Trends and Challenges with the Development of Pediatric Formulations after the Implementation of the Current Regulations: Industry Perspective

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PQRI Workshop: Model-Informed Drug Development Approaches in Pediatric Formulation Development

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Overview

Background

Trends & Challenges

- Formulation platform selection
- Dose flexibility
- Infant dosing
- Biopharmaceutics

Concluding remarks

Background

US and EU regulations require all new drugs to be evaluated in pediatric patients, where there is a likelihood for the drug to be used in that population

- Development plans defined in Pediatric Study Plans (PSPs) & Pediatric Investigation Plans (PIPs), respectively
- Plans developed around end of Phase 2, informed by knowledge of the dose-response in adults
- Pediatric clinical development usually occurs post filing/registration of the adult product

Age-appropriate formulation(s) required for pediatric clinical studies ± registration, at least for oral products

- "Adult" parenteral products usually suitable for pediatric dosing, perhaps with modification of dilution/administration procedures

Pediatric drug development is generally slow relative to "adult" development programs

- Occurrence of condition usually lower in pediatric population → more difficult to enroll patients
- Sequential nature of pediatric studies: adolescents → 6-11 yr olds → 2-5 yr olds → toddlers → infants

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Pediatric Formulation Platform

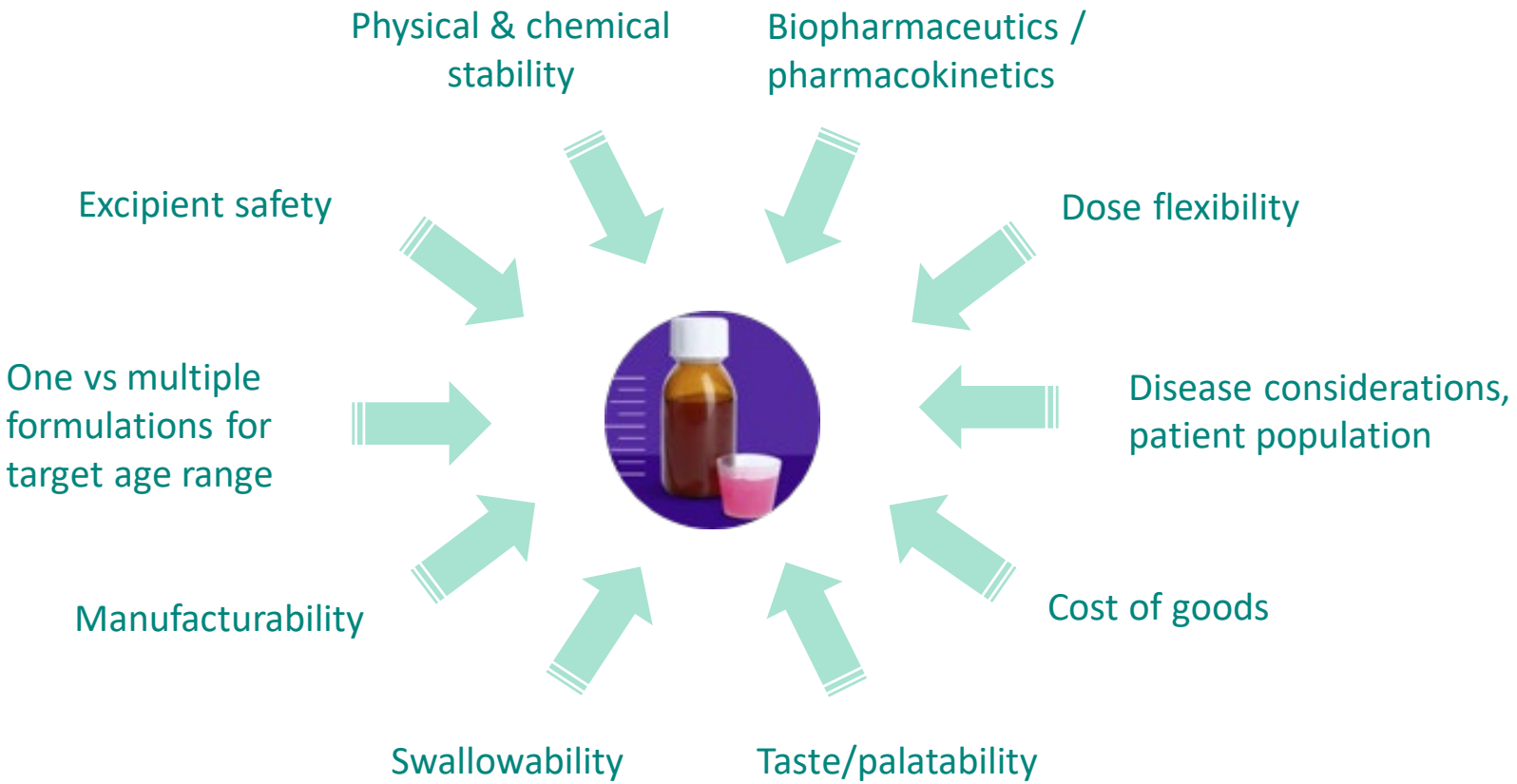
An age-appropriate formulation almost always needs to be developed for oral dosing of pediatric patients

