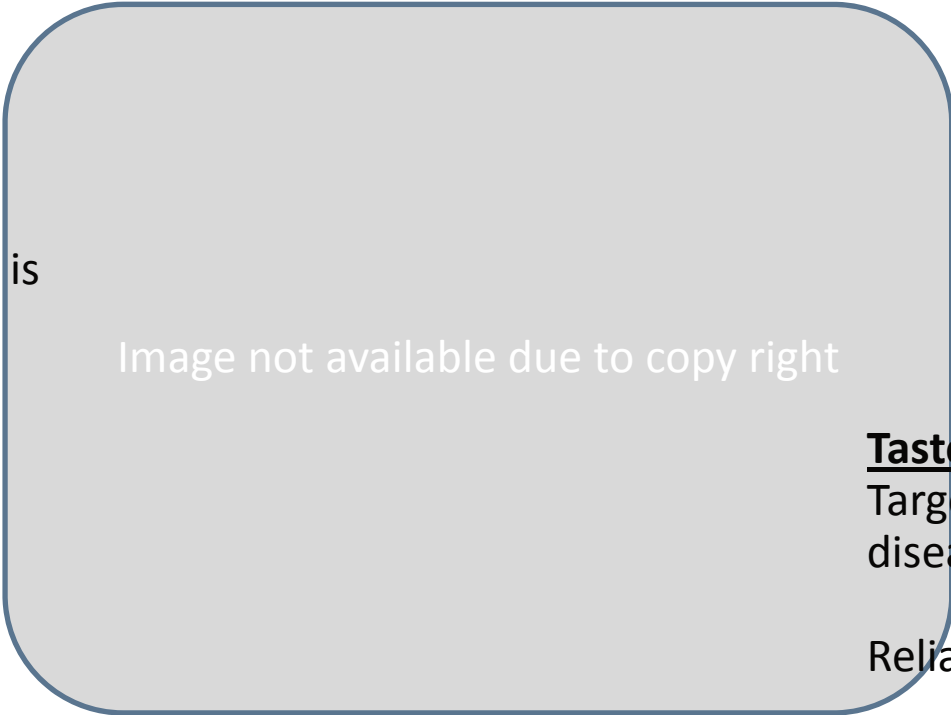


Adults vs Children

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

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.

A. Cram et al, *Int J Pharm*, 365 (2009) 1-3.; P. Kozarewicz, *Int J Pharm*, 469 (2014) 245-248.

Study Methodology: Recommendation

REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION

EMA/CHMP/PEG/194810/2005.

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**”

P. Kozarewicz, *Int J Pharm*, 469 (2014) 245-248.

HOW

Study Methodology: Assessment Methods

Image not available due to copyright

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

E. Greimel et al, Physiology & Behavior 89 (2006) 261–269

Image not available due to copyright

Hedonic Scales to determine preference in pre-school children

A.W. Chen et al, J Sen St, 11 (1996) 141-163

Image not available due to copyright

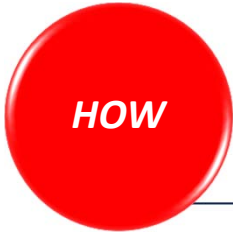
Forced-Choice Tracking Procedure

S.E. Coldwell et al, Neurology 80 (Suppl 3) S20-24.

Image not available due to copyright

Visual Analogue Scale

D.A. van Riet-Nales et al, Arch Dis Child, 2013, 98:725-731.



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 Excerpt from E.F. Davies et al, Journal of Pediatrics 153 (2008) 599-604.

Measurement tool	Age group (years)
2-point Hedonic scale	3-5
3-point Hedonic scale	4-7
4-point Hedonic scale	5-13
5-point Hedonic scale	8 studies: 3-12, 4-9, 5-8, 5-9, 5-10, 5-11, 6-11
Sex-specific 5-point Hedonic scale	4-8
Sex-specific 5-point Hedonic scale	4-8 <i>Half use hedonic scale</i>
10-point Hedonic scale	3-8 <i>hedonic scale</i>
10-cm VAS (very bad to very good)	15-19
10-cm VAS (really good to really bad)	4 studies: 8-17, 5-9, 4.2-11, 4-7
Rank order in between 2 products	4-8
Rank order in between 3 products	Not specified
Verbal response	
Taste "good", "not good", or "very bad"	
Converted to 1-3 scores	Old enough for verbal assessment (>1)-7
Converted to 1-5 scores	2 studies: 3-10; 3-12
Converted on scale 1 to 10	8-17
No details	5-10

E.F. Davies et al, Journal of Pediatrics 153 (2008) 599-604; L.A. Squires, TIRS, 47 (5) 533-541; J. Mennella et al, Clin Ther, 2013, 35 (8): 1225-1246

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

E.F. Davies et al, Journal of Pediatrics 153 (2008) 599-604.

