# Patient Centric Pediatric Product Development: A Caregiver Perspective

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PQRI WORKSHOP

MIDD Approaches in Pediatric Formulation Development

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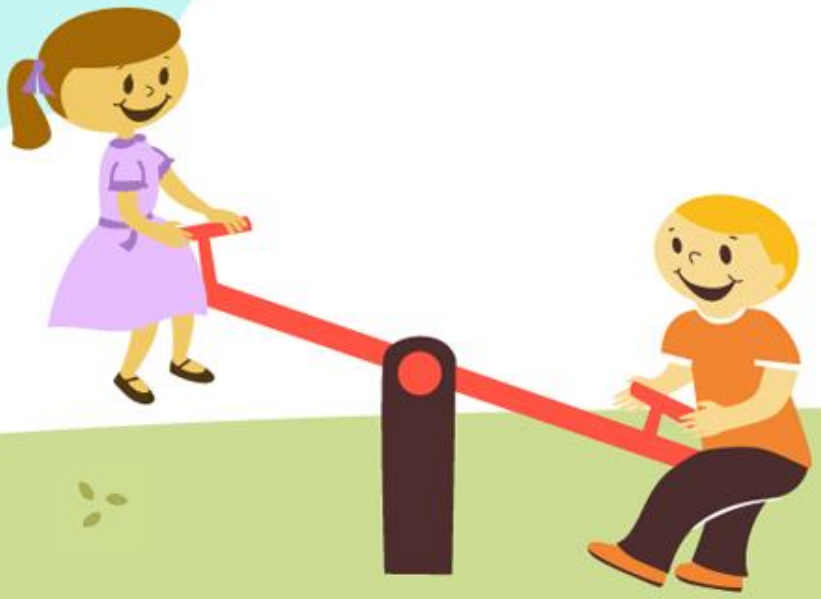
PQRI Product Quality Research Institute

# Disclosures

- Consultant for
  - Baxter
  - BBraun/CAPS
  - Fresenius Kabi
  - Wolters-Kluwer

# Learning Objectives

- Describe the challenges faced by pediatric providers regarding administration of medications.
- Compare and contrast potential solutions to common pediatric drug formulation challenges.
- Determine the advantages and disadvantage of outpatient strategies for pediatric medication administration.



# Who are the patients?

- Less than 500 grams to 100+ kilograms
- Many different disease states
- Inpatient and outpatient

# Today's Pediatric Patients

Images generated by Microsoft AI Co-Pilot

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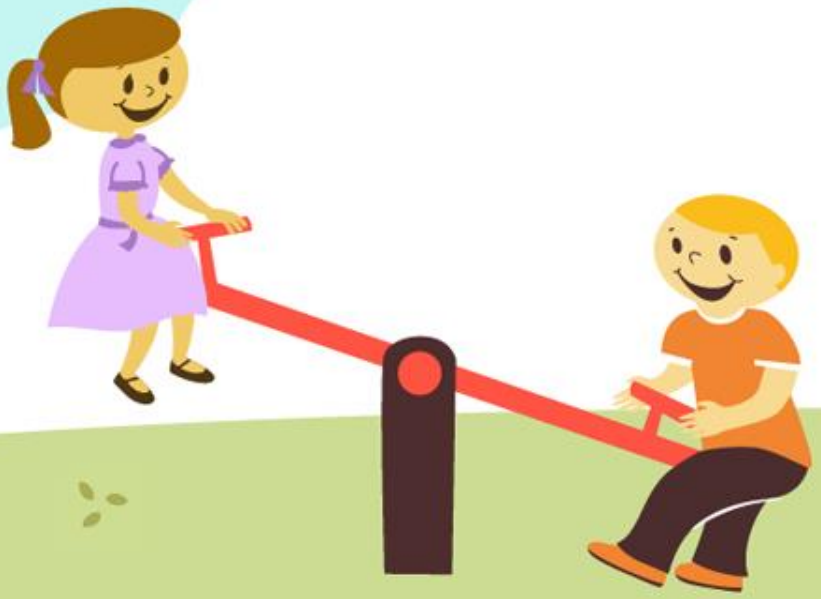


# What are the problems?

- Availability
- Formulation
- Measurability
- Financial impact

# What we need in a pediatric medication?

- A dosage form that is
  - Acceptable for pediatric patients
    - Including studies on the use of the product in various pediatric patient populations
  - Easily measured
  - Appropriate for their age and weight

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Pediatric dosage form considerations