- Adult formulation (& dose) may be suitable for adolescents (12-17 yrs), but not for younger patients
- Formulation platform of choice depends on many factors
    - Drug properties
    - Patient age range
    - Disease
    - Company capabilities

Unique challenges in pediatric formulation development

- Dose flexibility
- Patient acceptance (taste, swallowability)
- Need for admixtures with soft food, liquids to enable dosing
- Low commercial volumes

Formulation Considerations



Many of these considerations would drive formulation development in conflicting directions, so this becomes an exercise in compromise

Preferred Pediatric Formulations by Age: Best (++) to Worst (--)

FORMULATION	Preterm newborn infants	Term newborn infants (0 – 28 d)	Infants and toddlers (1 m – 2 y)	Children (pre-school) (2 – 5 y)	Children (school) (6 – 11 y)	Adolescents (12 – 18 y)
Oral						
Solution/ Drops	-	+	++	++	+	+
Emulsion/ Suspension	-	o	+	++	+	+
Powders/Multiparticulates	--	-	-	+	+	++
Tablets/Capsules	--	--	-	o	+	++
Orodispersable dosage form	--	-	o	+	++	++
Chewable tablets	--	--	-	o	++	++
Parenteral						
i.v. Solution	++	+	+	+	+	o

Adapted from: REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION, EMEA/CHMP/PEG/194810/2005

Pediatric Formulations – Challenges & Opportunities

Many pediatric products in development, under PSP/PIPs, but relatively little industry experience with registration of these products