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

C. Thompson et al, TIRS, 2015 49 (5) 647-658.

TaStation – High Throughput Taste evaluation through a game

Image not available due to copyright

<http://www.opertechbio.com/#!t-station/oe2w>; 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

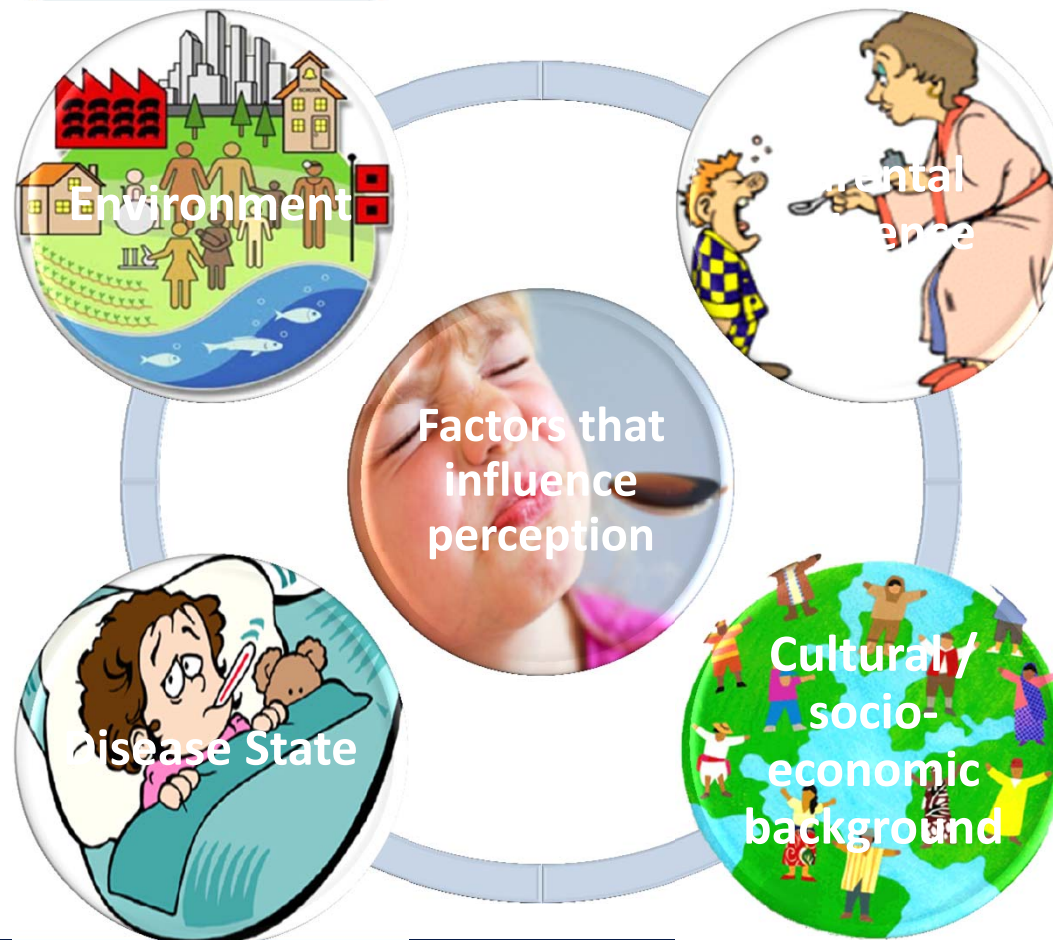
Image not available due to copyright

Illustration from
<http://www.dailymail.co.uk/sciencetech/article-3442201/BBC-plans-start-using-face-tracking-technology-reveal-REALLY-feel-shows.html>; Accessed 11 May 2016.

Other considerations in palatability assessment

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

J.A Mennella et al, Clin Ther 35 2013 (8): 1225-1246.



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.