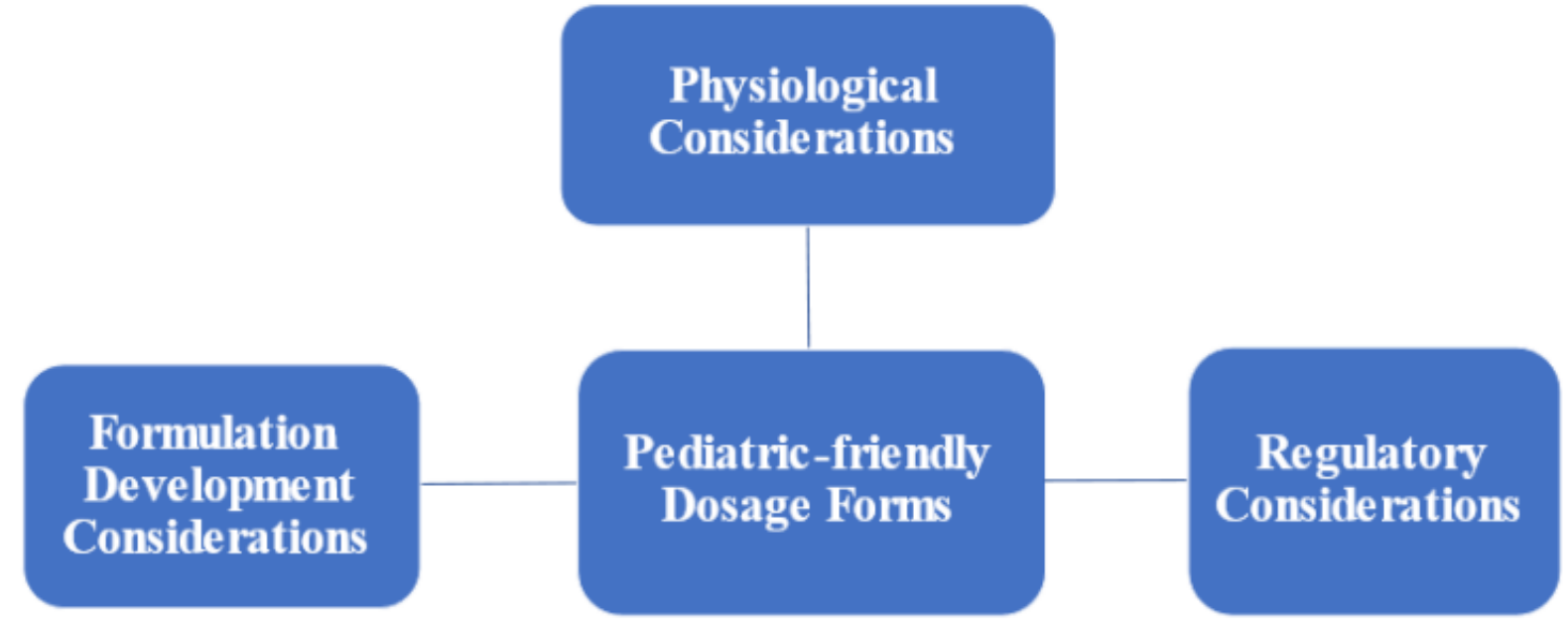
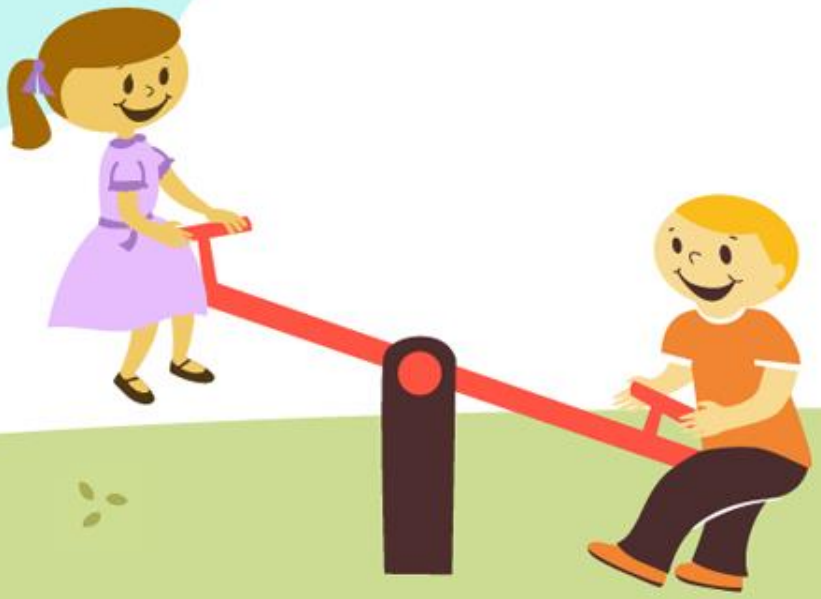



**Figure 1.** Challenges associated with developing pediatric-friendly dosage forms.

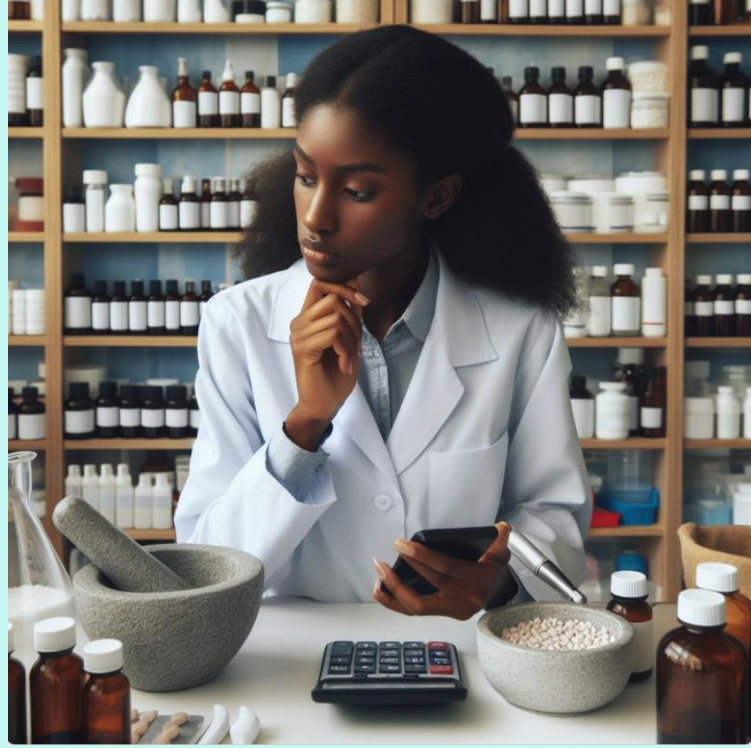
Malkawi WA, et al. *Children*. 2022;9(4):488.