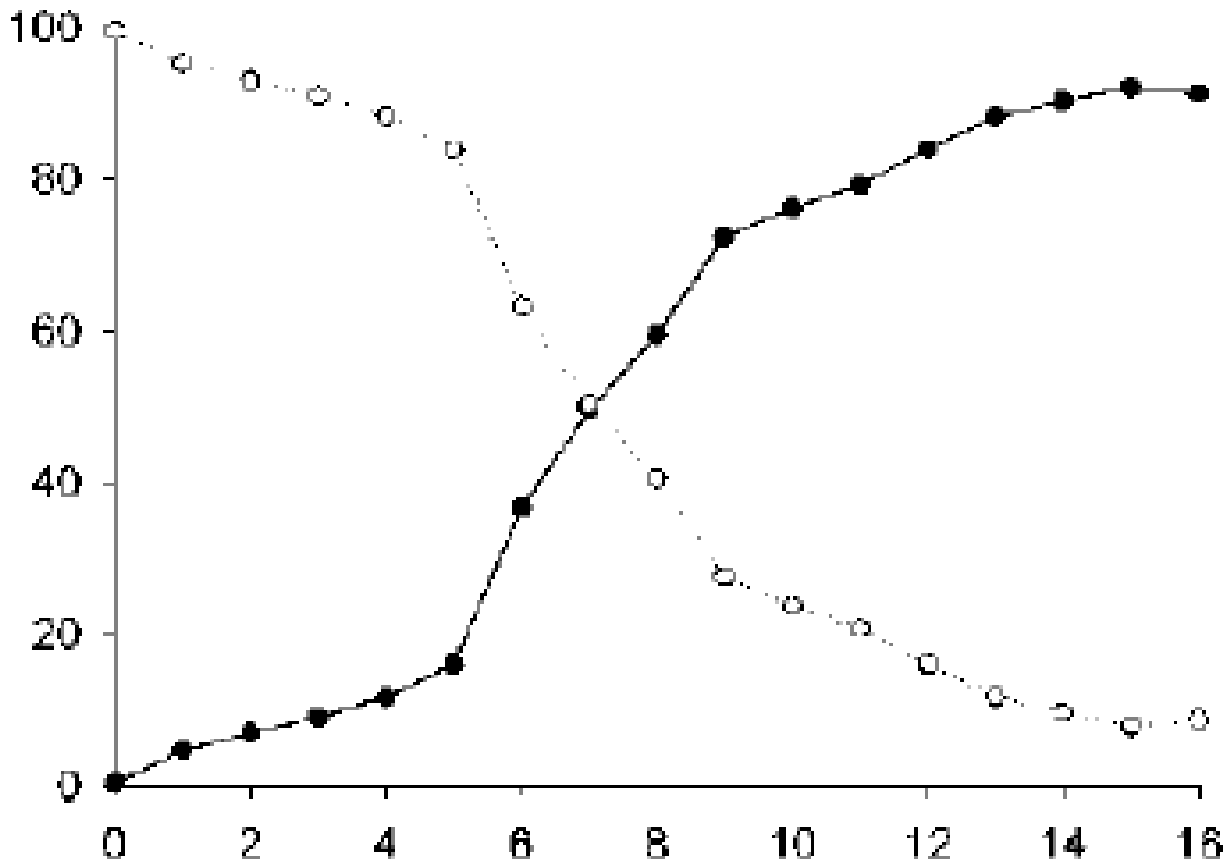
- Function of the long clinical timelines, and attrition (drugs found to have no clinical benefit in pediatric patients)
- Regulatory expectations are not always well-defined, well-understood:
  - Control strategy – bulk vs package release for mini-tablets, multiparticulates?
  - Rigor of admixture studies with soft foods, liquids?
  - Swallowability / palatability – how good is good enough, if 100% acceptance not attainable?
- "Mini-tablets", multiparticulates, granules widely selected for < 11 yr old population
  - Dispersions of these in liquid for children unable to take granules in soft food

Suitability of conventional tablets/capsules children, 6-11 yrs of age?

- Leverage "adult" formulation for granulation/blend → compress/encapsulate for lower dose
- Children 6-11 yrs largely able to swallow tablets/capsules, particularly if living with chronic disease
- Teaching tools exist, widely used in hospital pharmacy where age-appropriate formulations of older drugs not available
- How do we manage the fraction of patients unable to swallow the tablet/capsule?

Precedents for use of tablets/capsules in children (1)

Percent of all oral prescriptions of licensed drugs for children 0-16 yrs of age that were for liqud (open symbols) vs solid (closed symbols) formulations



Schirm et al, Lack of appropriate formulations of medicines for children in the community. Acta Paediatrica (2003) 92: 1486-9

Precedents for use of tablets/capsules in children (2)

Age of conversion of children from liquid to solid formulations of antiretrovirals

