Unique Elements of the Pediatric Quality Target Product Profile (QTPP)

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

February 28-29, 2024

Outline

Putting into context (earlier presentations)

- Complexity of Pediatric Drug Development
- Moving Targets
- MIDD as project accelerator

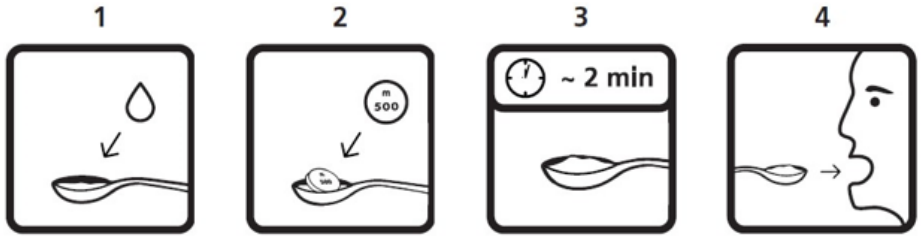
Pediatric Quality Target Product Profile (ped QTPP)

- Patient & CMC Centric
- TPP – your contract with management/project team
- QTPP – your GPS
  - What's unique?
  - Decision making
  - Living Document
  - Benefit of having/downsides of not having one

Outlook

Example simple: VERMOX® (mebendazole) Chewable Tablet

- Chewable Tablet 500 mg – rapidly disintegrating
- HDPE Bottle, 200 count (NDC 50458-675-20)
- Intestinal worm infections (helminths) – "mass administration" (school-aged; pre-school aged; ≥ 1y)
- Donation program 200 million tablets/year – WHO, INMED Partnership for Children
- Tablet chewed or given by spoon with minimal amount of water



https://www.jnj.com/caring-and-giving/how-deworming-medicine-helps-treat-children-globally

Ascaris (roundworm)

Young children wait in line to receive dose of chewable mebendazole for intestinal parasites

Clinical: Silber et al. *Am. J. Trop. Med. Hyg*. 2017, 97, 1851–1856 https://doi.org/10.4269/ajtmh.17-0108

CMC: Van Hove et al. *Eur. J. Pharm. Biopharm*. 2023, 188, 217-226 https://doi.org/10.1016/j.ejpb.2023.05.013

Example complex: - ISENTRESS® (raltegravir)

