

**M-CERSI Symposium:  
Challenges and Strategies to Facilitate Formulation  
Development of Pediatric Drug Products**

**Acceptability of Pediatric Formulations:  
Palatability and Swallowability  
FDA/CDER Office of Pharmaceutical Quality  
(Chemistry and Product Performance) Perspective  
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**Food and Drug Administration/Center for Drug Evaluation and  
Research/Office of Pharmaceutical Quality**

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**Disclaimer:** The material discussed in this document also include individual and collective opinions for generating discussion and are not being formally disseminated by the United States Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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# Outline

## **Desired State**

- Age-appropriate formulations for all age groups, all patients
- Are supported by methods that are sensitive, reliable and robust for optimizing pediatric formulations

## **Where we are**

### **(Challenges and Opportunities for Palatability and Swallowability)**

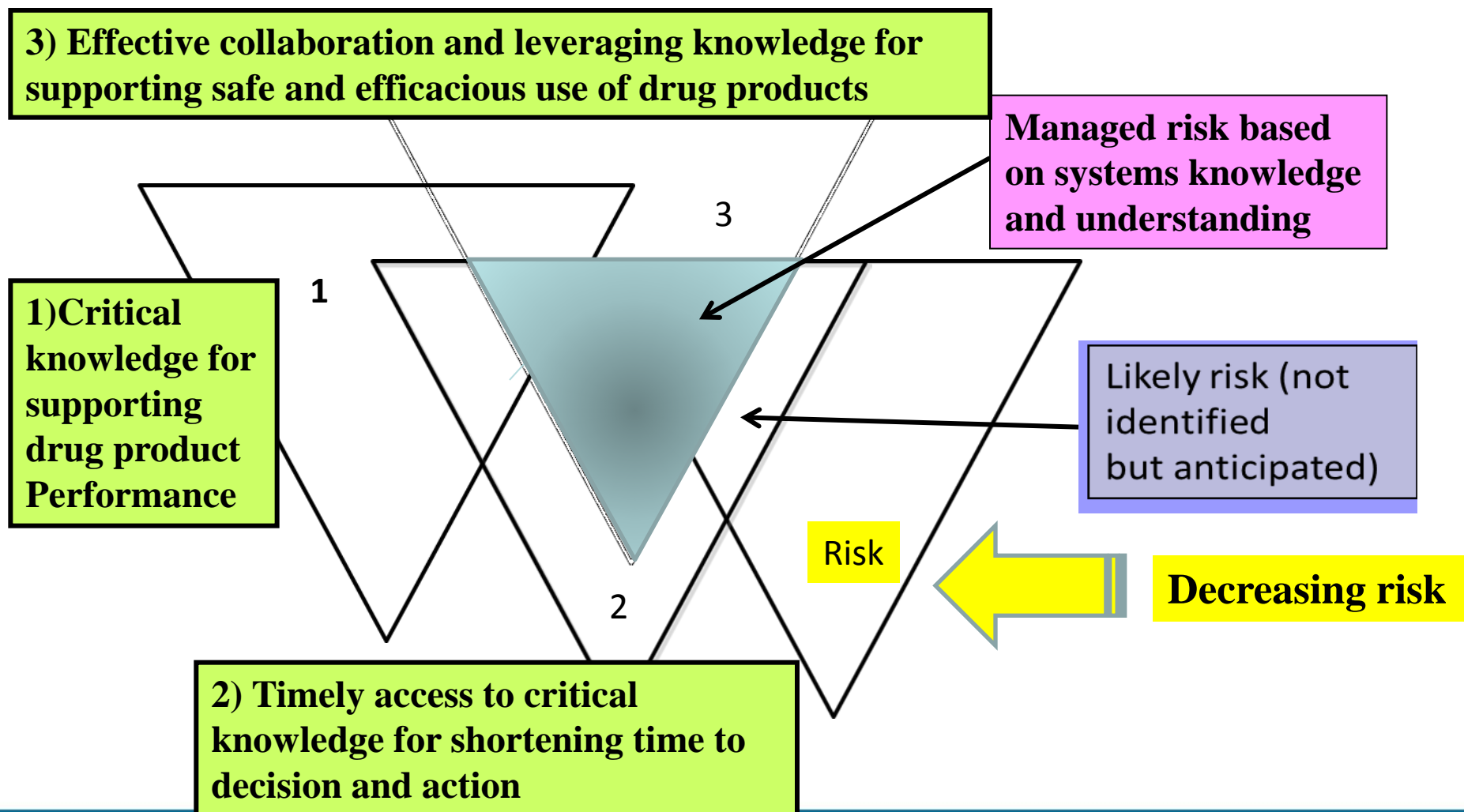
- Patient related
- Pediatric drug product attributes
- Methods
- Sharing and leveraging knowledge

