

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



PQRI WORKSHOP
MIDD Approaches in Pediatric Formulation Development



A Virtual Event - 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)

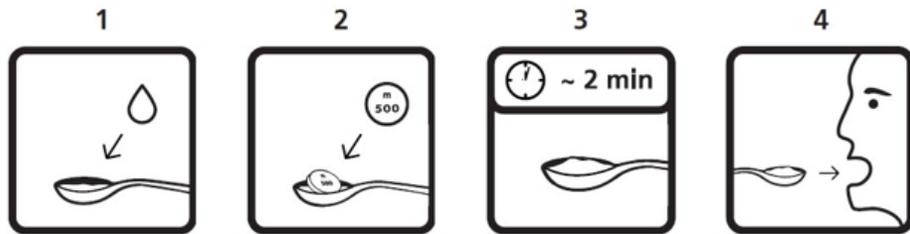
- Patient & CMC Centric
- TPP – your contract with management/project team
- QTPP – your GPS
 - What's unique?
 - Decision making
 - Living Document
 - Benefit of having/downsides of not having one

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; $\geq 1y$)
- Donation program 200 million tablets/year – WHO, INMED Partnership for Children
- Tablet chewed or given by spoon with minimal amount of water



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>

Intestinal worms



CARING & GIVING

At the Heart of Science: How a Small Chewable Tablet Is Helping Tackle a Disease That Impacts Nearly 1 Billion Children Globally

<https://www.inj.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



Example complex: - ISENTRESS® (raltegravir)

ISENTRESS®

Film-coated tablets

400 mg

HD film-coated tablets 600 mg

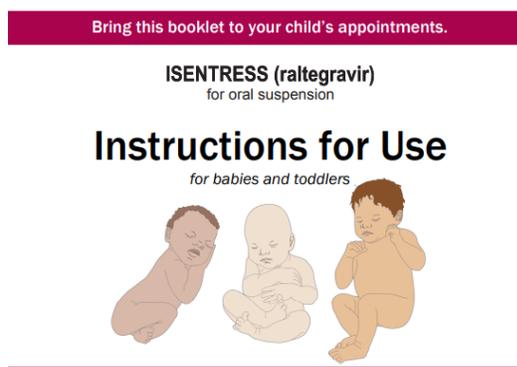
Chewable tablets

25 mg, 100 mg

ISENTRESS® for Oral Suspension



(single-use packet 100 mg)



Kit Contents

- Prescription (on box)
- Instructions for Use (this booklet)
- Prescribing Information
- 6 syringes
- 2 mixing cups
- 60 packets of ISENTRESS

2 blue (10mL) syringes 2 green (3mL) syringes 2 white (1mL) syringes

The kit has an extra cup and set of syringes in case one is lost or damaged.
3 Do not use any damaged cups or syringes.