ISENTRESS®

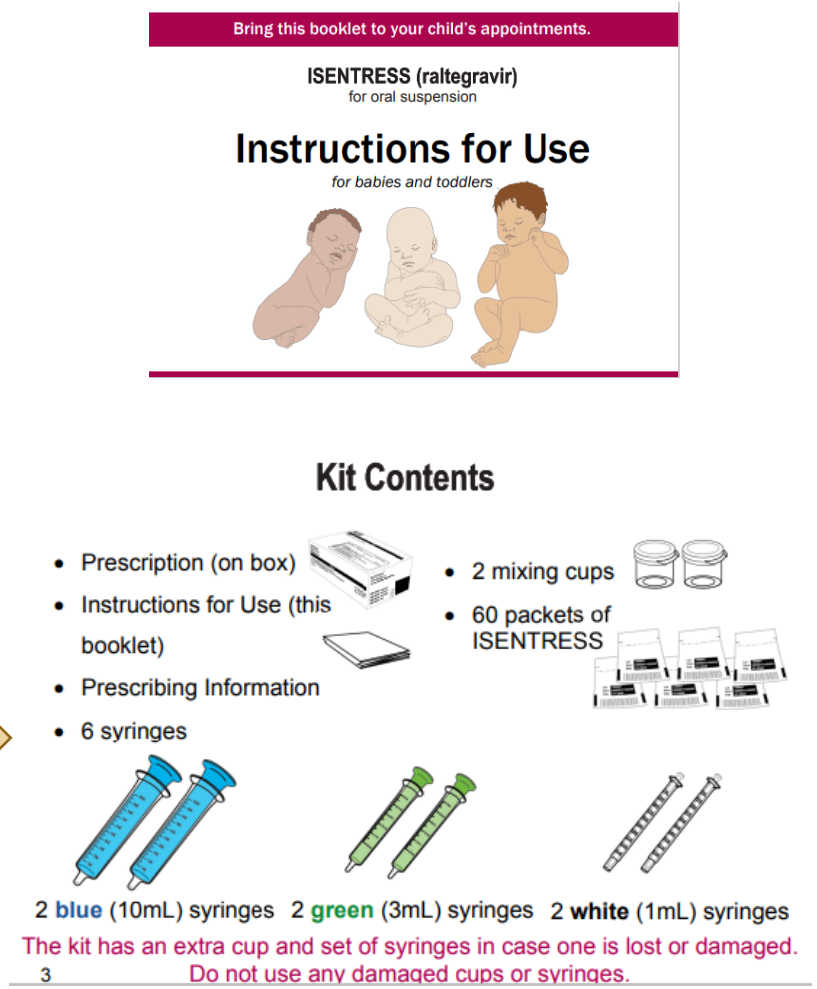
Film-coated tablets
400 mg

HD film-coated tablets 600 mg

Chewable tablets
25 mg, 100 mg

ISENTRESS® for Oral Suspension

(single-use packet 100 mg)



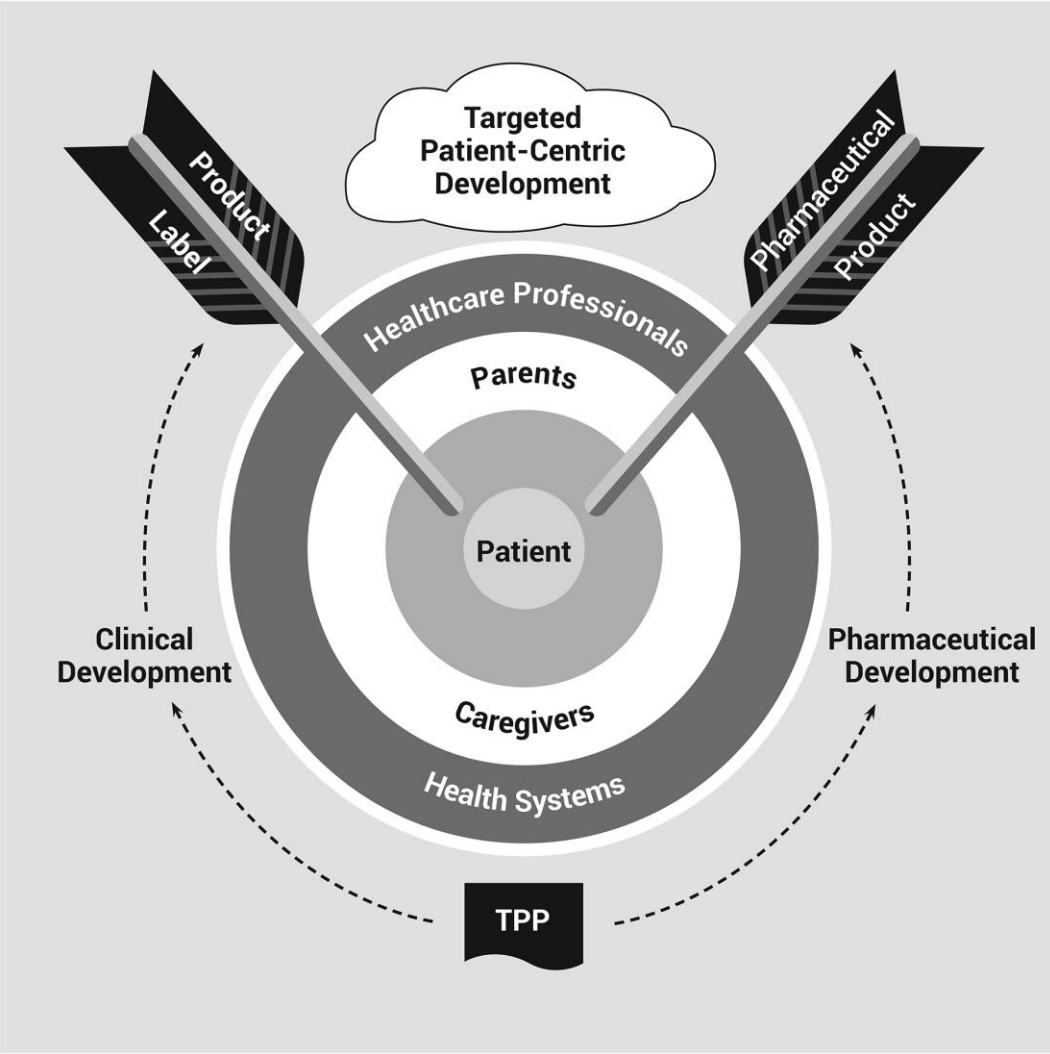
Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing†	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily

*The dosing recommendations are based on approximately 1.5 mg/kg/dose.
†The dosing recommendations are based on approximately 3 mg/kg/dose.