Is it available?



# Creativity at its best . . .

- Extemporaneous compounding
  - Different concentrations
  - Different recipes
  - Lack of published stability data
- Results in potential patient safety issues
  - Wrong dose
  - Ineffective dose
  - Toxicity



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Nifedipine capsule pierced with needle and syringe for dose removal

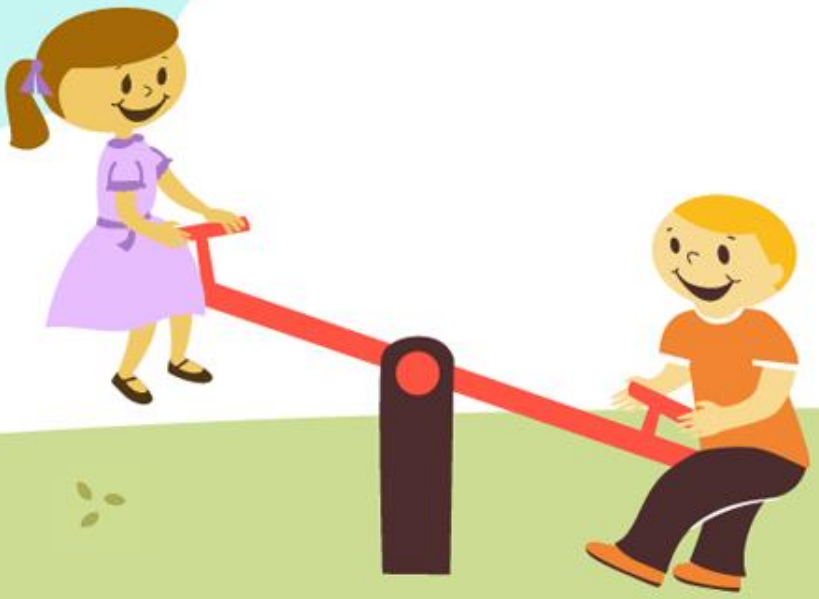
Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Despite creativity . . . may simply not be possible

- Enteric coated or extended-release product
- Not soluble in available diluents or not easily dispersed in a suspension
- May require multiple manipulations leading to potential for errors
- Extemporaneous recipe may be too complex for most outpatient pharmacies
  - Require equipment (e.g., heat, pH meter)
  - Require chemical grade ingredients not readily available

# Available but formulation issues



# Formulation issues

- Caregivers identified difficulty in getting children to take medication (McDonald 2018)
  - Most common reason = taste
  - Second reason = medication being in formulation that child could take
- Oral liquids have been dosage form of choice for pediatric patients
  - Easier to swallow
  - Overcome many administration issues
    - Measurability
    - Enteral feeding tubes
    - Can be utilized for geriatric patients

Meyers RS. *J Pediatr Pharmacol Ther*. 2024;29(1):22-31.
McDonald D, et al. Medication administration to children: The caregiver perspective. Poster presented at: The European Paediatric Formulations Initiative Conference; September 2018; London, United Kingdom

# Taste and smell

- Most active pharmaceutical ingredients (API) are bitter
- Inclusion of excipients to mask taste
  - Sweeteners
  - Flavoring agents
  - Acid/salt
- Aftertaste? The drug that keeps on giving
  - Example - Prednisone
- What children prefer is different from what adults prefer
- Poor smells
  - Example – Clindamycin
  - Oral syringes can be used to contain smell until administration

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Texture

- Children more sensitive
  - Surveyed caregivers and children determined 8% of medications affected and significant predictor of medication refusal (Venables 2015)
- Many suspensions gritty
  - Example – Change in antimicrobial coverage from amoxicillin to amoxicillin/clavulanate
- Consider viscosity of product

Meyers RS. *J Pediatr Pharmacol Ther*. 2024;29(1):22-31.
Venables R, et al. *Int J Pharm*. 2015;480(1-2):55-62.
Liu F, et al. *In J Pharm*. 2015;492:341-343.

# Volume

- Taste can be further complicated by concentration of oral formulation
- Some standard doses require 20 mL or more
  - Recommendation from European Medicines Agency in 2011
    - Children < 4 years of age = max of 5 mL
    - Children 4-12 years of age = max of 10 mL
  - After comments, removed from current recommendations which were published in 2013
- Can divide into multiple doses but concerns for completing entire dose
- Concerns about adding larger volumes into liquids/foods
  - Compatibility issues
  - Required to consume entire amount medication added to to receive full dose

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Dose frequency

- Immediate release products easier to administer to smaller pediatric patients but more likely to miss doses
  - Medications administered more than twice daily are hard to give due to childcare/school
- Extended-release formulations avoid this problem but come as hard to swallow larger tablets/capsules and in adult dosage amounts

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Pediatric gastrointestinal tract differences