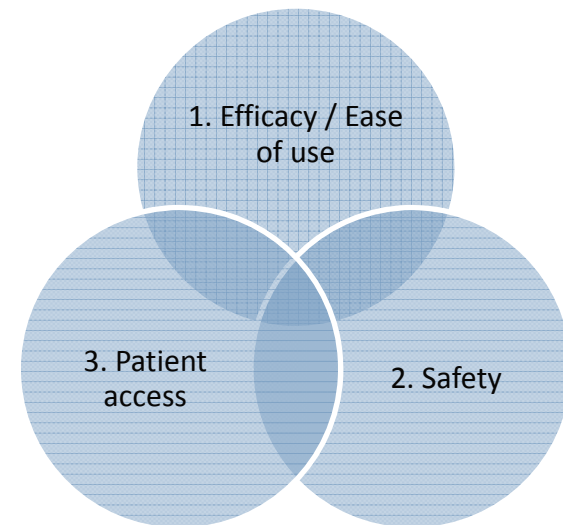
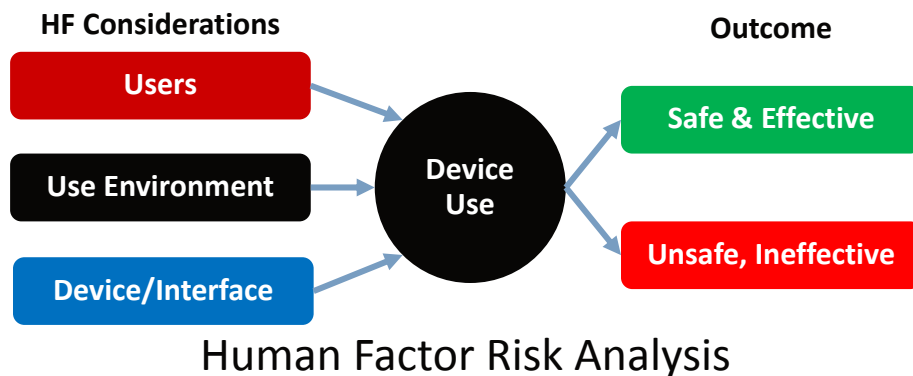
- Lack of validated scale of assessment
- Definition of “acceptability”
- Difficulty in interpretation of data
- Ethical issues in palatability assessment in children
- Differences in taste acuity and preference across different cultures
- Number of test subjects

A. Cram et al, Int J Pharm, 365 (2009) 1-3.; E.F. Davies et al, Journal of Pediatrics 153 (2008) 599-604.; P. Kozarewicz, Int J Pharm, 469 (2014) 245-248.

Food for Thought

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

What are the attributes in this risk-based approach?