## **Moving Forward**

Converging on the next steps to reach the desired state

# Drug Product Quality (Drug Product Performance)

## Understanding Patient Needs and Understanding and Managing Risk- Utilizing the three principals



# Where we are-- Challenges and Opportunities

## Critical knowledge\* related to pediatric patients

- **Patient needs and characteristics:**
  - Growth/maturation stage, acute or chronic indication/treatment, influence of disease states and other factors affecting drug exposure and patient experience
- **Patient response and preferences:**
  - cultural, age/growth- related, likely to vary over time
- **Training**
  - child's ability to learn
  - learned acceptance or rejection

\*: not an exhaustive list

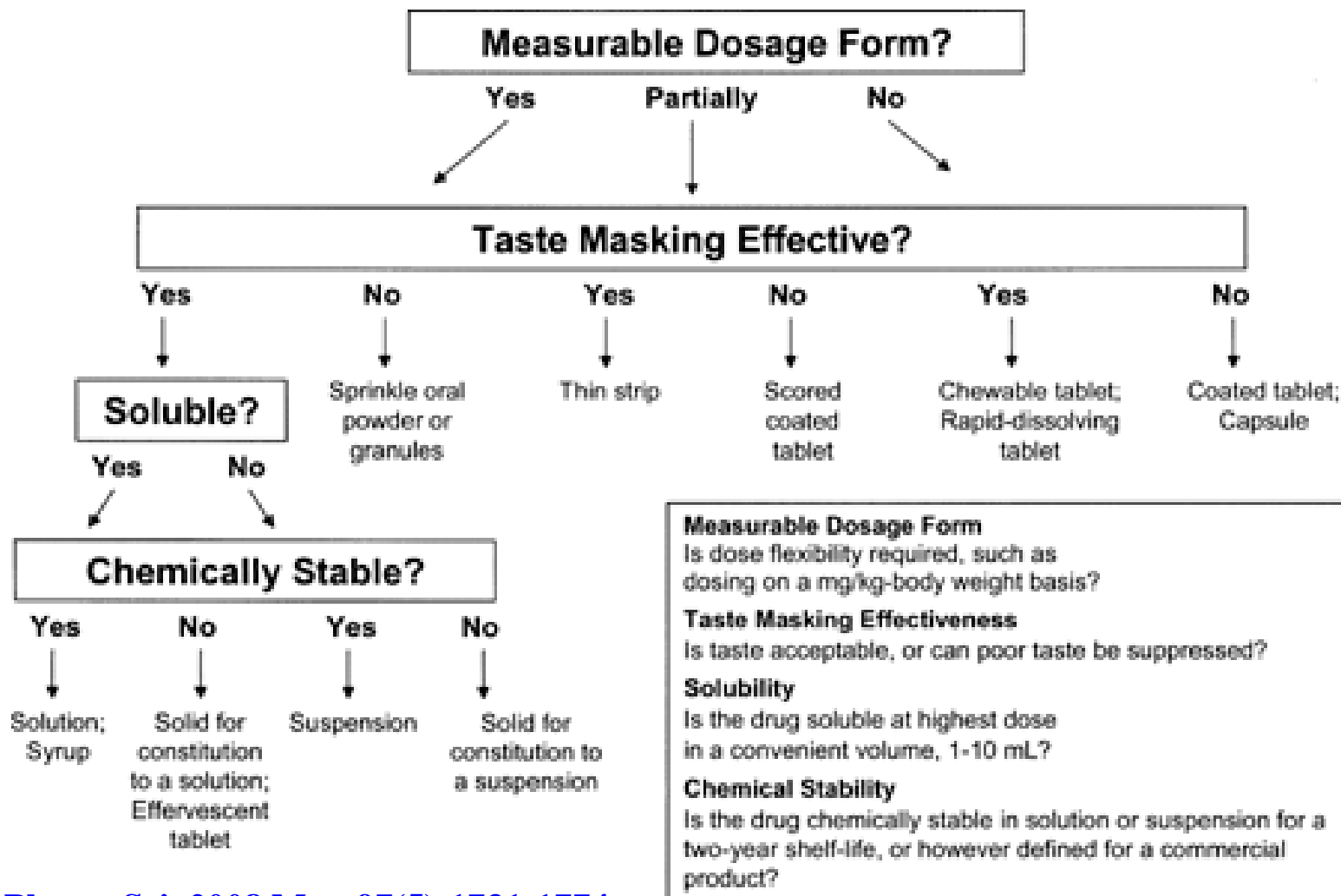
# Critical knowledge\* related to the oral pediatric dosage forms

- Age-appropriateness
- Dose accuracy and flexibility—for low doses and small volumes as well
- Size/shape/thickness appropriate for swallowing
- Drug product attributes for palatability
- Of acceptable taste, smell, texture (mouthfeel) for compliance/adherence
- If given in liquids and/or soft-foods, drug product per not compromised
- Formulation attributes (taste masking vs. taste concealing)



shutterstock - 125468438

# Flow Chart for Making Oral Dosage Formulations



J Pharm Sci. 2008 May;97(5):1731-1774.



