Pediatric Formulation Development: Challenges of Today and Strategies for Tomorrow

Formulations:

Pediatric Patients Inspiring and Shaping Drug Development

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Some Topics for Generating Discussion

1) Pediatric patients inspiring change through

- Advances of age-friendly pediatric formulations and dosage forms, potential impact on global health care
- Advancing alternate/innovative approaches for better assessment of the patient needs, and for knowledge generation/sharing/leveraging for labeling of drug products for pediatric patients (e.g., alternate study designs such as enrichment study designs, as will be discussed on Day 2 in the clinical session).
- Engaging multispecialty/multidisciplinary stake-holders for carving a path forward with new questions, tools/technologies, methodology and ultimately, new/modified dosage forms

2) Pediatric patients are shaping drug development

- **What does the future of pediatric drug development look like?**

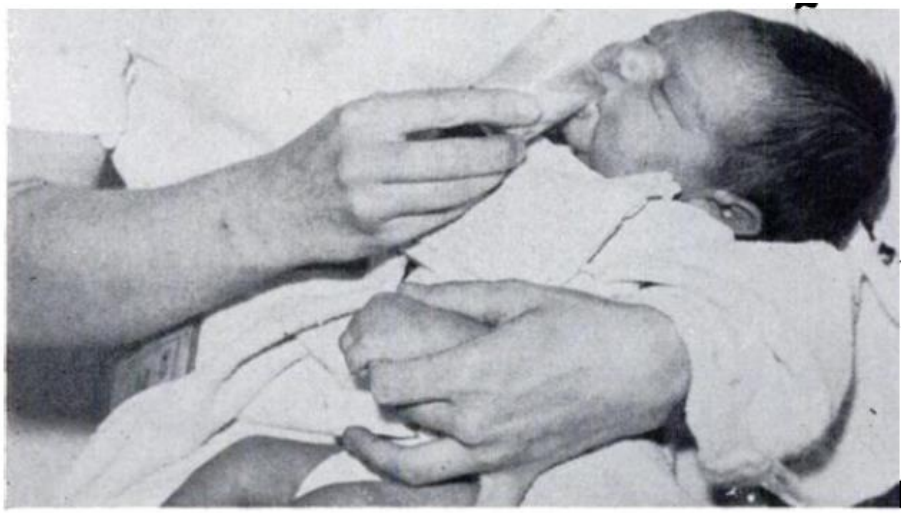
Outline of my talk

1. Discussion topics
2. Outline
3. The subgroup topics in the formulation session
4. How it all started: The beginnings and where we are
   - The timeline of regulations in USA and impact on pediatric drug development
5. The global journey continues: Going from complex to simple and successful outcomes
6. Focusing on the patient, drug product and their interface
   - What do we know about the pediatric patients (particularly, the youngest)
   - How can we optimize pediatric dosage forms? Learning tools, methods?
   - Learning from experience and generating knowledge as a community
7. Other Highlights and Looking Ahead

Topics in the Formulations Subgroups

- Excipients
  - Challenges with novel excipients and opportunities
- Acceptability of oral dosage forms
  - Expectations and methodology considerations
- Multi-particulates/devices
  - Possibilities: Now and in the future