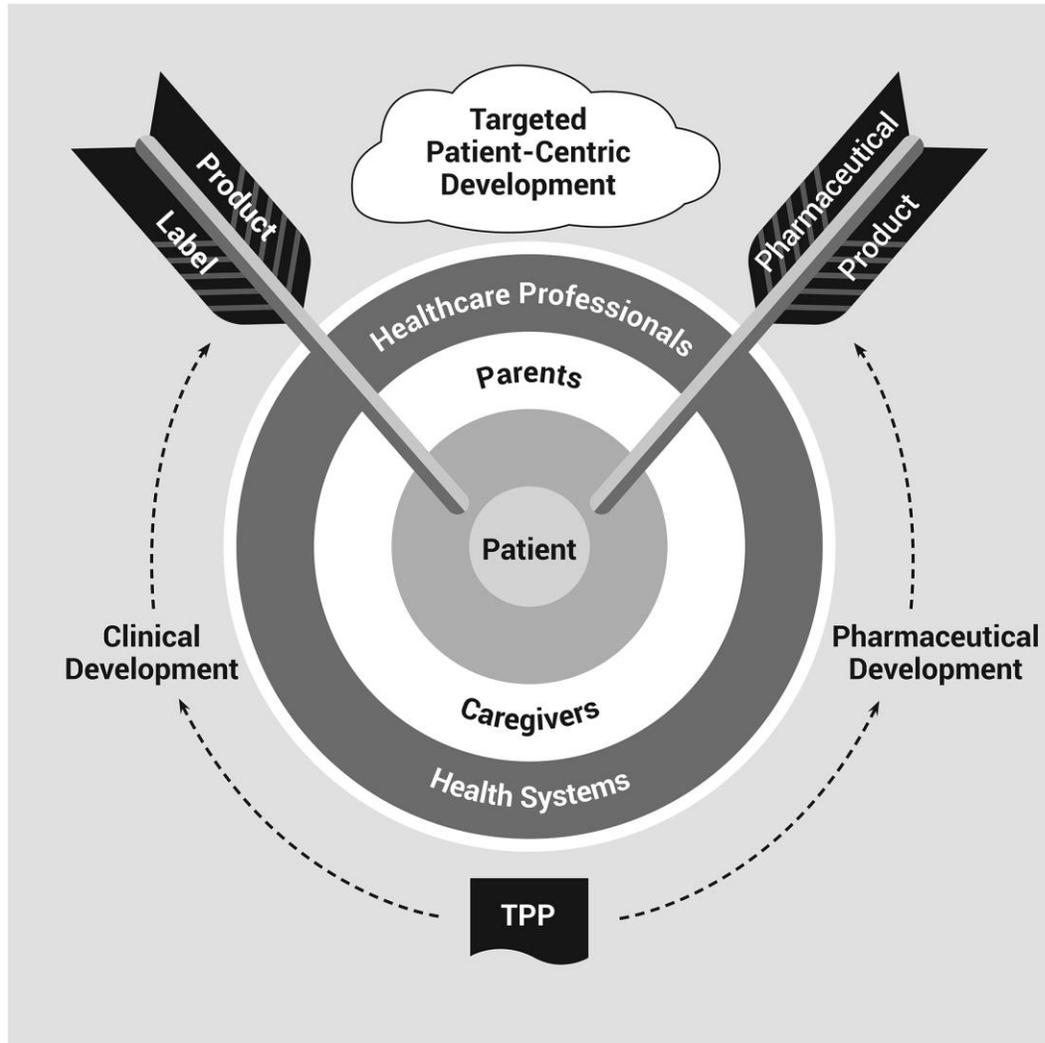
Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing†	
2 to less than 3	0.8 mL (8 mg) twice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