# FDA Expectations for Oral Solid Dosage Forms for Pediatric Patients

- Easy to swallow
- Palatable
- Stable
- Can be dosed accurately (small volumes)
- Age-appropriate excipients (safety considerations)
- If vehicle is used for administration, liquid and/or soft food should be **acceptable** for use
- Suitable package for good compliance
- Clear identification when several strengths of the same product are presented
- Use/dosing instructions are clear and accessible



# FDA Expectations for Liquid Formulations for Pediatric Patients

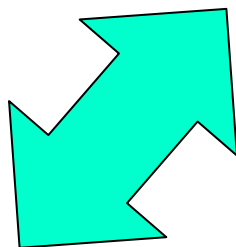


- Palatable (taste, texture, smell)
- Stable
- Proper Measuring Device
- Suitable Container/Closures
- Age-appropriate excipients (safety considerations)
- Use/dosing instructions are clear and accessible

Connecting the product with the patient

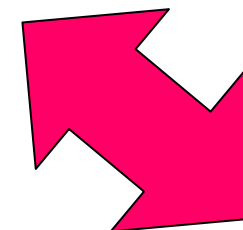
## Mouthfeel

(includes taste, smell, texture, palatability, swallowability assessments– numerous mouthfeel wheels)



**Translates the drug product for the patient**

- Can be performed by in vitro methods and sensory panels



**Develops relationship between the product and the consumer (such as in food science)**

## Some methods for assessing acceptability

- Quantitative for taste-masking
  - Analytical methods (e.g. measuring drug release for screening (for bitterness), coating efficiency, monitoring stability of taste, etc.)
  - In vitro taste sensors (electronic tongue, e-tongue) and hybrid approaches
- Preference, liking assessments (questionnaires)
  - Sensory assessments in taste panels
  - Facial and/or verbal hedonic scales (various scales, including 5-, 9- or 11-point)

# Sensory Testing and Analysis

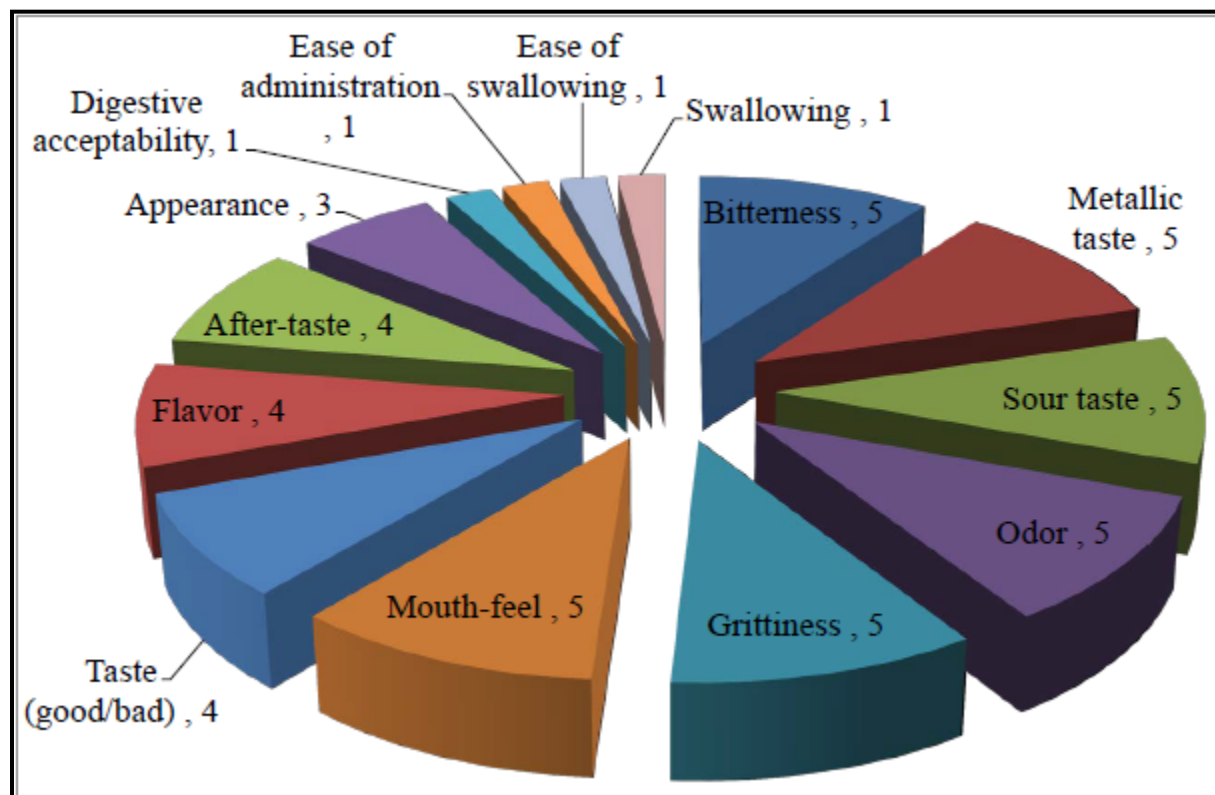
<b>Test for</b>	<b>Evaluators</b>	<b>Methods</b>
Differences between products	Experienced with test methodology	a) Triangle b) Duo-trio c) Directional
Acceptability	Target consumers	a) Monadic b) Paired
Preference	Target consumers	a) Monadic b) Paired c) Ranking
Descriptive analysis	Highly trained panel calibrated to reference standards	a) Quantitative b) Spectrum