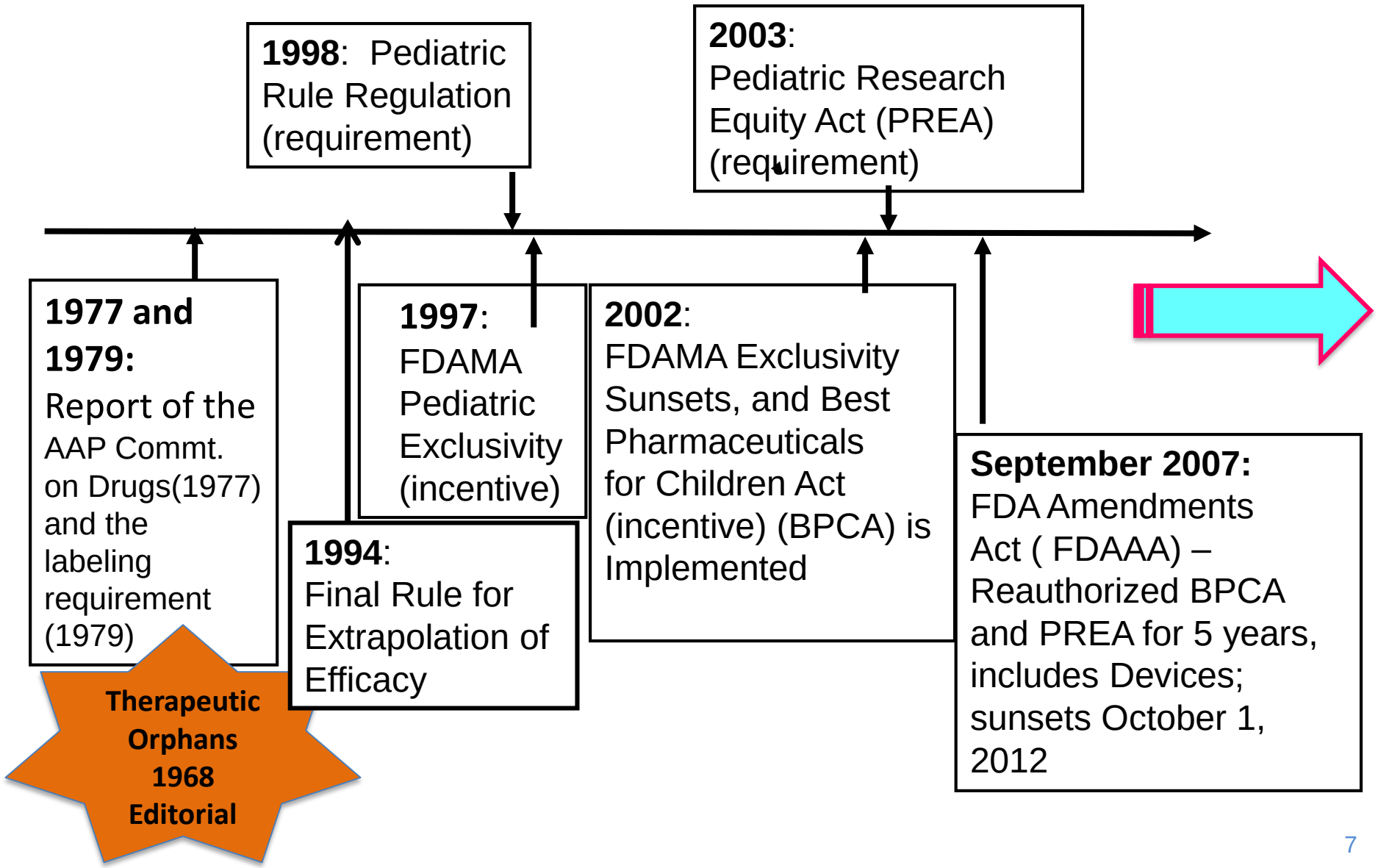
How did it all start: Where we were



Robert C. Freeden "Cup feeding of newborn infants". Pediatrics, Vol.1 , pages 544-548, November 1948

Harry Shirkey, "Editorial Comment: Therapeutic Orphans ", The Journal of Pediatrics, Vol. 72, No. 1, p119-120, 1968

Timelines of Pediatric Requirements and Rules and Regulations (1977-2007)



Timelines of Pediatric Regulations (2007-2019)
(continued)

July 9, 2012: FDA Safety and Innovation Act (FDASIA) signed into law, BPCA and PREA become permanent and other amendments

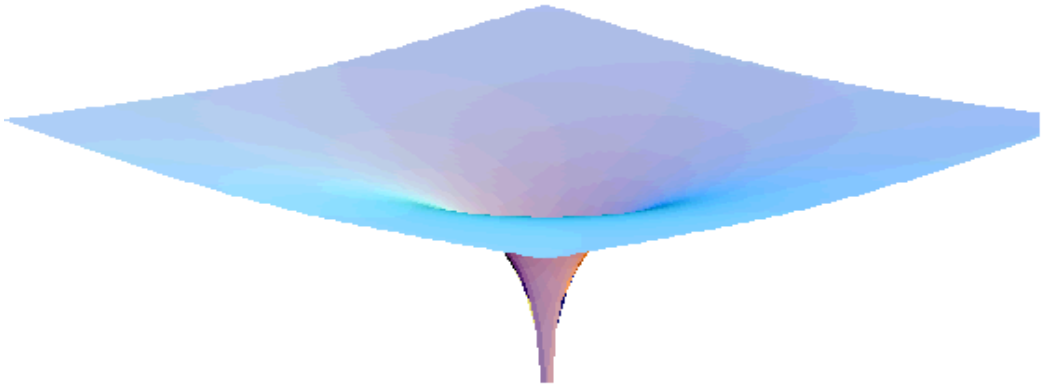
September 27, 2007: FDA Amendments Act (FDAAA) – signed into Law : reauthorized BPCA and PREA; Sunset is October 1, 2012

August 18, 2017: FDA Reauthorization Act (FDARA) singed into Law.
Title V– Pediatric Drugs and Devices
Title VI– Reauthorizations and Improvements Related to Drugs, sunsets October 1, 2022
https://www.congress.gov/115/bills/hr2430/BILLS-115hr2430enr.pdf

Research to Accelerate Cures and Equity for Children (RACE) Act: comes into effect August 18, 2020

Where we are: the global journey continues

Tireless efforts and commitment of many for improving health and well-being of children (via many organizations, collaborations)



Path: Going from complex and uncertainty to simple and successful outcomes

Some websites:

https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm

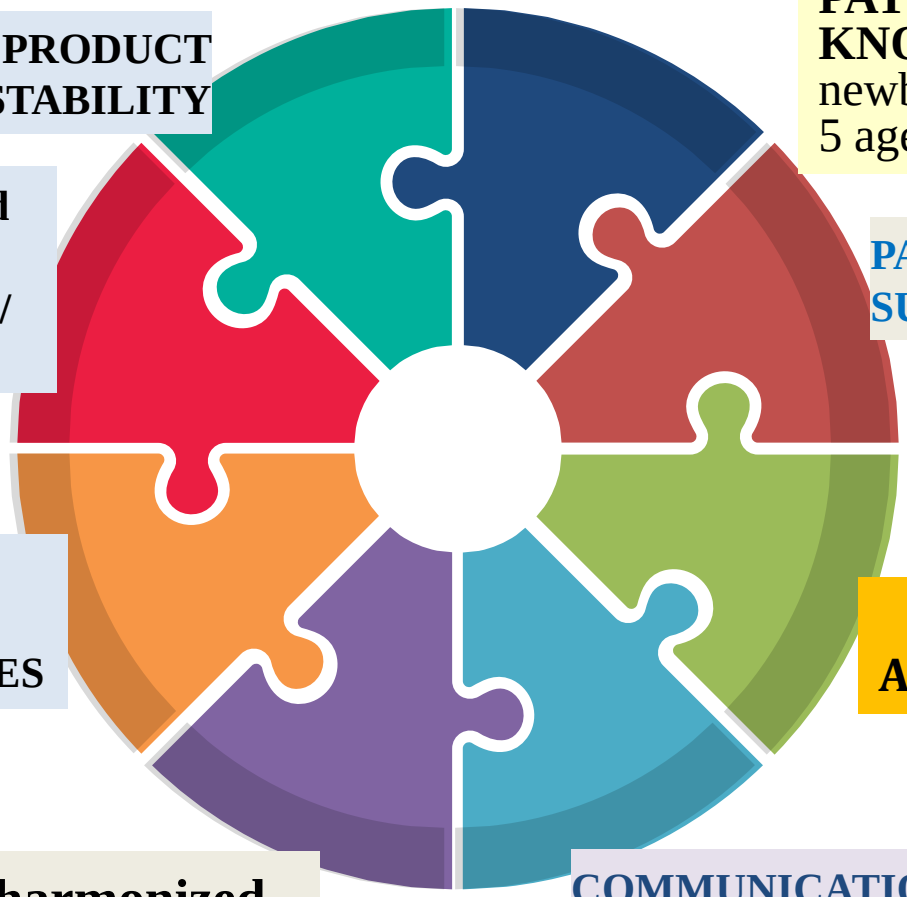
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

https://ec.europa.eu/health/human-use/paediatric-medicines_en

https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Integrating Multidisciplinary and Multidimensional Expertise: Patient-Friendly Formulations



PRODUCT STABILITY

PATIENT KNOWLEDGE: newborn to adolescents: 5 age groups

DOSAGE FORMS and FORMULATION CHARACTERISTICS/ COMPOSITION

PATIENT NEEDS/ SUITABILITY

DOSING ACCURACY and DEVICES, MEASURES

ACCEPTABILITY

Standardized/harmonized, reliable, reproducible Techniques and methods (across use areas)

COMMUNICATION OF CLEAR USE AND PREPARATION INSTRUCTIONS

Going from Complex to Simple and Successful Outcomes: Some Considerations

- **Knowledge on the targeted patient population** needs and patient characteristics (growing child, pgenomic make-up) and understanding of the disease progression and response to proposed therapy and time- and maturation-dependent changes on PK, PD of the drug and its intended delivery profile
- **Knowledge on drug product and its intended in vivo performance** with "predictive" methodology
- **Optimizing the patient and drug product interface** (which will include broader accessibility of patients to therapy and adherence to prescribed treatment)

Working from patient related considerations

1) Unique patient characteristics (ranging from daily liquid intake, feeding patterns, meals/diet, GI physiology and GI environment for orally administered drugs)
2) Patient preferences (such as mouthfeel, and texture of the dosage form)
3) Knowledge generation and leveraging (assumptions and methodology)
4) Framing questions for developing in vitro methods mimicking in vivo conditions (e.g. learning or confirming methods)