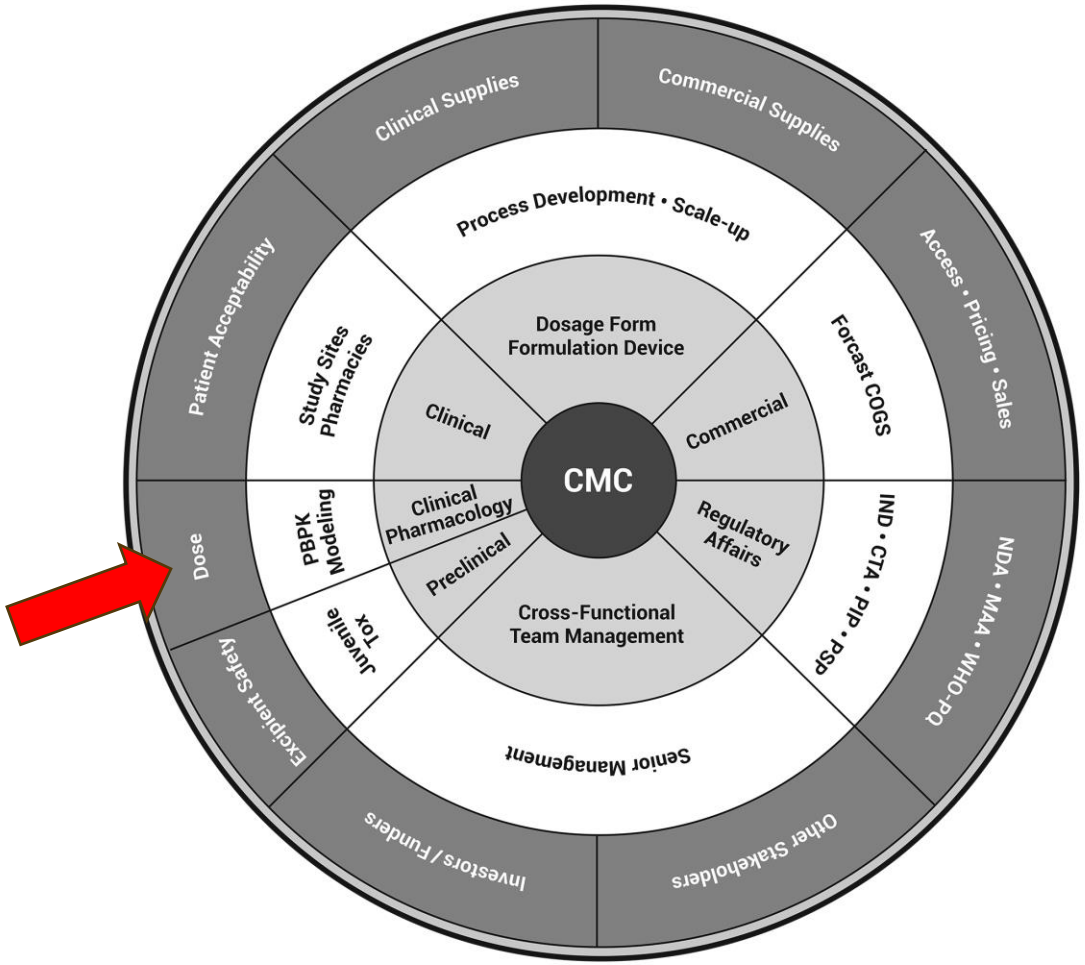
https://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_ifu.pdf
https://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf

Patient-Centric

CMC-Centric



CMC = Chemistry, Manufacturing & Control

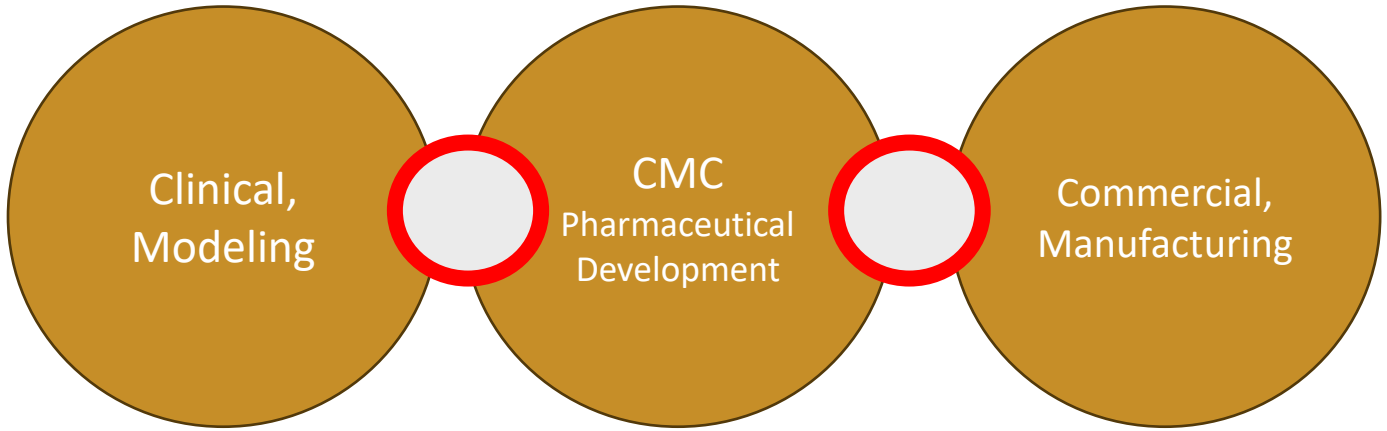


Source: D. Schaufelberger, in "Pediatric Formulations, A Roadmap", AAPS Adv. Pharm. Sci, Springer; H. Batchelor and K. Rose (eds.) - Chapter in preparation

Collaboration

Source: www.EuPFI.org

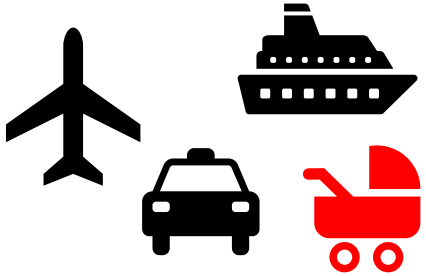
Learn -> Talk –> Debate –> Agree -> Decide -> Document



Target Product Profile (TPP)

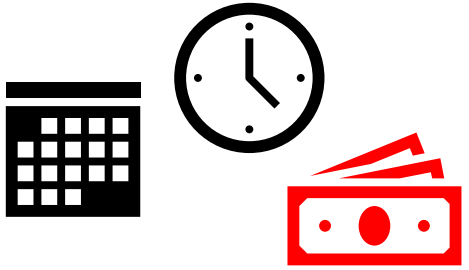
Target Product Profile (TPP)

Where? What?



Product Development Strategy

How?



Development Plan

Timelines

$$

How long? How much?

Pediatric Quality Target Product Profile (pedQTPP)

Target Product Profile (TPP)

→

Quality [=CMC] Target Product Profile (QTPP)

→

Pediatric Quality Target Product Profile(s) (*ped*QTPP)

Typical CMC Attributes:

- ➔ Storage/Shelf life
- ➔ Costs
- ➔ Critical (Product) Quality Attributes
- ➔ Control Strategies API, DP
- ➔ etc.

Typical Pediatric Attributes

- ➔ Age-appropriate formulation(s)
- ➔ Acceptability (Taste etc.)
- ➔ Dose flexibility
- ➔ Administration, reconstitution
- ➔ Food compatibility
- ➔ Dosing aids/devices
- ➔ etc.