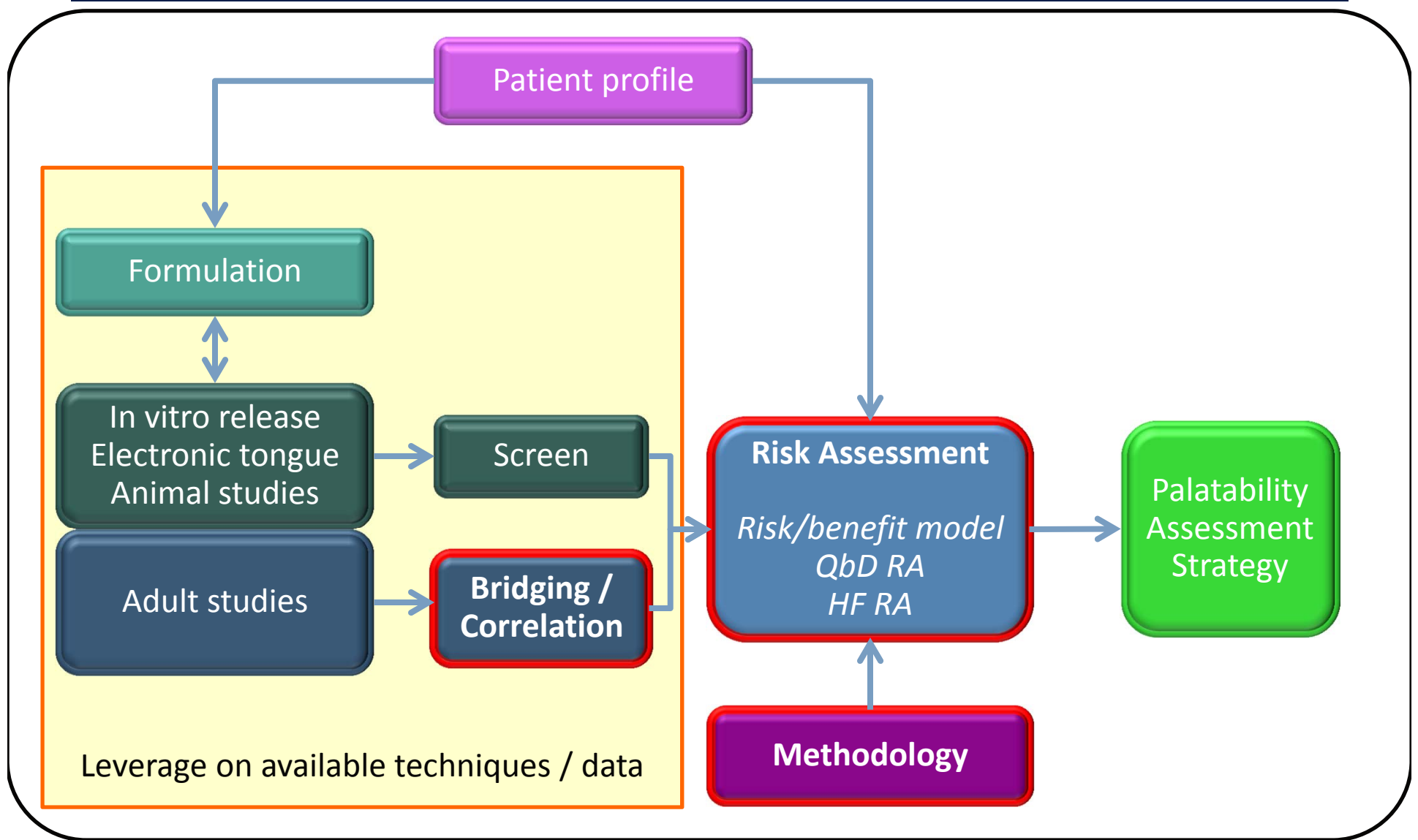


A benefit/risk approach
T. Sam, Int J Pharm 435 (2012) 115–123

Drug Product CQAs	Drug Substance Attributes								
	Solid State Form	Particle Size Distribution (PSD)	Hygroscopicity	Solubility	Moisture Content	Residual Solvents	Process Impurities	Chemical Stability	Flow Properties
Assay	Low	Low	Medium	Low	Low	Low	Low	High	Medium
Content Uniformity	Low	High	Low	Low	Low	Low	Low	Low	High
Dissolution	High	High	Low	Low	Low	Low	Low	Low	Low
Degradation Products	Medium	High	Low	High	Low	Low	Low	High	Low

QbD Risk Assessment

Food for Thought



abbvie

References

- A. Cram et al, *Int J Pharm*, 365 (2009) 1-3.; P. Kozarewicz, *Int J Pharm*, 469 (2014) 245-248.
- C.-P. Milne et al, *Clin Ther* 2008 30 (11) 2133-2145.
- C. Thompson et al, *TIRS*, 2015 49 (5) 647-658.
- Davies et al, *Journal of Pediatrics* 153 (2008) 599-604
- D.A. van Riet-Nales et al, *Arch Dis Child*, 2013, 98:725-731
- *Development of Paediatric Medicines: Points to consider in Pharmaceutical Development, Working Document AS/08.257/Rev.3 August 2011. Retrieved from http://www.who.int/medicines/areas/quality_safety/quality_assurance/Rev3-PaediatricMedicinesDevelopment_QAS08-257Rev3_17082011.pdf*
- E. Greimel et al, *Physiology & Behavior* 89 (2006) 261–269
- E.F. Davies et al, *Journal of Pediatrics* 153 (2008) 599-604
- EMA, *List of criteria for screening PIPs with regard to paediatric specific Quality issues and referring them to the PDCO FWG for discussion, EMA/174404/2013. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159380.pdf*
- EMEA/CHMP/PEG/194810/2005. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf
- *Guideline on pharmaceutical development of medicines for pediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2, 1 Aug 2013. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf*
- Illustrations and art courtesy of Microsoft clipart and Microsoft.com clip art image gallery
- J.A. Mennella et al, *Clin Ther*, 2013, 35 (8): 1225-1246

References (cont)

- *K Sikka et al, Pediatrics, 136 (1) 2015.*
- *L.A. Squires, TIRS, 47 (5) 533-541*
- *Mennela, Physiology & Behaviour, 152 (2015) 502-507; J. Mennella, Am J Clin Nutr 2014, 99 (suppl) 704S-11S.*
- *O'Hare, R. BBC plans to start using face-tracking technology to reveal how you REALLY feel about its shows. 11 February 2016. Accessed 11 May 2016. Retrieved from <http://www.dailymail.co.uk/sciencetech/article-3442201/BBC-plans-start-using-face-tracking-technology-reveal-REALLY-feel-shows.html>*
- *Opertech bio, Taste Technology. Assessed 11 May 2016. Retrieved from <http://www.opertechbio.com/#!t-station/oer2w>*
- *P. Kozarewicz, Int J Pharm, 469 (2014) 245-248.*
- *Report - Workshop on Paediatric Formulations for Assessors in National Regulatory Agencies EMA/432389/2011. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500121608.pdf*
- *S.E. Coldwell et al, Neurology 80 (Suppl 3) S20-24.*
- *T. Sam, Int J Pharm, 435 (2012), 115-123*
- *T. Vallet et al, EuPFI Conference, 2015*
- *Venables, R., Int J Pharm, 480 (2015) 55-62.*