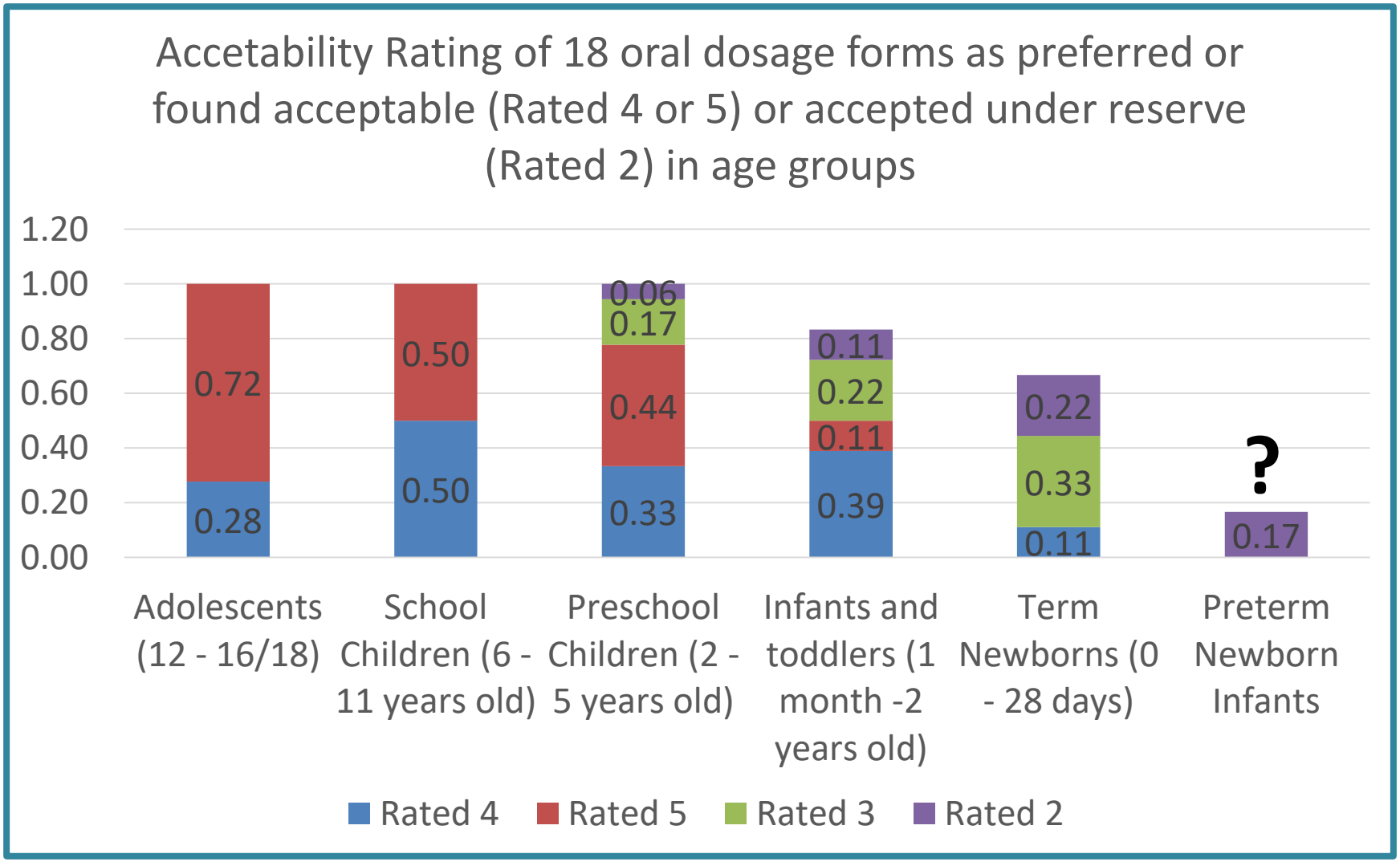
Age-Appropriate/Friendly Formulations: Possibilities?

Adult formulation, dosage form
And experience

Scaled down
for pediatric
patients

Quality Target Product Profile
Driven (based on patient needs)

What's our Experience?



Breitkreutz 2008

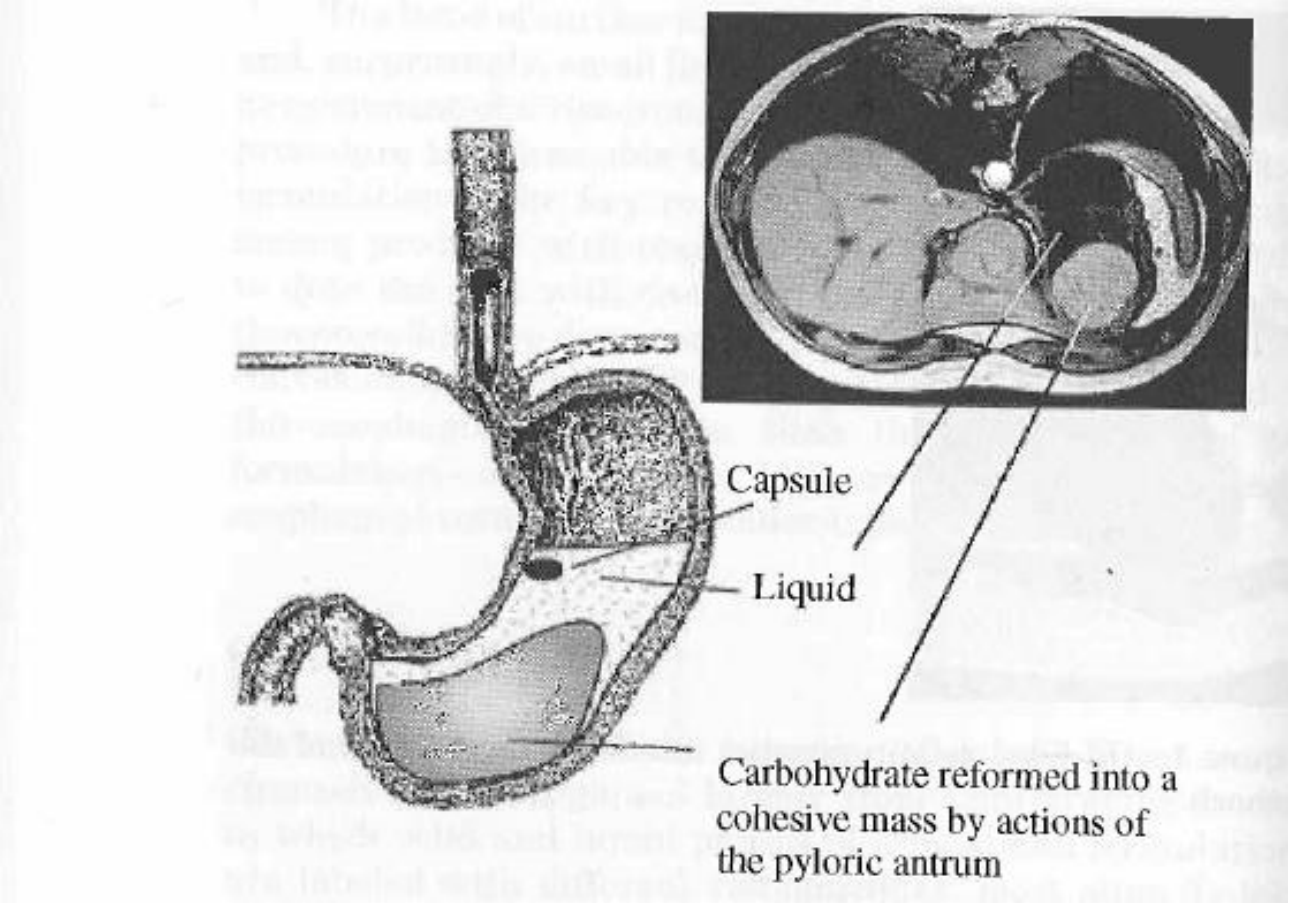
Typical FDA Expectations for Pediatric Formulations