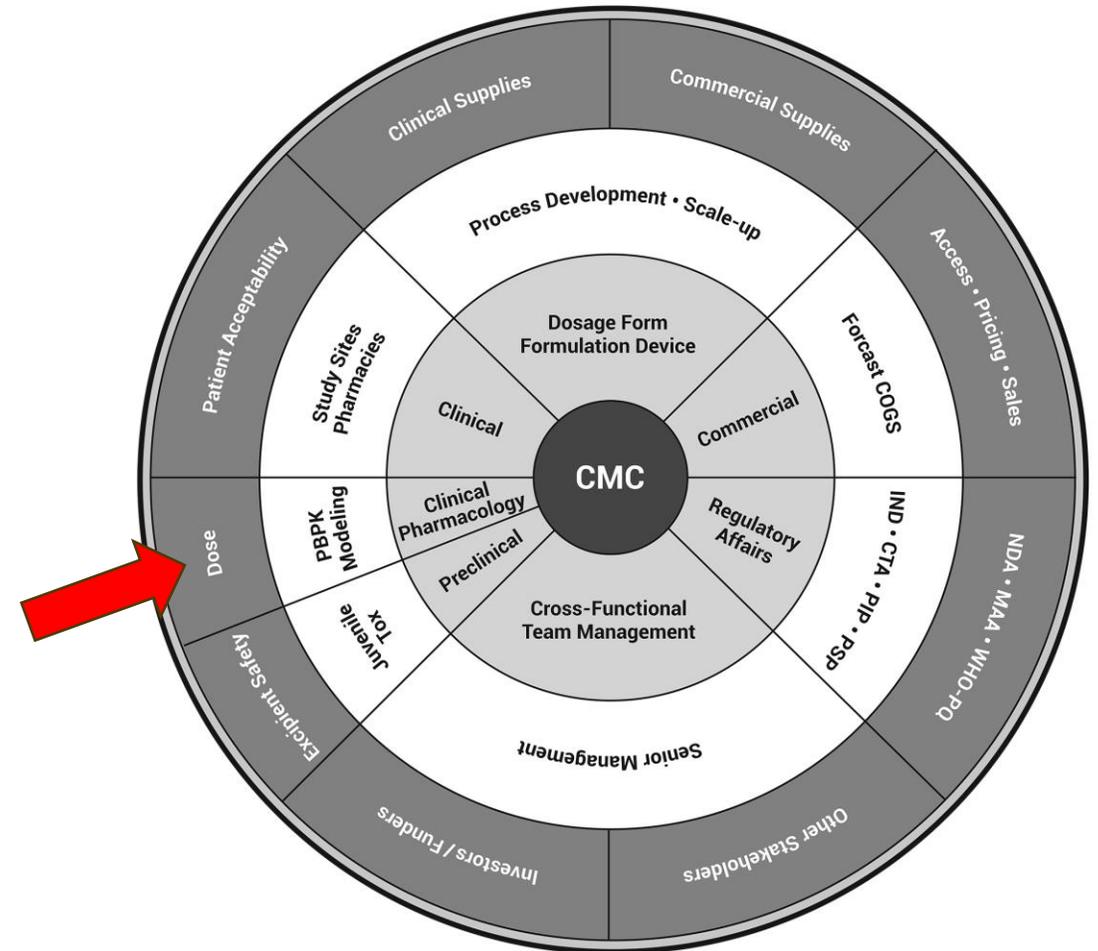


Patient-Centric

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

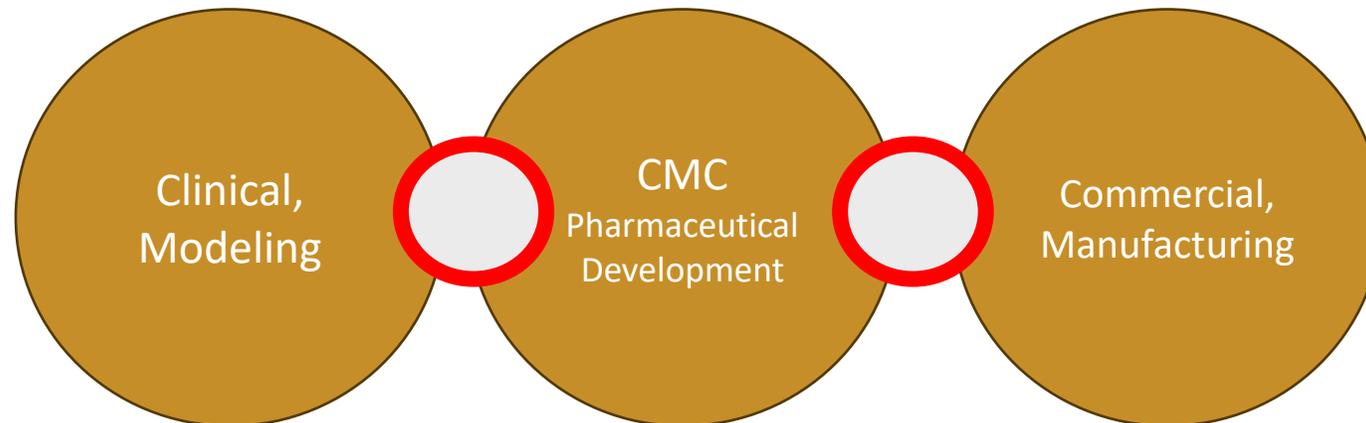


Collaboration



Source: www.EuPFI.org

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



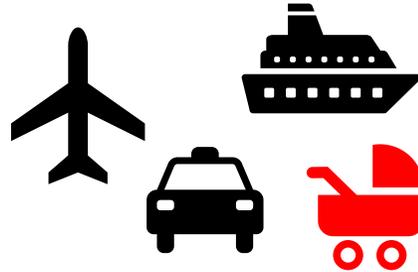


Target Product Profile (TPP)



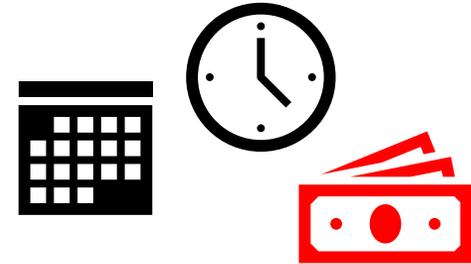