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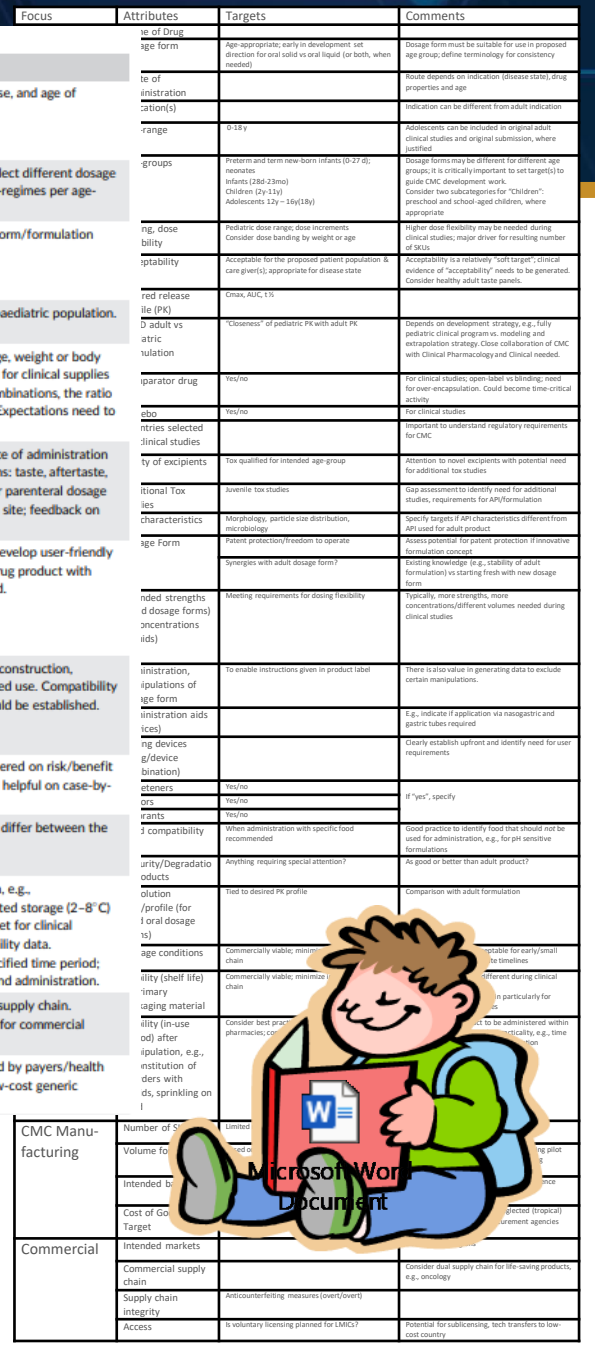
Pediatric QTPP

- **Collaboration Tool** for Formulation Scientists, Clinical Pharmacologists and Clinicians
- Attributes (approx. 10 – 30) and corresponding targets
- Separate QTPP for different dosage forms
- Different targets for clinical & commercial supplies
- Distinguish between “desirable” and “minimally acceptable”

TABLE 3 Key attributes for a paediatric Quality Target Product Profile [a] (pQTPP)

Attribute	Target[b]	Comments
Route of administration	Auricular/buccal/intramuscular/ intravenous/nasal/ophthalmic/oral/ pulmonary/rectal/subcutaneous/ topical/transdermal etc.	Route depends on indication and drug properties, disease, and age of patient.
Patient age range	Entire range 0–<18 y, or more restricted. Define age groups, as needed.	Define age groups to: (i) sequence clinical studies; (ii) select different dosage forms for different age-groups; and (iii) define dosing-regimes per age-group (dose bands).
Target release profile	Desired pharmacokinetic and in vitro drug release profiles, i.e., for immediate or controlled/delayed release.	To provide guidance to formulators on type of dosage form/formulation concepts to choose from.
Dosage form	According to administration route; *age appropriate*.	Dosage form must be suitable for use in the proposed paediatric population.
Dose and dose flexibility; dosage strength(s)	Paediatric dose range; dose increments, *dose banding*.	Identify need for flexible dosing, according to patient age, weight or body surface area. More dosing flexibility might be needed for clinical supplies comparted to commercial product. For fixed dose combinations, the ratio of active ingredients may change across age groups. Expectations need to be established upfront.
Patient acceptability	Acceptable for the proposed patient population/care giver, and disease state.	*Acceptability* depends on patient age, disease state, route of administration and dosage form. Considerations for oral dosage forms: taste, aftertaste, texture, swallowability, administration volume etc. for parenteral dosage forms: injection volume, pain (discomfort) at injection site; feedback on *acceptability* should be collected from clinical studies.
Dose preparation—manipulations	Can be easily prepared and accurately administered with low risk of dosing errors. Applies to manipulations, i.e., mixing with vehicles, food/ beverage; reconstitution with water or specified diluents.	Establish user requirements (patients/care givers) and develop user-friendly handling instructions. Compatibility and stability of drug product with administration vehicle and food should be determined.
Dose administration—devices	Define type of dosing device appropriate for disease state, dosage form and dose ranges to be delivered, to ensure ease and accuracy of dosing.	Administration device (design, dimensions, materials of construction, instructions for use) should be appropriate for intended use. Compatibility with and accuracy of dosing of the drug product should be established.
Excipients (safety)	No safety concerns for the proposed patient population.	Safety of excipients for selected age group to be considered on risk/benefit basis. Regulatory acceptance and precedence may be helpful on case-by-case basis.
Primary packaging material and container closure system	Suitable for hospital and home use.	Child-resistant closure; primary packaging material may differ between the clinical and commercial products.
Stability and storage conditions	Stable for 2 years minimum under long term storage conditions (ICH), according to climatic zones intended for marketing. For reconstituted products: set targets for *in-use* stability.	Sufficient stability required to facilitate the supply chain, e.g., nonrefrigerated storage and transportation. Refrigerated storage (2–8°C) may be accepted but is less favourable. Shelf-life target for clinical supplies may be shorter due to lack of long-term stability data. *In-use stability*: product to be administered within a specified time period; consider practicality, i.e., time between preparation and administration.
Manufacturing	Minimal number of different pack types and sizes; estimate of commercial forecast.	Easy to manufacture, freedom to operate, noncomplex supply chain. Typically, low volume forecasts; risk of obsolescence for commercial product; consider launching at pilot scale.
Patient access	Broad access or limited to certain patient subpopulations.	Age-appropriate paediatric products need to be adopted by payers/health insurances. For low- and middle-income countries low-cost generic versions may be needed