- If oral, palatable (taste, texture, smell)
- Suitable for clinical use conditions
- Drug delivery profile and bioavailability are consistent with the intended therapy
- Stable
- Proper Measuring Device
- Suitable Container/Closures
- Age-appropriate excipients (safety considerations)
- Robust/reliable commercial manufacturing process
- Use/dosing instructions are clear and accessible

For Optimizing Drug Product Performance to Meet the Targeted Patient Population Needs

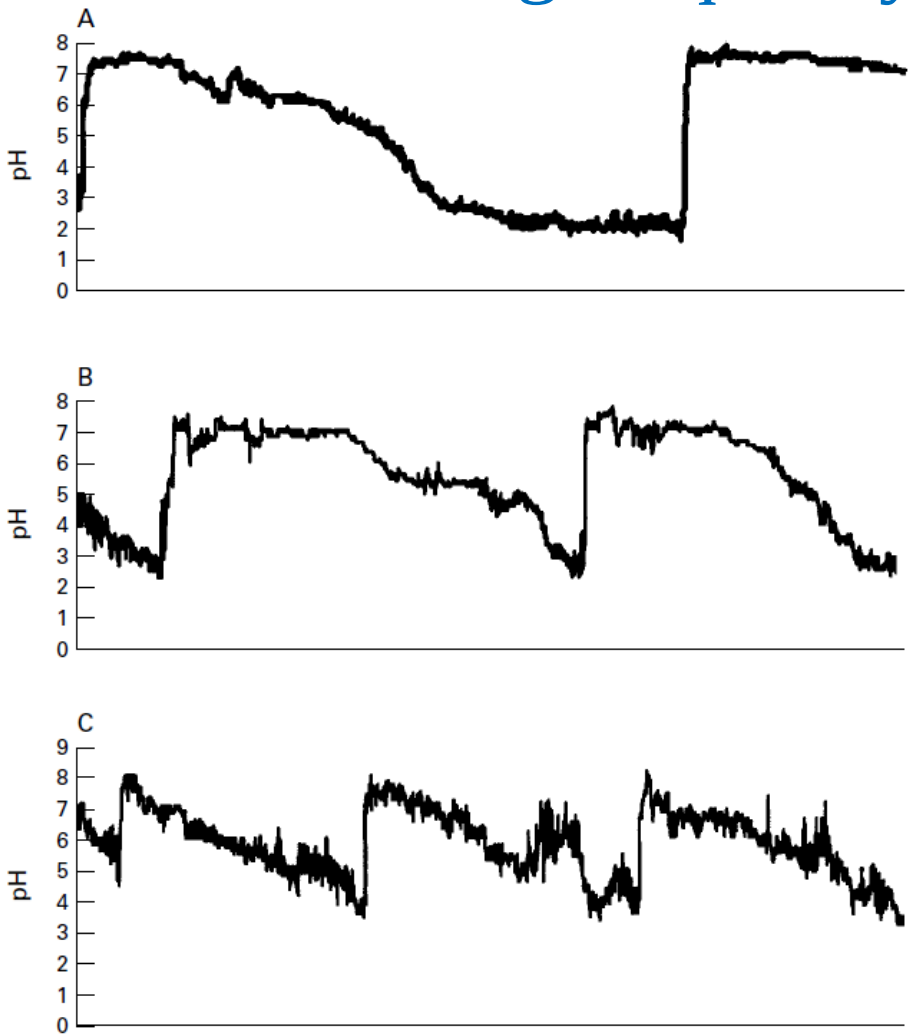
Considerations for Mimicking in vivo conditions:
How changes in gastric contents and other factors such as feeding frequency, digestion of meals, stomach emptying rate can affect solubilization and "bioaccessibility" and possibly, bioavailability?

What would be the effect of feedings (baby formula or milk) on drug absorption in pediatric (neonate and young infant) patients?