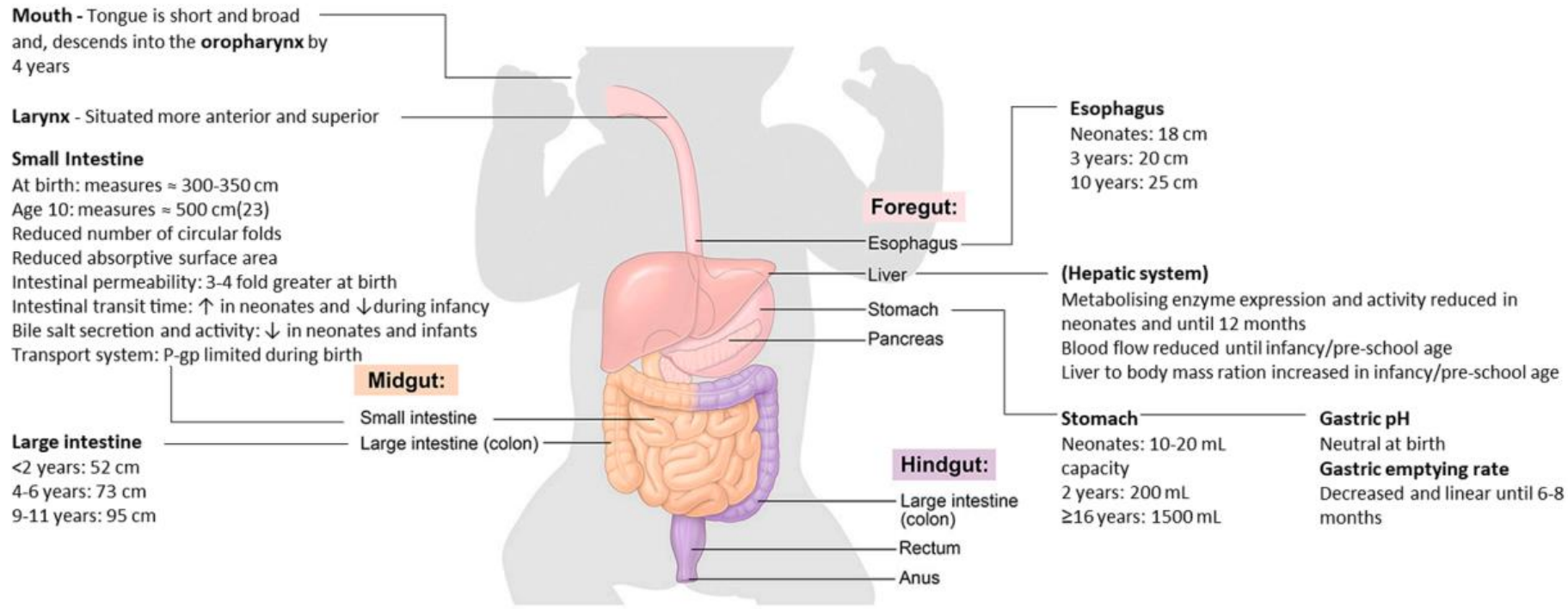



**Fig. 1.** Diagram showing the anatomical and physiological differences of the paediatric gastrointestinal tract when compared to that of an adult. Figure adapted from Leach, J. (2020), "Fetal development: your baby's digestive system.

Khan D, et al. *Int J Pharm*. 2022;616:121501.

# Pediatric hepatic and renal system differences

**Table 2**
Differences in hepatic and renal system physiology between children and adults and subsequent pharmacokinetic effect on commonly used pharmaceutical excipients.

| Differences in hepatic and renal system anatomy and physiology | Neonates (1 day to 1 month) | Infant (1 month to 2 years) | Adults | Effect on Pharmacokinetic profile | Types of Excipients affected | Example Excipient |
|---|---|---|---|---|---|---|
| Hepatic system *(metabolism)* | | | | | | |
| Metabolising enzymes (CYPs) expression and activity | Immature | Reduced (until 12 months) | Increased | Reduced metabolism | Those metabolised through CYP enzyme family | Ethanol *(solvent)* |
| Blood flow through liver | Lowest | Adult levels | Increased | Reduced hepatic clearance until infancy/pre-school age | Those undergoing high degree of metabolism | Propylene Glycol *(solvent)* |
| Liver to body mass ratio | Smaller | Larger (in infants and pre-school children) | Smaller | Increased hepatic clearance in children (infants and pre-school)<br>↓ AUC (plasma drug concentration over time) | Those undergoing high degree of metabolism | Benzyl alcohol *(preservative)* |
| First pass metabolism | Decreased | Increased (due to liver to body mass ratio) | Increased | ↑ Bioavailability | Those undergoing significant first pass metabolism | Fructose *(sweetener)* |
| Renal system *(elimination)* | | | | | | |
| GFR | Reduced (up to the age of 12 months) | Adult levels reached by 12 months | Increased but decreases in the elderly | Slower elimination up to the age of 12 months<br>↑ Levels in blood | Those renal excreted | Cyclodextrins *(solubility enhancer)* |
| Maturation of tubular transport (reabsorption/ secretion) system | Reabsorption – Immature<br>Secretion - Immature | Reabsorption- Adult levels reached by 1–3 year<br>Secretion – Adult levels reached by 12 months | Increased | ↑ Tubular reabsorption with age<br>↑ Tubular secretion with age | Disposed to tubular reabsorption/ secretion | Glucose *(sweetener)*, Sodium bicarbonate *(alkalizing agent)*, Propylene glycol |
| Urinary pH value | Decreased | Decreased | Increased | ↑ Reabsorption at lower pH values | Weak acids/bases | Citric acid *(antioxidant)* |

Khan D, et al. *Int J Pharm.* 2022;616:121501.