Drug	*Number of patients (boy/girl)*	*Mean start age of the liquid formulations (95% CI)*	*Number of patients changed to solid formulations (%)*	*Mean age change from liquid to solid formulation (95% CI)*
Stavudine	22 (10/12)	2.9 (1.8–4)	16 (73)	3.6 (2.7–4.6)
Abacavir	25 (14/11)	8.1 (5.2 –10.9)	10 (40)	9.2 (6.7–11.7)
Didanosine	27 (11/16)	5.8 (3.5–8.1)	13 (48)	7.2 (5–9.5)
Lamivudine	74 (42/32)	6.5 (4.8–8.2)	15 (20)	10 (8.5–11.4)
Zidovudine	34 (19/15)	4.0 (1.8–6.2)	7 (21)	6.9 (5.5–8.4)

Yeung & Wong, When do children convert from liquid antiretroviral to solid formulations? Pharmacy World & Science, (2005) 27: 399–402

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Dose Flexibility

Need for flexible dosing, both during clinical trials and also once on the market, is a key driver in formulation selection

Age/weight range:

- Need to support age/weight-based dosing across the expected patient population
- 40 kg 11-yr old to 3 kg newborn → 10-fold range in body weights, and likely doses

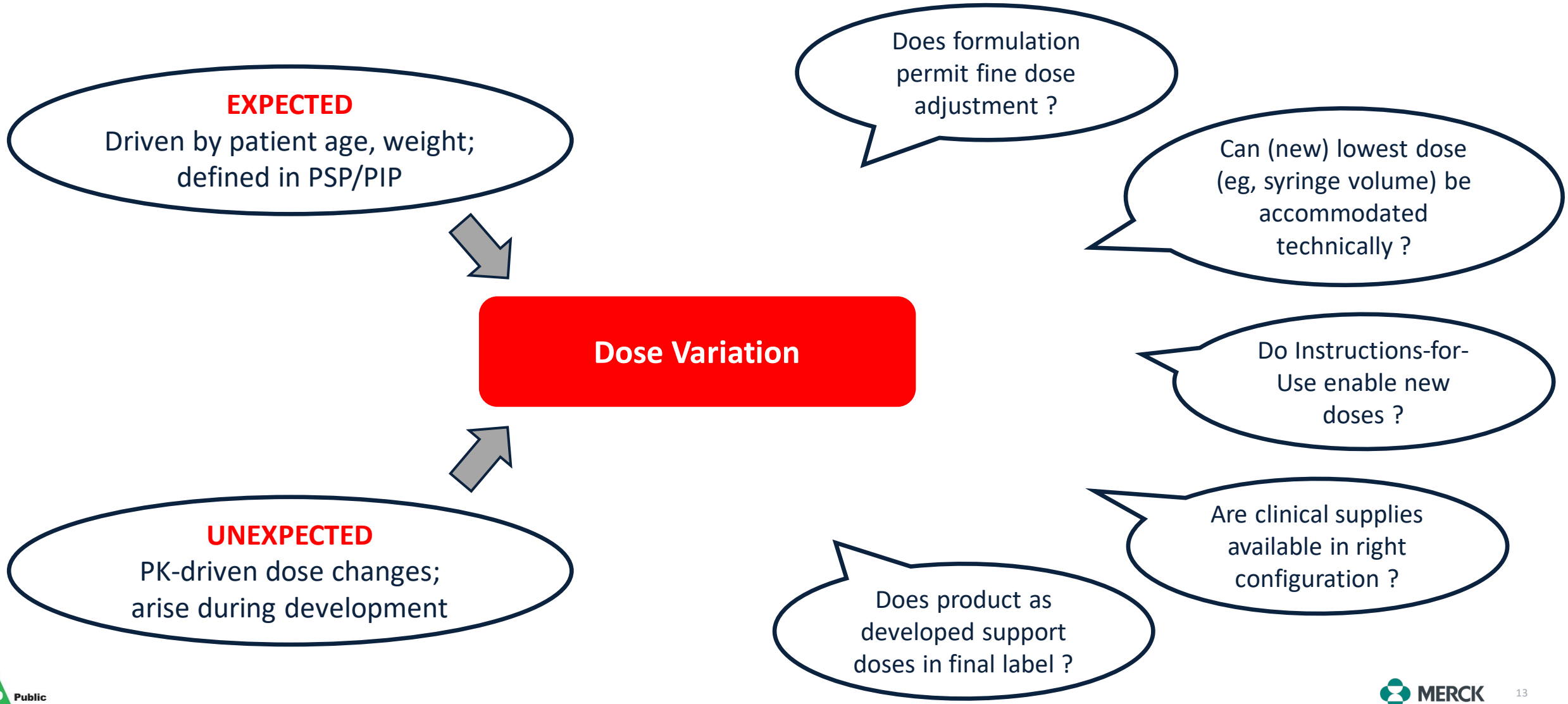
PK differences:

- Age-based differences in volume of distribution, clearance, maturation of metabolic enzyme systems → differences in PK → differences in mg/kg doses by age
- Particularly relevant for newborns/infants (lowest doses)

Changes in dosing regimens:

- Differences in PK profile may prompt the need to change dosing frequency to meet target PK parameters – e.g., dividing the dose & administering BID instead of QD
- Particularly a risk for youngest patients (lowest doses)

Managing Dose Variations



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Infant Dosing

Requirement in many, though not all, pediatric development programs

- Depends on incidence of disease or condition in that population

Formulation options significantly limited relative to those for older children

- ***Ready-to-use solutions / suspensions / syrups***
  - Technically-challenging or infeasible for many drugs with solubility, stability, taste challenges
- ***Powder/granules-for-suspension or dispersion of other solid dosage form***
  - Generally require constitution steps to be performed by the parent / caregiver
- ***Direct swallowing of intact minitablet or small tablet***
  - Demonstrated in academic studies[1] but not yet widely embraced by companies & regulators as a safe, robust approach to product development
- ***Film strips or other orally-disintegrating dosage form***
  - Theoretically feasible but not in widely used; challenging for poor-tasting drugs; limited expertise & manufacturing capabilities in companies

1: Klingmann et al, Acceptability of Uncoated Mini-Tablets in Neonates – A Randomized Controlled Trial. Journal of Pediatrics (2015) 167: 893-6

Infant Dosing (cont'd)

In practice, a commonly approach is dispersion of a powder / granule / other solid form to give suspension for liquid dosing … leveraging the formulation developed for older children

➕ Addresses most of the product design challenges (dose flexibility, patient acceptability, stability); suitable for patients unable to take soft foods

➖ Generally requires constitution steps to be performed by the parent / caregiver

↳ Depends on availability of suitable components (e.g., mixing cups, oral dosing syringes)

↳ Company may need to co-package the drug product with these components

↳ Drug-Device Combination Product

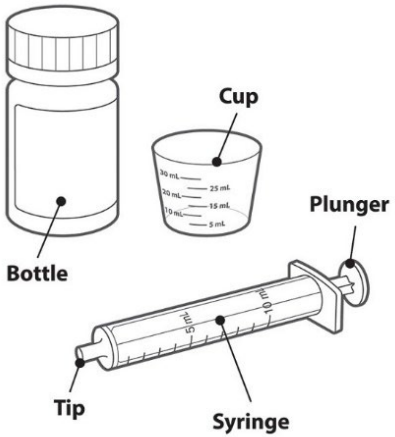
↳ Higher complexity in development, longer development timeline, higher COG

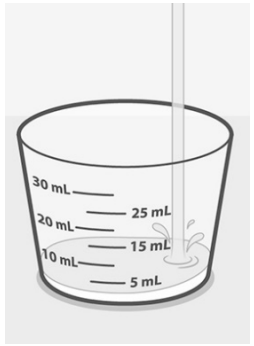
- Important to be able to predict the expected lowest dose / dose volume as early as possible in development
  - ➢ Needed to enable definition of device components, dosing procedure, instructions-for-use
- Infant population is usually a small fraction of an already-small commercial volume → small batch sizes, high discard rates