Summarized from “Food Texture Design and Optimization”  
edited by Y.L. Dar and J.M. Light published by John Wiley & Sons, Ltd. 2014

*What is the experience with palatability and swallowability studies?*

# Sifting for Opportunities

From a 2013 survey on current practices in palatability and swallowability assessments—breakdown of positive responses (n=5) to organoleptic assessments— showing the type of assessments.



*(total responses, n=10)*

C.A. Thompson, D.P. Lombardi, P. Sjostedt, and L.A. Squires. 2013. Industry Survey on Current Practices in the Assessment of Palatability and Swallowability in the Development of Pediatric Oral Dosage Forms  
Therapeutic Innovation & Regulatory Science 47(5) 542-549

# Results of a systematic literature review of assessment of palatability and swallowability of pediatric oral dosage forms

**Purpose:** to identify

- 1) palatability and swallowability assessment scales in clinical trials
- 2) any potential relationship between palatability and adherence

**Period covered:** January 2008-March 2013

**Source:** 137 citations were identified (and 102 excluded)

  
**27** articles identified with primary clinical data on palatability  
(*qualified for the final full-text analysis*)



## Results of a systematic literature review (continued)

### Breakdown of the 27 articles:

Palatability assessment tools, n=2

Palatability only, n=19

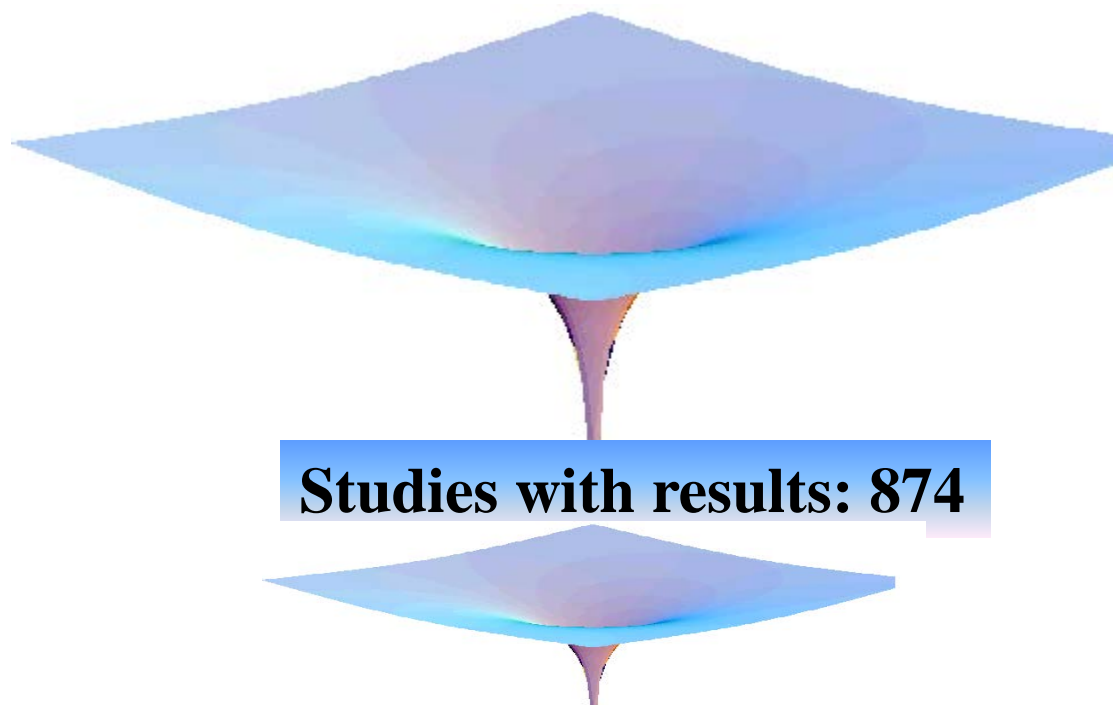
Palatability and adherence, n=6

### Findings:

- palatability assessed using two visual scales  
(not suitable for across-study comparisons)
- Limited evidence regarding correlation between palatability and treatment adherence