# Excipients

- Can lead to potential toxicities particularly in pediatric patients
- Seven excipients listed on Key Potentially Inappropriate Drugs in PediatricS (KIDS) List
  - Benzyl alcohol – associated with gasping syndrome in neonates
  - Ethanol – associated with CNS depression, hypoglycemia
    - Enhances solubility of API
    - No regulated maximum for prescription medications, unlike over-the-counter medications
    - Examples
      - Dexamethasone elixir
        - Use of injectable product orally
      - Phenobarbital elixir
        - Available alcohol-free extemporaneous compound but availability outpatient and concentration are concerns

Meyers RS. *J Pediatr Pharmacol Ther*. 2024;29(1):22-31.
Meyers RS, et al. *J Pediatr Pharmacol Ther*. 2020;25(3):175-191.

**Table 2.** Excipients With Known or Potential Harms When Used in Pediatric Patients

| Excipient | Rationale | Recommendation | Strength of Recommendation | Quality of Evidence |
|---|---|---|---|---|
| Benzyl alcohol, sodium benzoate, benzoic acid[33,34,160–163] | Gasping syndrome | Avoid exposure of >99 mg/kg/day in neonates (with the exception of sodium phenylacetate/ sodium benzoate used for the treatment of urea cycle disorders) | Strong | High |
| Ethanol/ethyl alcohol[34,164] (this excludes ethanol lock) | CNS depression, hypoglycemia | Caution in <6 years; maximum of 5% vol/vol ethanol with clinician supervision | Strong | Moderate |
| Isopropyl alcohol[165,166] | Chemical burn | Caution in very low birth weight neonates | Strong | Low |
| Methylparaben, propylparaben[167] | Kernicterus | Caution in <2 months | Strong | Very low |
| Phenylalanine[168] | Cognitive and behavioral problems | Avoid in children with an unknown phenylketonuria test | Strong | High |
| Polysorbate 80[169–171] | E-Ferol syndrome | Avoid in <1 year (any amount) | Strong | High |
| Propylene glycol[33,34,172,173] | Lactic acidosis, CNS depression, hypoglycemia, hemolysis, seizure | Avoid doses >3 g/day in neonates; caution doses >34 mg/kg/day in neonates | Strong | Moderate |

Meyers RS, et al. *J Pediatr Pharmacol Ther.* 2020;25(3):175-191.

# Excipients

- To mask taste, utilize sweeteners that may increase risk of dental caries
  - If too sweet, may lead to poisoning risk because too desirable by children
- Safety of excipients = STEP database
  - STEP = Safety and Toxicity of Excipients for Paediatrics by the European Paediatric Formulation Initiative

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Osmolality

- Increased osmolality can lead to
  - Bloating
  - Abdominal pain
  - Diarrhea
  - Electrolyte abnormalities
  - Necrotizing enterocolitis
- Often must mix medication in another fluid to decrease osmolality so now must consider greater volume
- Larger concern for medications administered to premature infants
  - Study discovered 86% of commonly administered oral liquid medications to infants were greater than 500 mOsm/kg (recommended maximum; Shah 2021)

Meyers RS. *J Pediatr Pharmacol Ther*. 2024;29(1):22-31.
Shah DD, et al. *J Pediatr Pharmacol Ther.* 2021;26(2):172-178.

# Shelf life

- Many oral liquids available as powders that must be reconstituted into suspensions
  - Once reconstituted, beyond-use-date assigned
    - Typically, 30 days or less
    - Proposed revisions to United States Pharmacopeia chapter 795 recommend maximum BUD of 35 days for preserved aqueous dosage forms
    - Shorter dates require patients to receive more frequent dose refills than once a month

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Newer potential options

- Mini-tabs and granules
  - Newer measuring devices
    - Examples – Sympfiny syringe, IQ-dose
- Modified release oral liquids
  - May need to consider pharmacokinetic differences between dosage forms
    - Example – spironolactone, methylphenidate

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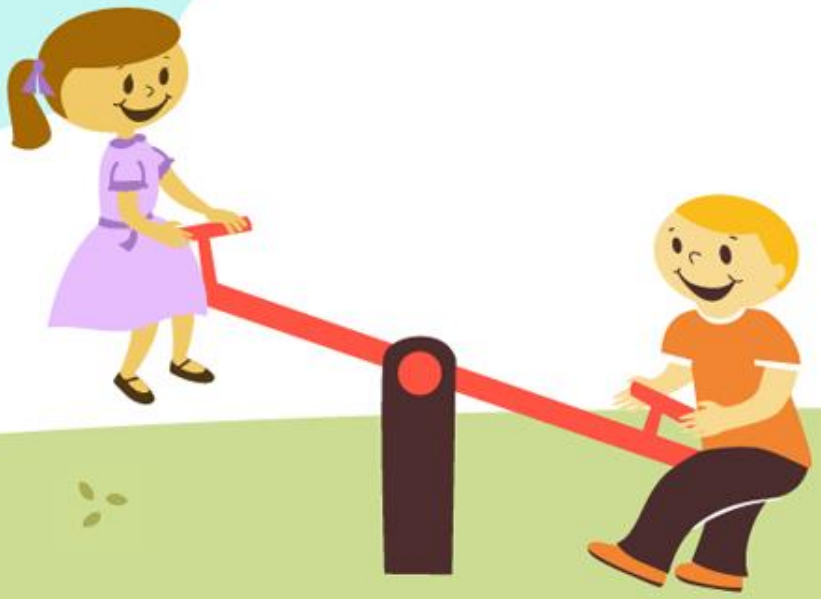
Is it measurable?