Walsh J, Schaufelberger D, Iurian S, et al. Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a **conect4children expert group white paper**. *Br. J. Clin. Pharmacol.* 2021;1-18. https://doi.org/10.1111/bcp.14989

D. Schaufelberger in “Pediatric Formulations”, AAPS Adv. Pharm. Sci, Springer; H. Batchelor & K. Rose (eds.), Chapter in preparation

Unique Elements Ped QTPP

DEVELOPMENT

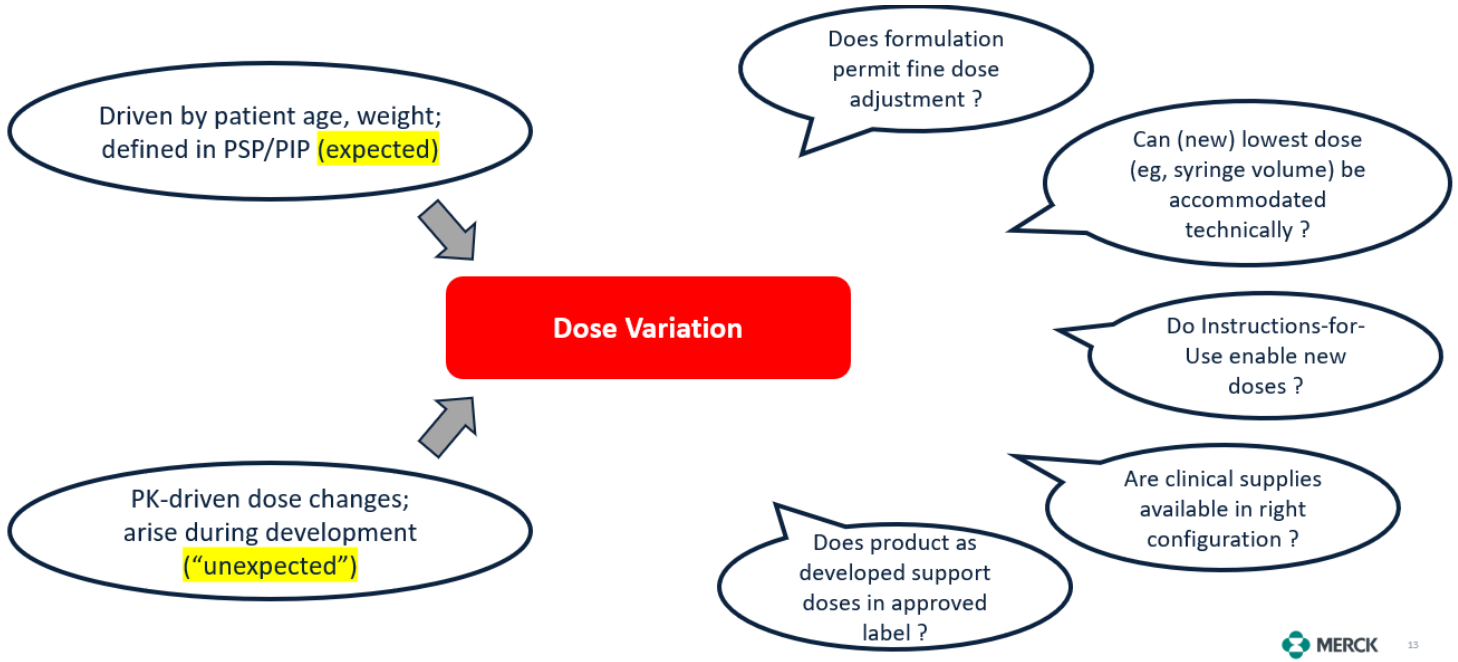
- Dosage form(s) by age-group & terminology
- Formulation, excipients
- PK profiles (immediate/delayed/modified/controlled release)
- Age groups, weight bands?
- Dosing accuracy, dose bands, increments?
- Administration (preparation, manipulations, “don’t do’s”)
- Dosing devices/aids
- Food effect
- Food compatibility
- Palatability (taste/mouthfeel)
- Flavors, sweeteners
- Acceptability (patient/care givers)
- Relevance of dissolution testing? IV/IVC?
- Clinical vs commercial supplies
- Countries for clinical trials/marketing
- Specific CMC product attributes
- Analytical control strategy