# Additional information in ClinicalTrials.gov?

**Pediatric studies: 7259**



**Studies with results: 874**

**Completed pediatric & palatability study with results: 2 suspension studies**

(None completed pediatric and swallowability study with results)

# Study 1

**Study design: Twice a day and given multiple days**

Total n <20, two age groups (< 5 years old and 5-18 years of age)

Taste assessment by the older patient group (Primary outcome):

Taste scores: 5 (very good taste)--1 (very bad taste).

Results (last dose): Median (range): 4.0 (2.0 to 5.0)

Acceptability grading by parents for the younger patient group (primary outcome):

Acceptability scores: 5 (very well)--1 (very badly).

Results: Median (range) 5.0 (4.0 to 5.0)

## Study 1 (Continued)

Palatability assessment by the older patient group (secondary outcome):

Palatability scores: 5 (very good), 4 (good), 3 (neither good nor bad), 2 (bad) and 1 (very bad)

**Results: Median (range)**

**Day 1:** 4.0 (3.0 to 5.0),

**Day 2:** 4.0 (2.0 to 5.0),

**Day 3:** 4.0 (2.0 to 5.0)

## Study 2

- Two age cohorts (different than in Study 1)
- Patients in the older age group directly responded to the questionnaire, and the caregiver/parents responded for the younger group
- Extended dosing

### Palatability Questionnaire

Q1) How Does This Medicine Taste? (5 options, 5: very good, 1: very bad)

Q2) How Does This Medicine Smell? (5 options, 5: very good, 1: very bad)

Q3) Based on Its Taste, Smell, and How it Felt in the Mouth, How Easy or Difficult Was it for You / Your Child to Take This Medicine Every Day

(5 Options: very easy, easy, neither easy or difficult, difficult and very difficult)

Q4) Would You/Your Child Have Preferred This Medicine to Have Been Flavored, e.g. Fruity (3 Options: yes, no and don't mind)

## ***Observations:***

- *Not many palatability and swallowability studies with methods and results are published*
- *Developing/making standardized methods and tools may help sharing and building on learnings, and may facilitate leveraging published acceptability (palatability, swallowability) studies.*

## ***Leveraging Opportunities***

- 1) *Mouthfeel from food science?*
- 2) *What would evidence-based palatability, swallowability assessment methods look like for pediatric oral dosage forms?*

# *What is oral processing and mouthfeel?*

# Oral processing

## Rheology/tribology

Particle size and shape (gritty, grainy, coarse)

Particle shape and orientation (fibrous, crystalline)

Juiciness

Fat content (greasy, oily)