Reference: Wilson and Kelly in Pharmaceutical Dissolution Testing, Eds. J. Dressman and J. Kramer, Publisher: Taylor and Francis Group, NY, 2005, page 102

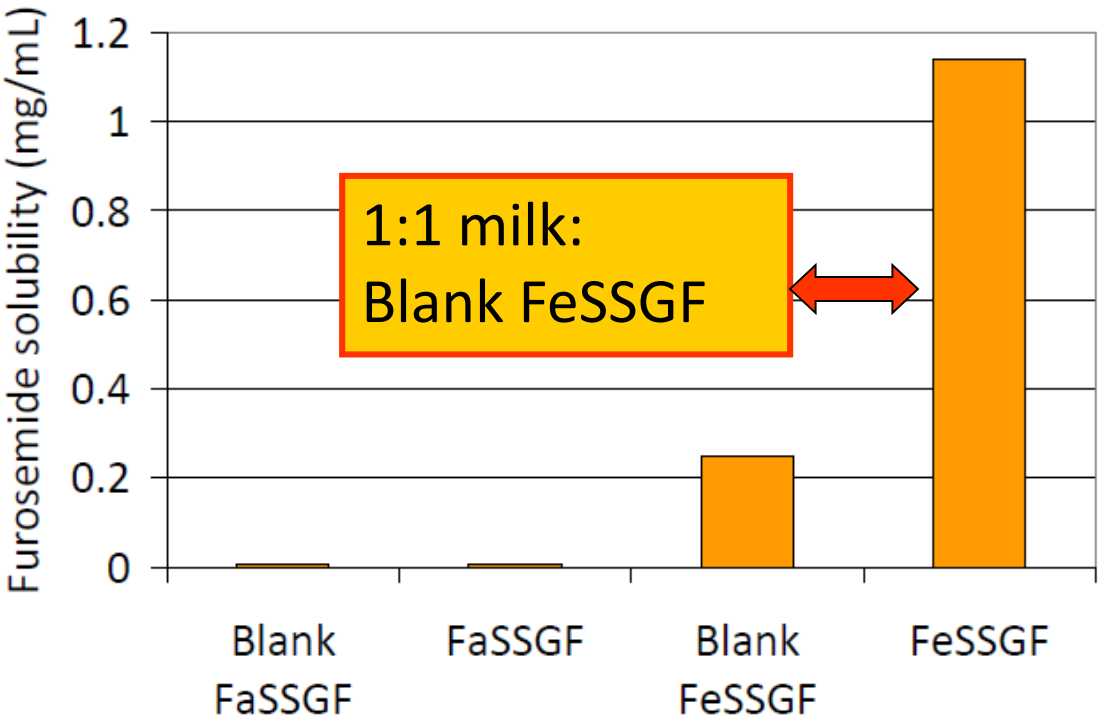
Feeding frequency and gastric pH



Gastric pH records as 6 hour intervals:
A)4 hourly feeds
B) 3 hourly feeds
C) 2 hourly feeds

Reference: D.J. Mitchell, B.G. McClure, T.T.J. Tubman, "Simultaneous monitoring of gastric and oesophageal pH reveals limitations of conventional oesophageal pH monitoring in milk fed infants", Arch. Dis. Child,2001, 84: 273-276

Furosemide Solubility in Simulated Gastric Media



FaSSGF (Fasted-State Simulated Gastric Fluid, pH 1.6) and FeSSGF (Fed State Simulated Gastric Fluid, pH 5), and corresponding blank buffers (without surfactant)

Reference: From the 2011 AAPS poster presentation of Sarah Gordon, Anette Muellertz and others

Patient and Drug Product Interface: Approaches for assessing “acceptability”

Some methods for assessing acceptability with different degrees of "support"