# Measuring accuracy

- Concerns regarding inappropriate measurement leading to
  - Lack of efficacy
  - Toxicity
- Household teaspoons/tablespoons vs. oral syringes
  - Variability in household measurement devices
  - Potential for spillage
- Ability of caregivers to accurately measure dose
  - American Academy of Pediatrics recommended oral syringe (2015)
    - But most prescription products do not come with oral syringe leading to
      - Measurement issues
      - Increased cost

Meyers RS. *J Pediatr Pharmacol Ther.* 2024;29(1):22-31.

# Measuring accuracy

- Prescription often does not contain overfill to allow for loss of product
- Difficulty in obtaining medication from the container using syringe
- Many oral medications are suspensions so must be shaken immediately prior to administration to ensure adequate uniformity for measurement of API
  - Subtherapeutic at beginning of prescription
  - Supratherapeutic at end of prescription

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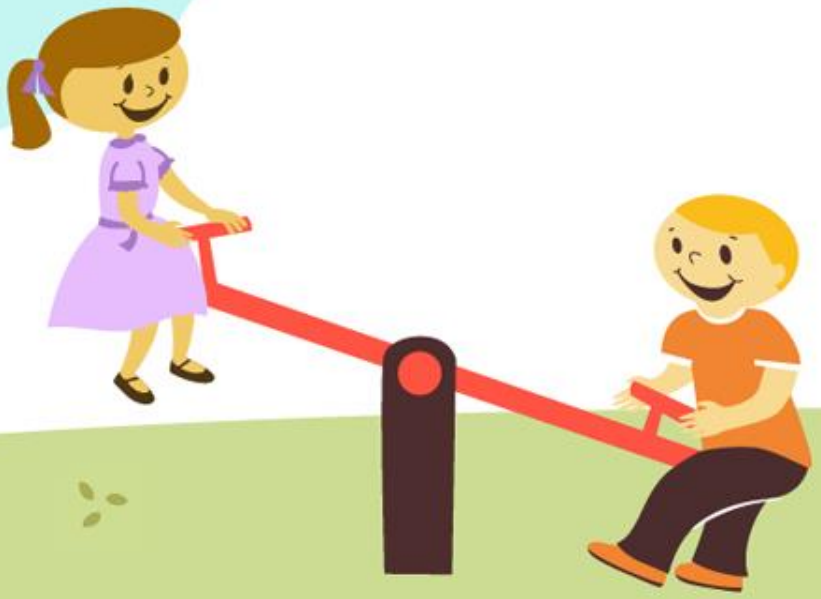
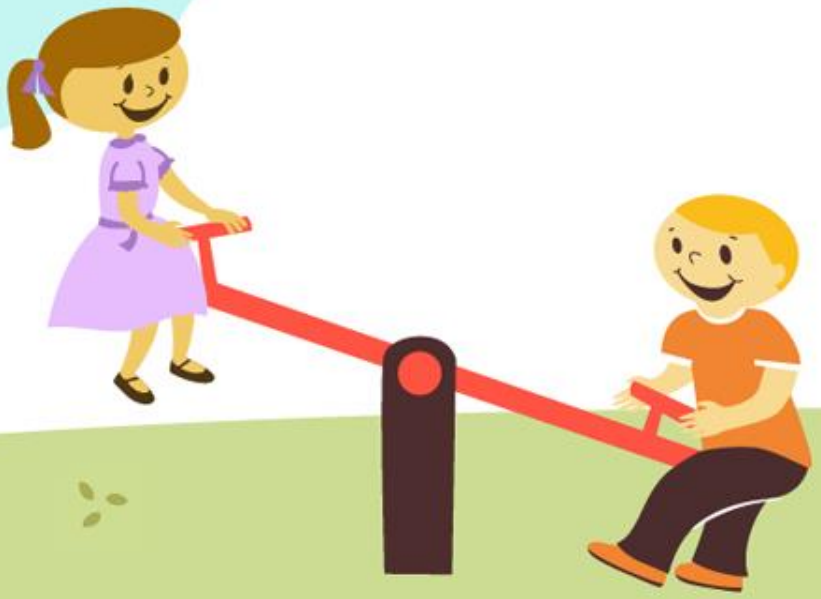