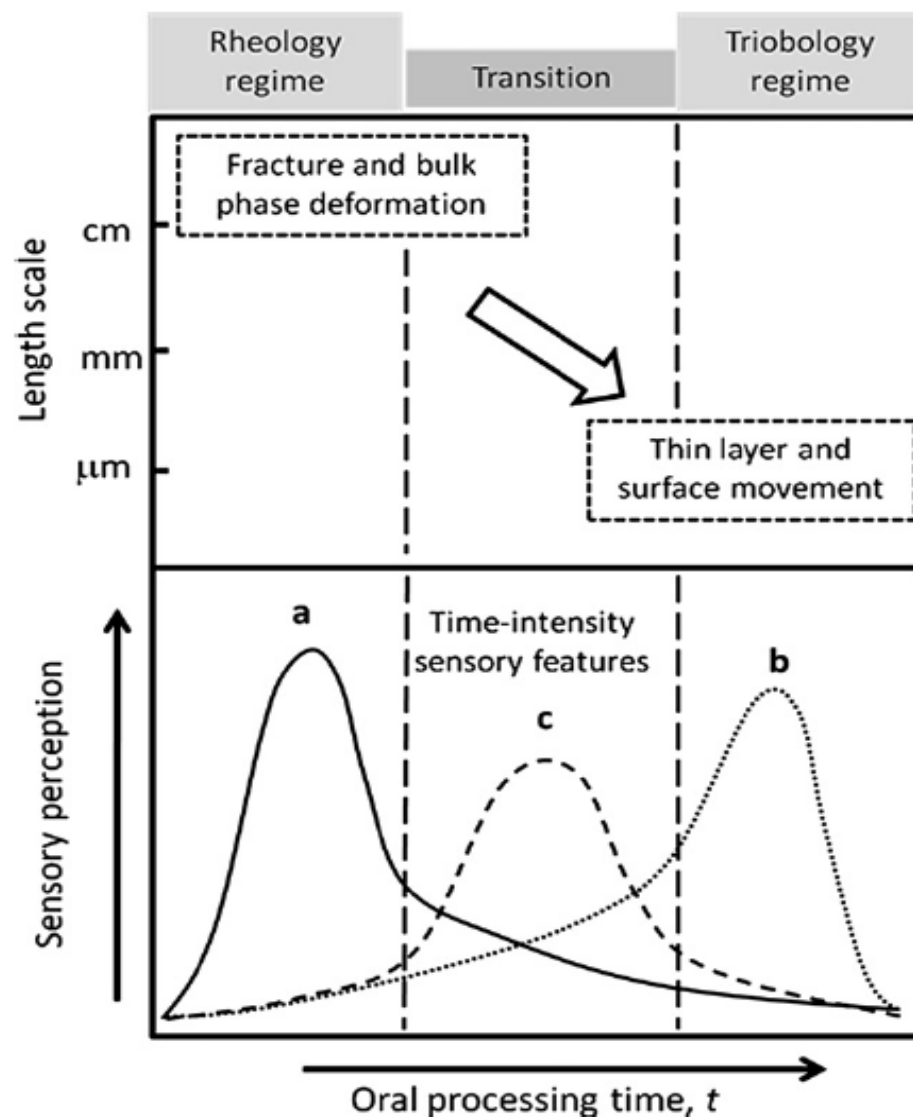
Creaminess

Slipperiness (slippery, smooth, rough)

Smoothness (smooth, rough)