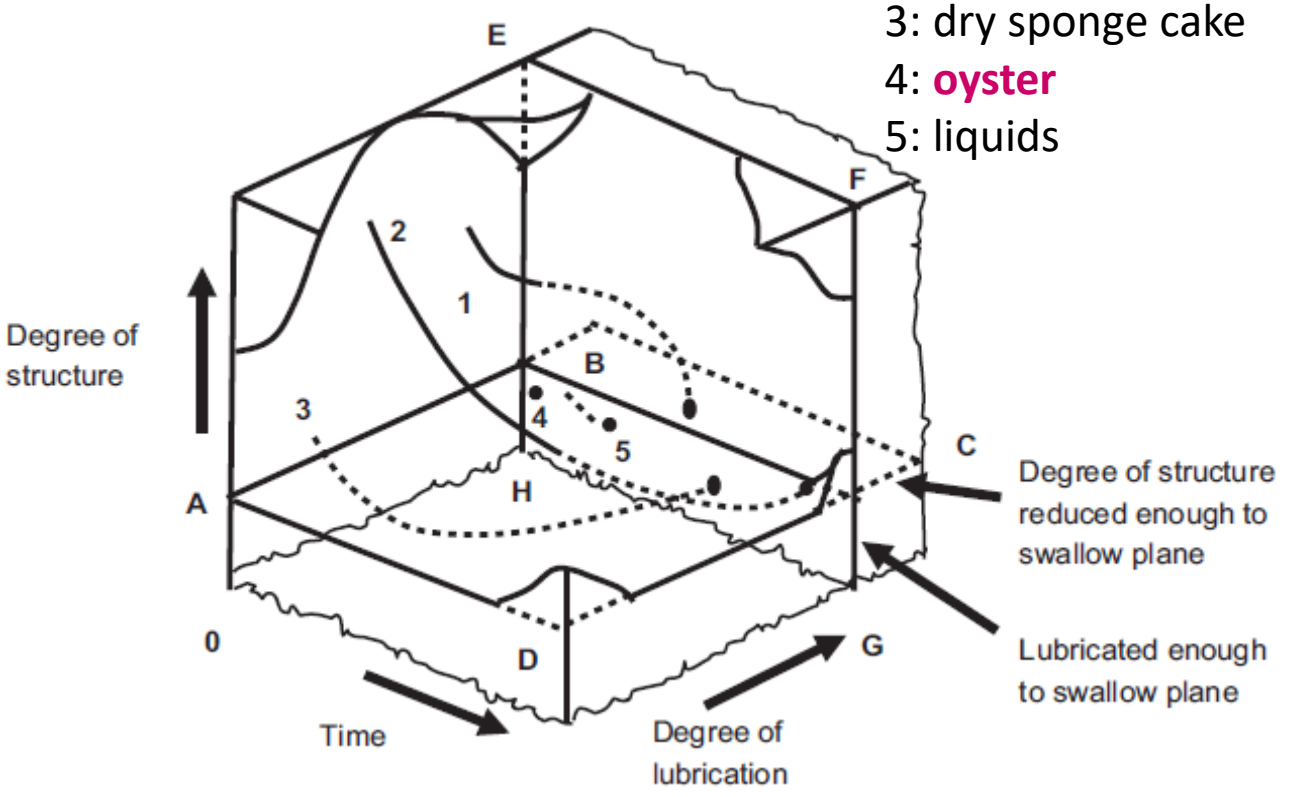
- Quantitative for taste-masking
  - Analytical methods (e.g. measuring drug release for screening (for bitterness), coating efficiency, monitoring stability of taste, etc.)
  - In vitro taste sensors (electronic tongue, e-tongue) and hybrid approaches
- Preference, liking assessments (questionnaires)
  - Sensory assessments in taste panels
  - Facial and/or verbal hedonic scales (various scales, including 5-, 9- or 11-point)
- Mouthfeel assessments: tribology (rheo-tribology)
  - using a rheometer configured as a tribo-rheometer for collecting coefficient of friction measurements as a function of sliding speed, highlights the differences in mouthfeel of the products. Reference.

"Mouth process model" for understanding mouthfeel

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

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



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

Ideas for coatings/acceptability?

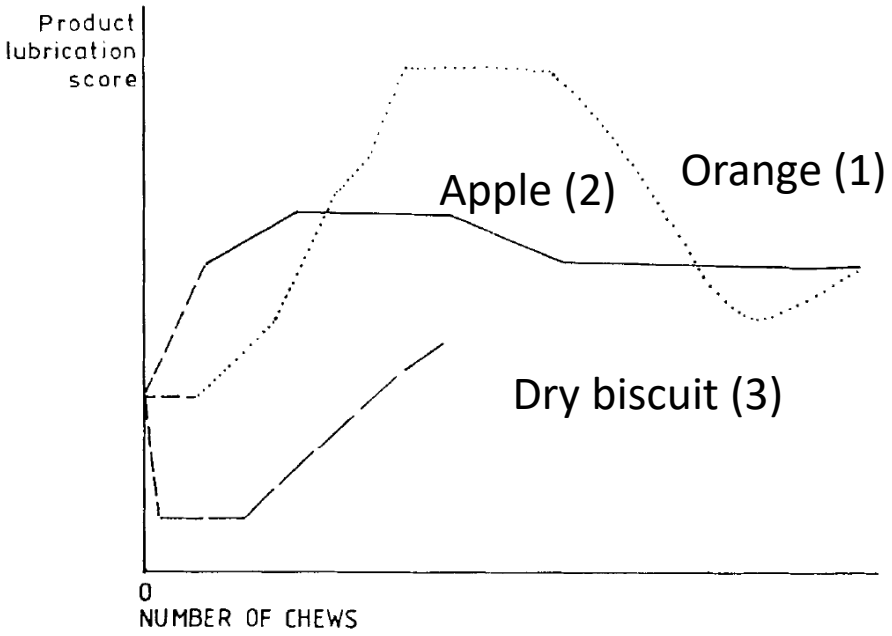


FIG. 2. CHANGE IN PERCEIVED PRODUCT LUBRICATION DURING PROGRESSIVE CHEWING

Three types of product:

1) Lubricant expressing product (e.g. orange)
2) Equilibrium juiciness product (similar to apple, always will seem moist)
3) Water absorbing product (e.g. dry biscuit)

From the Hutchings and Lillford model----- the lubrication process for "classifying" products

Other Highlights

- Accessibility to pediatric medicines and adherence to the recommended treatment, ultimately, affects all and can result in significant global health benefits.
- Definition of "Adherence/compliance" by a 5 year old preschooler:
  - 'medicine that's fun and tastes yummy- like lollipops wrapped in Disney princess paper'.
- Addressing "complexity" in the context of development of pediatric medicines, requires multidisciplinary, multispecialty and multidimensional collaborations and can lead to innovations, and advances in methodology, technology, best practices and more.
- Building communities build strong partnerships (based on conversations/reflections of some of us) and can result in greater benefit for all stake-holders including pediatric patients.