# How much is that going to cost?

# Financial impact

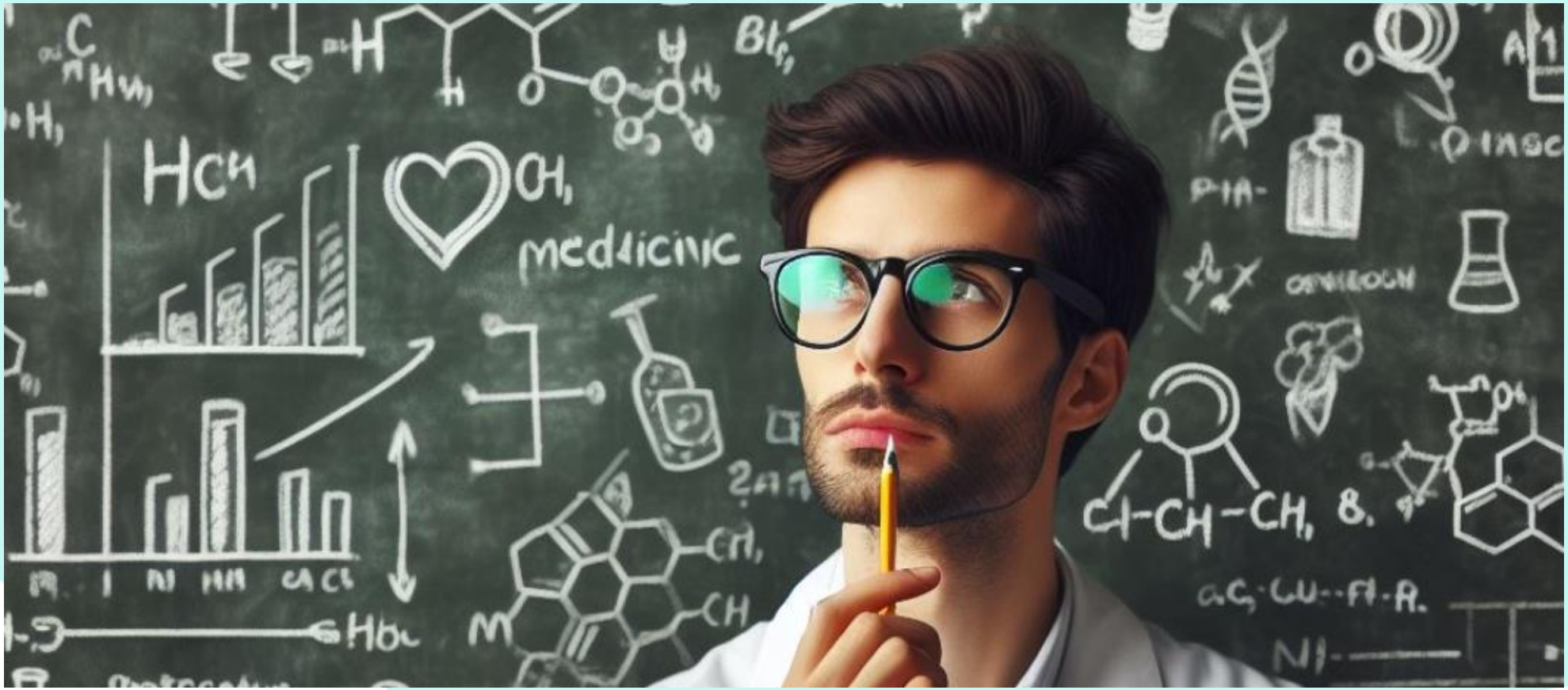
- Expense of extemporaneous compounding
  - Covered by patient's insurance?
  - Different settings may utilize different compounding recipes leading to potential medication errors and associated increased costs
- Newer oral formulations for pediatric patients
  - Availability of costly new formulations at all community settings?
  - May not be the same concentration as previous extemporaneously compounded product leading to potential medication errors and associated increased costs



# What do I have to do?

Methods we use when nothing else is available in the hospital

# Put on the thinking cap . . . Time to get creative

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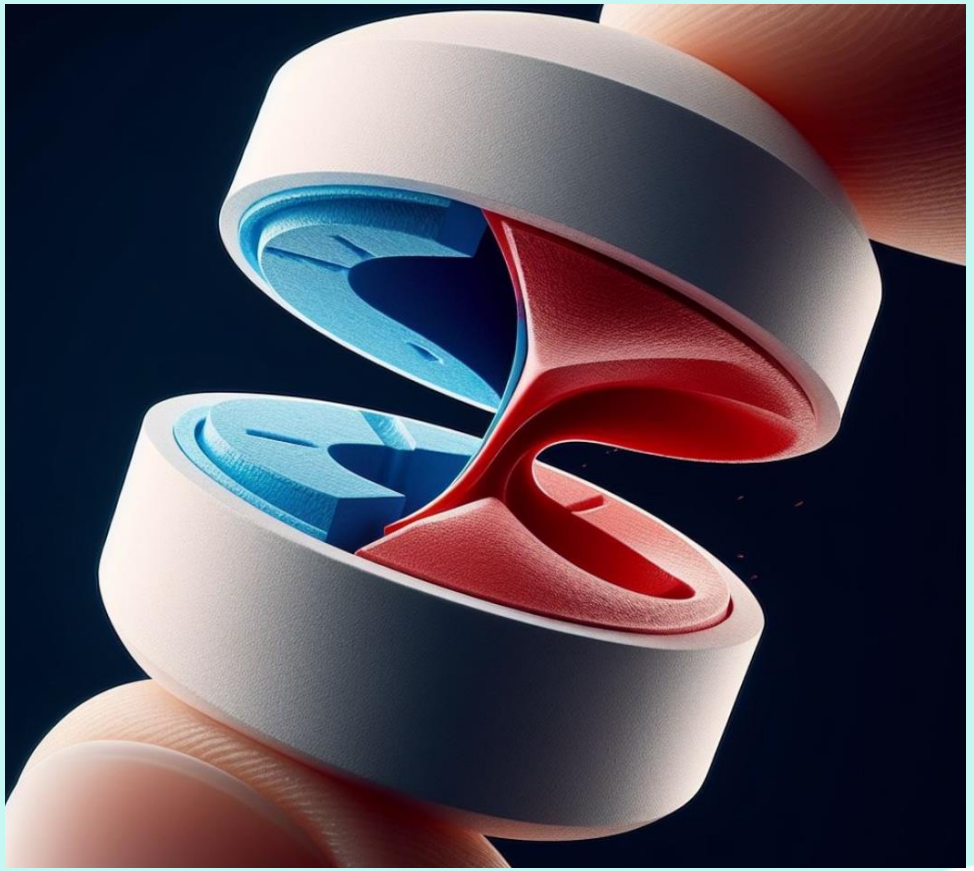
# Crush it? Split it?