## Tribology

Astringency



J. Chen and JR Stokes. Trends in Food Science and Tech. 2012, 25:4-12.

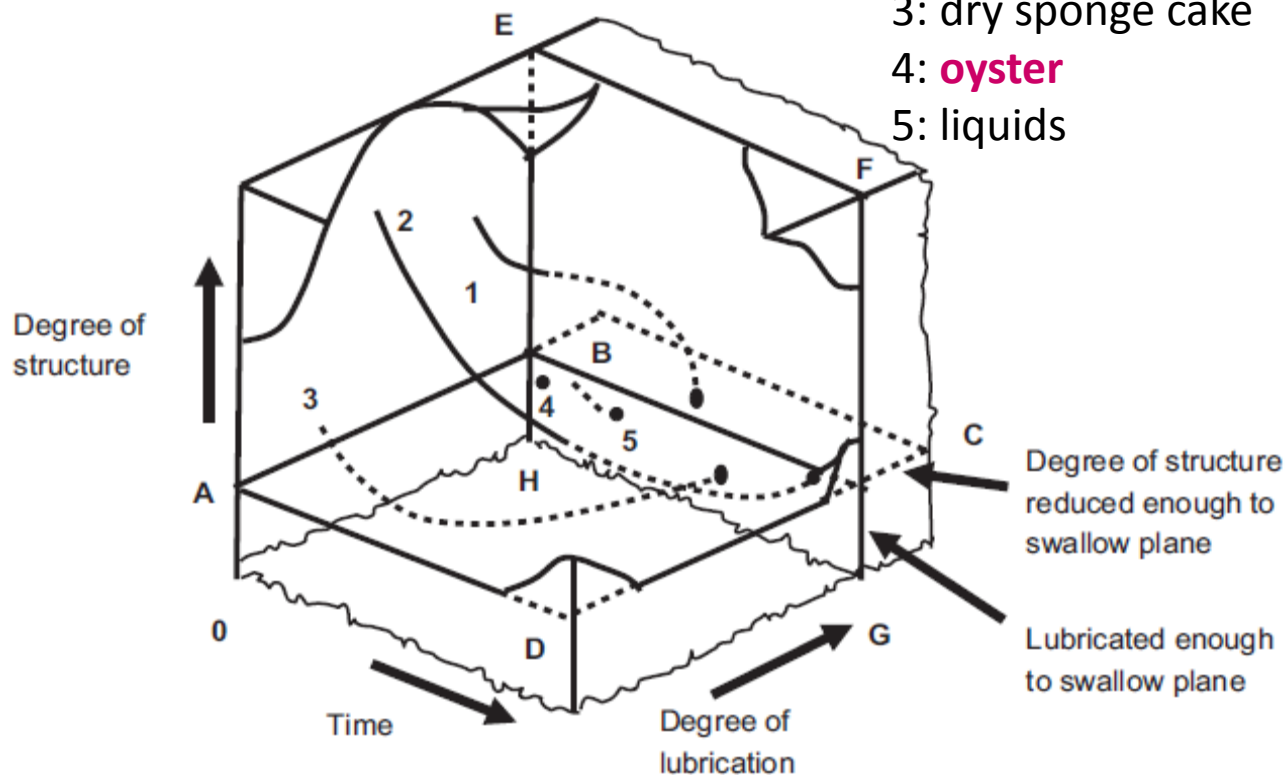


# “Mouth process model” for understanding mouthfeel

## Things that need to happen before swallowing:

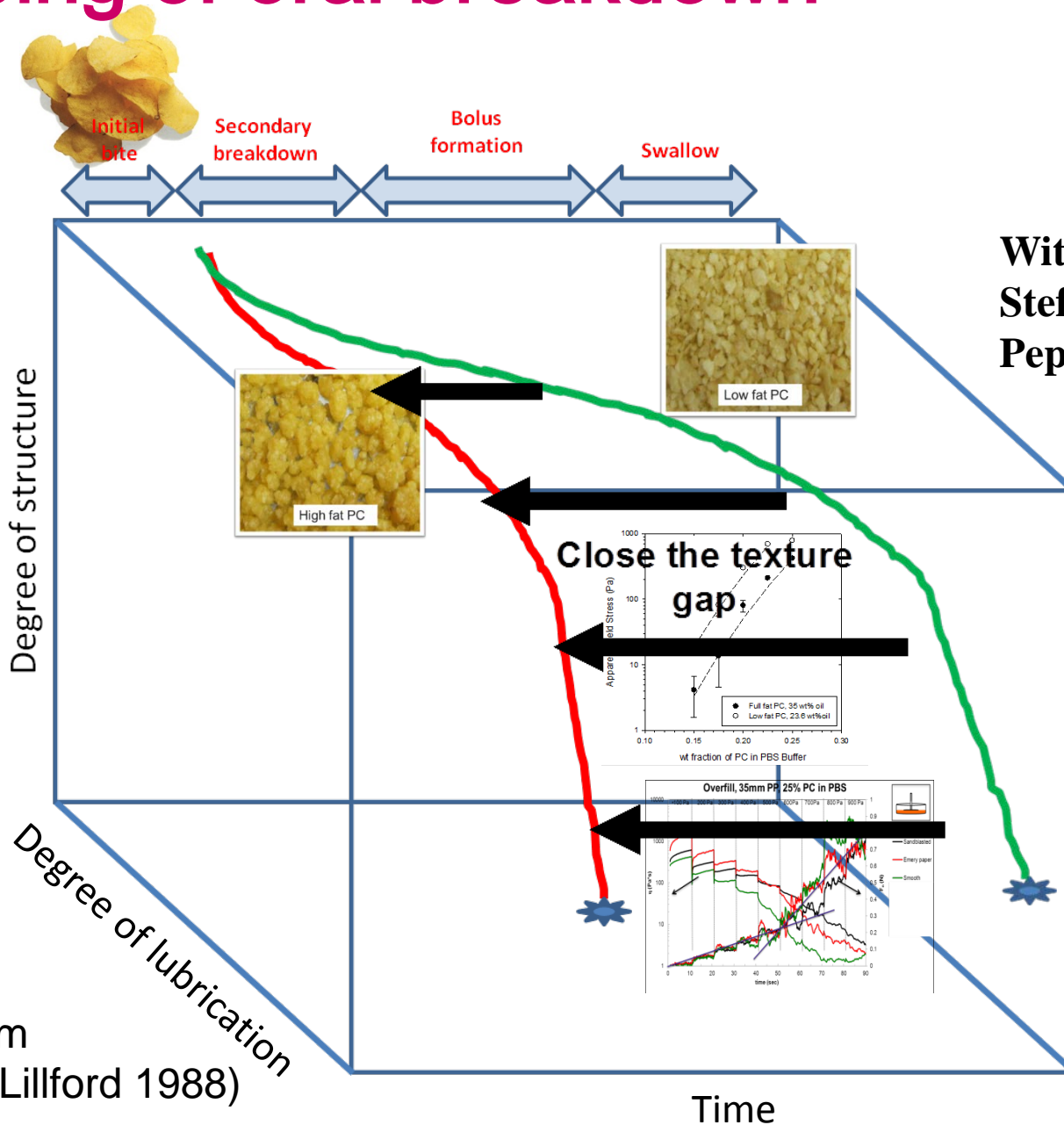
- 1) degree of structure of food must be reduced below the level of plane ABCD and
- 2) Its degree of lubrication must have crossed planed EFGH

- 1: Tender juicy steak,
- 2: tough dry meat
- 3: dry sponge cake
- 4: **oyster**
- 5: liquids



J. Chen. Food Hydrocolloids. 2009, 23: 1-25

# Mapping of oral breakdown



With permission from  
Stefan K. Baier, Ph.D.  
PepsiCo Research

(Modified from  
Hutchings & Lillford 1988)