LIFE CYCLE MANAGEMENT/
POST-APPROVAL CHANGES

- Change management?
- Equivalency?
- New product opportunities?

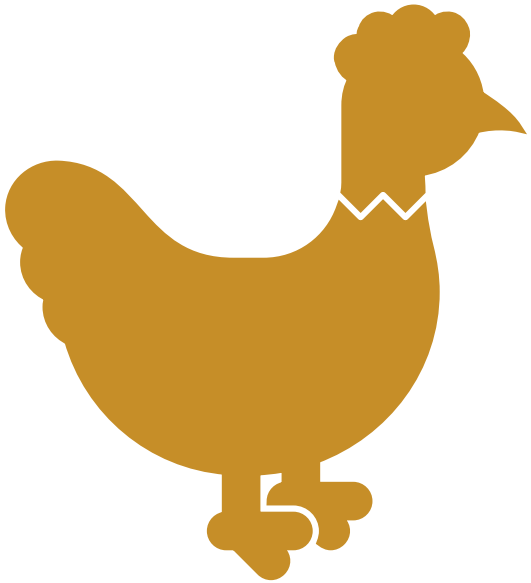
QTPP and Dose Selection

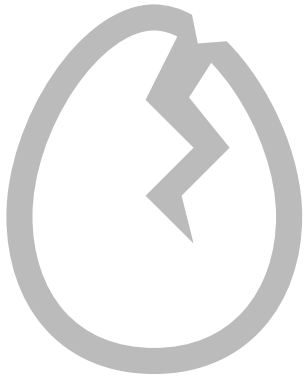
- Dose Variation
- Dosing Flexibility
- Competing interests
- Clinical vs commercial supplies
- Understand, compromise, agree
- Document in QTPP
- Write “Development Strategy”



Ref: Presentation David Harris, PhD

Dose & Strength – What Comes First?



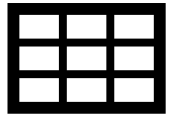


Strength?
(Concentration/Volume)

Dose?