Looking Ahead

- Continuing to build on the momentum
  - Ushered in by the pediatric patients and stake-holders inspiring change and advances in development of age-friendly/appropriate pediatric dosage forms/formulations

- Advancing as a community
  - Expanding resources for greater benefit, transdisciplinary learning (benefiting from others' experiences/learnings)
  - Creating "open space" for innovative approaches and innovations

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- Many other FDA and non-FDA Colleagues
- Ms. Ann Anonsen
- The pediatrics community

Additional Slides For Interest

From the Journal of Texture Studies, 19(2): 103-115, August 1988, DOI: 10.1111/j.1745-4603.1988.tb00928.x

The Perception of Food Texture – The Philosophy of the Breakdown Path.

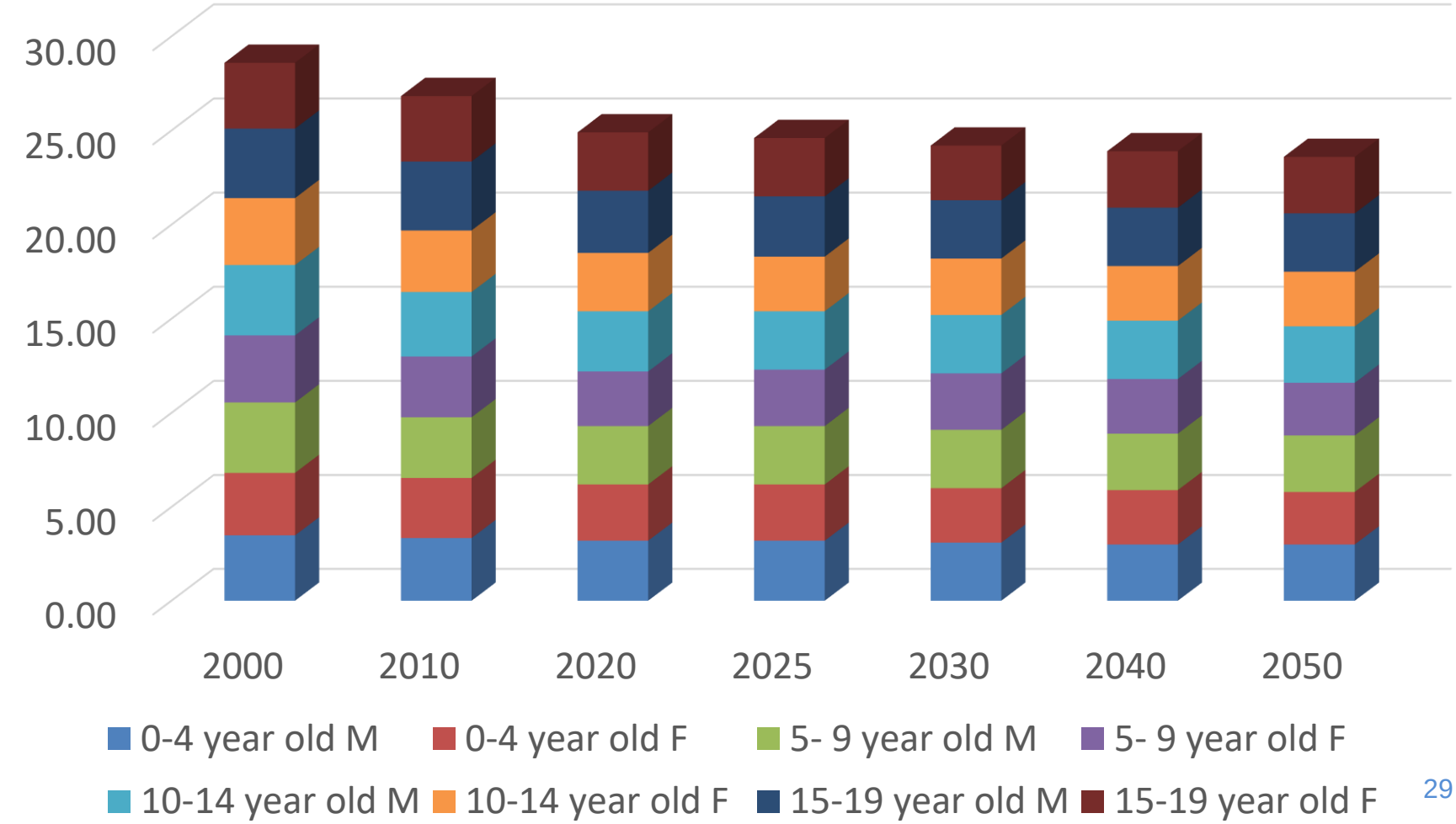
J.B. Hutchings and P.J. Lillford

cut/paste from the abstract

The present paper emphasises that texture perception is a dynamic sensory monitor of changes made to a food by processes occurring in the mouth. A general three dimensional model applicable to foods is postulated with ''Degree of Structure'', ''Degree of Lubrication'' and ''Time'' as its axes. As each food is changed in the mouth, it describes its own ''Breakdown Path'' throughout the three dimensions. This approach is seen as the start of a general hypothesis for the physics and psychophysics of mastication.

US Population: Male and Female Children in Age Groups as a Percentage of total population (both sexes and all ages)

Census data: 2000 and 2010, Projections: 2020, 2025,2030, 2040, and 2050

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