# Reducing oil, sugar, and salt

Oil

Regular



30-40%



>70%



Sugar

Regular



Mid-cal 50%



Zero-cal



From  
Stefan  
K. Baier, Ph.D.  
PepsiCo  
Research

Salt

Regular



25%

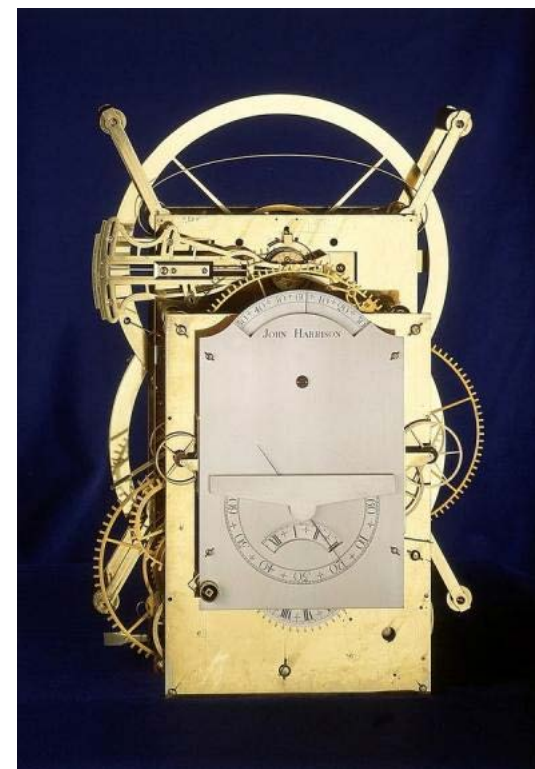


... while  
maintaining the  
same eating  
experience!

## *Ideas for standardizing methods and for identifying Critical Quality Attributes?*

*What if we could develop a “mouth process model” by age groups (taking into account various vehicles that may be used for dosing) and establish a texture target (as the red line in Slide #26) that can serve as a reference point for the study and across-study comparisons?*

*(Can we leverage from the food science and engineering?)*



## Moving Forward (Converging for the Next Steps)

- Explore and create possibilities for developing learning and confirmatory methods and tools for palatability and swallowability assessments.
- Identify critical quality attributes for achieving the intended drug product performance (e.g. mouthfeel) and support development of best practices for age-appropriate formulations
- Create a learning and collaborative environment for advancing pediatric formulations.

## Additional References

1. JK Lorenz, JP Reo, O Hendl, JH Worthington, VD Petrossian. 2009. Evaluation of a taste sensor instrument (electronic tongue) for use in formulation development. *Int J Pharm.* 367:65–72. doi:10.1016/j.ijpharm.2008.09.042.
2. Y Tahara and K Toko. 2013. Electronic Tongues – A Review. *IEEE Sensors Journal*, 13: 3001-3011.
3. R Latha and P Lakshmi. 2012. Electronic Tongue: An Analytical Gustatory Tool,” *J Adv Pharm Tech Res* 3: 3-8.
4. K Woertz, C Tissen, P Kleinebudde, J Breikreutz. 2011. Taste Sensing Systems (Electronic Tongues) for Pharmaceutical Applications,” *Int. J. of Pharm* 417: 256-271.
5. M Pein, XD Gondongwe, M Habara, G Winzenburg. 2014. “Interlaboratory testing of Insent e-tongues. *Int J Pharm* 469: 228–237
6. YL Dar, JM Light. *Food texture design and optimization*. Oxford: Wiley-Blackwell; published in 2014.
7. JS Chen, JR Stokes. 2012. Rheology and tribology: two distinctive regimes of food texture sensation. *Trends Food Sci Technol.* 25:4–12. doi:10.1016/j.tifs.2011.11.006.



## Additional References

8. JR Stokes, MW Boehm, SK Baier. 2013. Oral processing, texture and mouth feel: from rheology to tribology and beyond. *Curr Opin Colloid Interface Sci.* 2013;18(4):349–359
9. LA Squires, DP Lombardi, P Sjostedt and CA Thompson. A systematic literature review on the assessment of palatability and swallowability in the development of oral dosage forms for pediatric patients. *Ther Innov Reg Sci* 2013;47(5):533–41.
10. JA Mennella, GK Beauchamp. 2008. Optimizing Oral Medications for Children. *Clin Therap* 30: 2120-2132
11. D. A. vanRiet-Nales, J.A. Ferreira, A. F.A.M. Schobben, B.J. de Neel, T. C.G. Egberts, C.M.A. Rademaker. Methods of administering oral formulations and child acceptability. *Int J Pharm* 2015, 491: 261-267
12. Daniel Bar-Shalom. Chapter 13: The Challenge of Automated Compounding. In *Pediatric Formulations: A Roadmap*. Editors: Daniel Bar-Shalom and Rose Klaus. Published by aapspress and Springer. 2014. New York, Heidelberg, Dordrecht, London