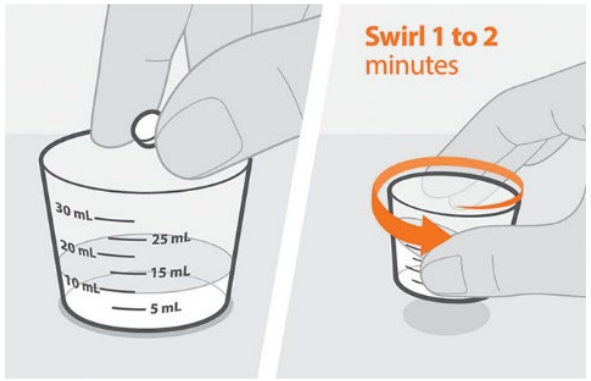
Case Study: TIVICAY PD (Dolutegravir)

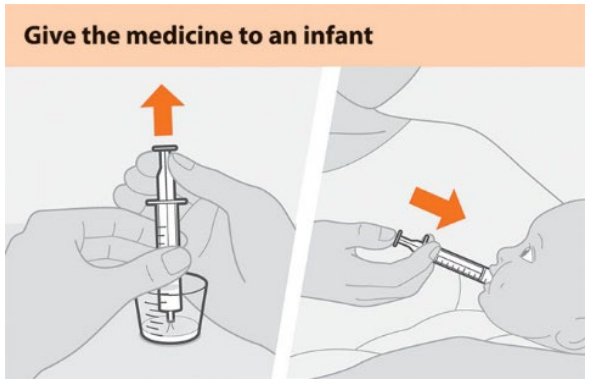
Indicated for treatment of HIV-1 infection in pediatric patients aged at least 4 weeks and weighing at least 3 kg

Cup & syringe provided → Add water to cup → Add tablet(s), swirl to mix → Draw up liquid, dose to child → Add water rinse, mix & dose









- Significant expertise in Human Factors Engineering needed to enable the design of appropriate handling steps & supporting Instructions-for-Use to minimize dosing errors
- Complexity & risks increase significantly if the parent / caregiver is required to administer only a portion of the liquid

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Biopharmaceutics - recap

Pharmacokinetics in children vary by age:

Adolescents (12 – 17 yrs)

- PK and dosing may be similar to adult PK/dosing

Children (2 – 11 yrs)

- PK and dosing predominantly driven by body weight and organ function

Infants (< 2 yrs)

- PK affected by maturation of physiological functions/processes (age-dependent) as well as body weight & organ function
- Numerous differences in physiological parameters – total body water, body fat, BBB functioning, P-gp expression, plasma protein levels, GI motility & pH, biliary function
- PK and dosing predictions increasingly uncertain

Predicting Drug Absorption & Formulation Performance

- Gaps remain in our knowledge of GI physiology, particularly in younger age groups
- Can we predict impact of formulation performance on absorption / PK, especially for younger children?
- To what extent can we use PK modeling data to design formulations specifically for pediatric patients?
  - E.g., weakly-basic drugs with pH-dependent solubility
    - Dissolve at gastric pH → Precipitate at intestinal pH
    - Dependent on GI physiology (gastric and intestinal pH, gastric emptying rate, bile salt levels, diet)
    - Differences in physiology may → differences in absorption, relative to adults or older children
- To what extent can we predict doses & dosing frequency for the youngest age groups? … late changes in dose can be challenging to manage

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Pediatric formulation platform selection remains challenging, especially for the youngest patient groups

- There is no “ideal” or one-size-fits-all solution
- Opportunities to leverage emerging knowledge of patient acceptance / preference, successful product executions and regulatory intelligence to direct formulation selections
  - Applicability of tablets/capsules for < 11 yr olds, leveraging training resources, etc
  - Expand our understanding of, and capabilities in, formulation approaches for safe, flexible dosing of infants
- Opportunities to leverage less-common delivery modalities (e.g., orally disintegrating dosage forms) in specific situations

Enabling dose flexibility, projecting pediatric doses, and managing dose changes during development

- Leverage pediatric PK models and experience to better project doses
- Understand the uncertainties around these projections, and where / how early dose projections may be in error

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MERCK

Thank you

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