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# Extemporaneous compounding

- Utilize published recipe
- Crush and mix in either water or simple syrup
  - Usually added to set volume of diluent and then take a portion of the “solution”
    - Aliquot method
    - Not always water soluble or evenly distributed in the mixture
  - API may be retained in the measurement device (e.g., syringe)
  - Must utilize immediately after preparation
- Must consider carbohydrate content for patients on ketogenic diet

Image generated by Microsoft AI Co-Pilot

# Can I measure it?

- Dilutions, dilutions, and more dilutions
  - Who dilutes it and with what?
  - What beyond-use-dating can I give the diluted product?
  - How much manufacturer product will I need for each dose?
    - Financial impact?
    - Shortage implications?

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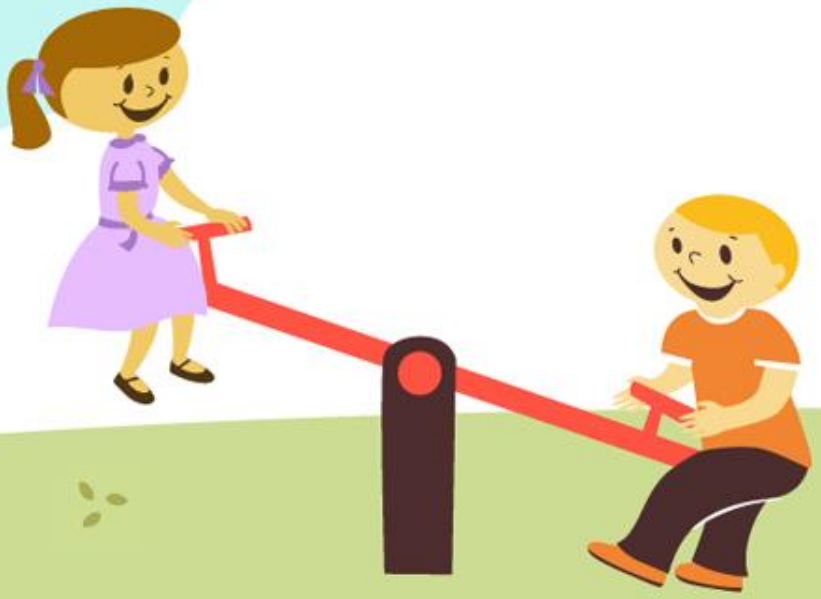


# What do caregivers do?

## Methods used when a patient goes home

# Avoid that nasty taste

- Use of outpatient flavoring agents
  - Commercially available products vs chocolate syrup
- “Numb the tongue”
  - Cold item prior to mediation to desensitize taste receptors
- Do not add to the child’s favorite food or drink
  - May become their least favorite food or drink
  - May figure out ways to take the favorite item but not the medication

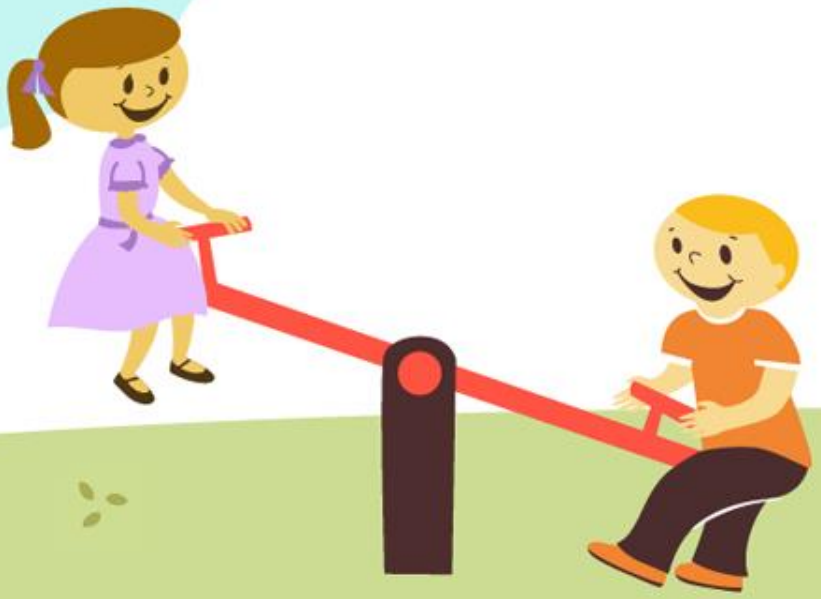
Image generated by Microsoft AI Co-Pilot

# Impossible expectations . . .

- Sometimes what can be done in the hospital is not realistic at home
  - Multiple dilutions
  - Aliquot method
    - Lack of uniformity can lead to differences in API between doses or subtherapeutic amounts
  - Do not have same equipment and may need to reuse items for multiple doses
  - Make sure they know how to measure the dose

# Key Take-Aways

- Pediatric providers face many challenges when administering medications to patients
- Potential solutions in the clinical setting to these formulation issues can lead to new problems or safety concerns
- What can be accomplished in the hospital setting is not always possible or realistic for the home setting



# Questions?

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