Age-appropriate strength

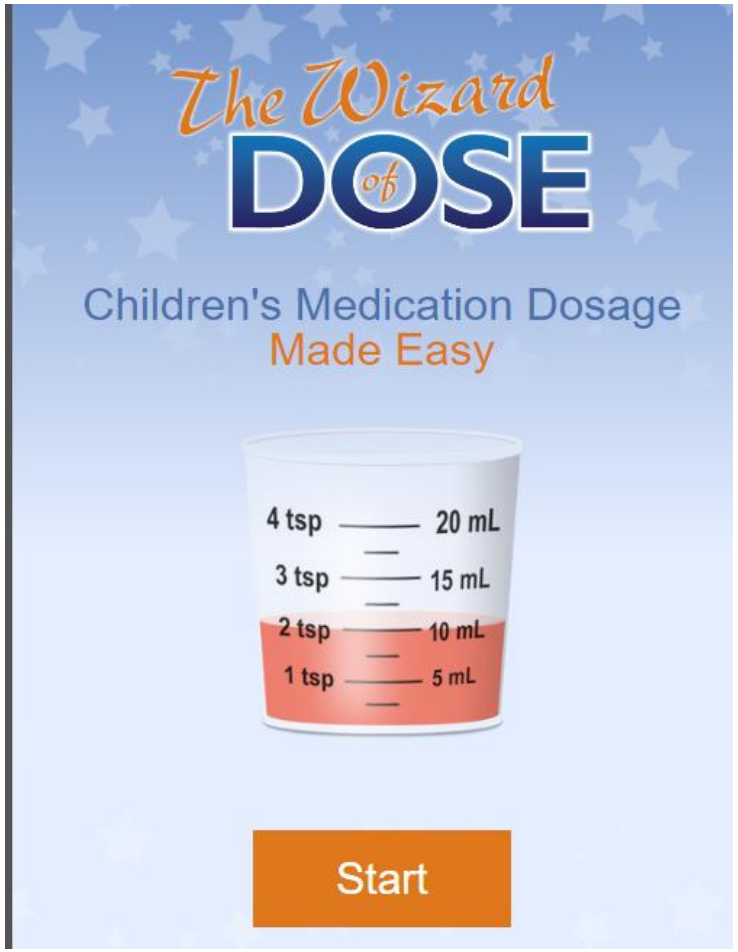
Right Dose?

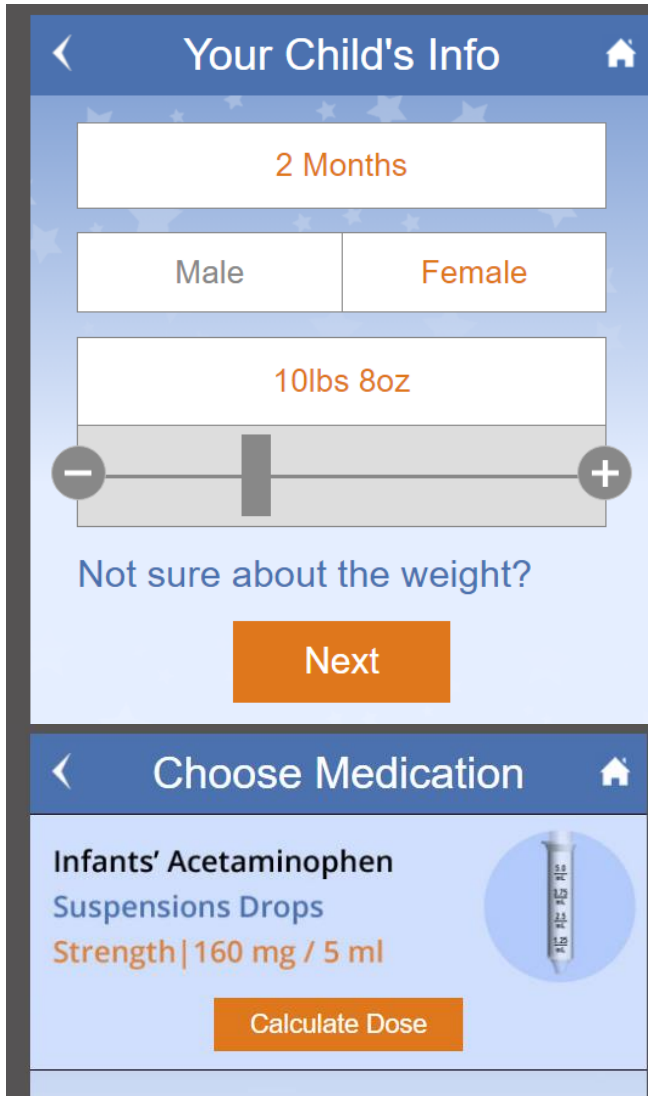


Dosing Tables

- Age ranges
- Weight ranges
- Strengths
- Resulting dose (ranges)

Dose Selection – “The Wizard of Dose”





www.wizardofdose.com

Tribeca Pediatrics

Outlook

- MIDD will accelerate pediatric drug development
- Blessing and curse for CMC
- TPP/QTPP: Agree early on what is needed, desirable vs minimally acceptable
- Be flexible, compromise, collaborate!

- ***Use a TPP and ped QTPP to document agreements and manage change***

Thank You! Questions?

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