Target
Product
Profile
(TPP)

Where? What?



Product
Development
Strategy

How?

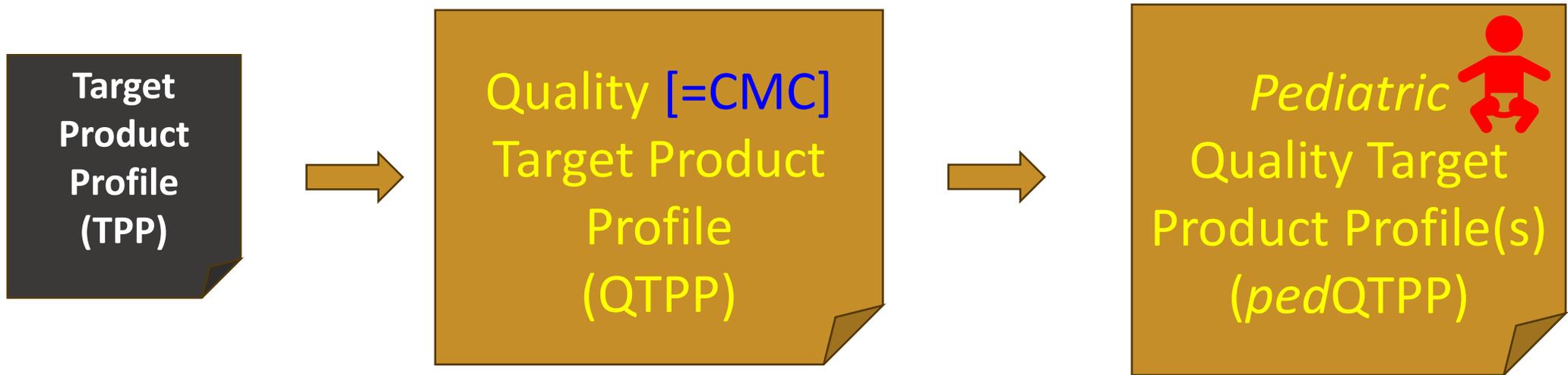


Development
Plan
Timelines
\$\$

How long? How much?



Pediatric Quality Target Product Profile (pedQTPP)



- 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.



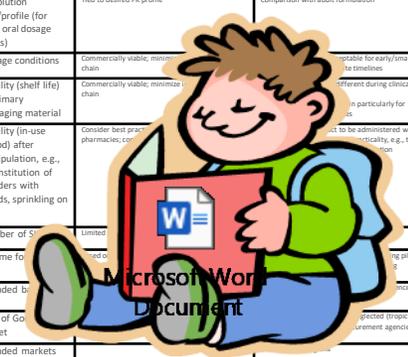
Pediatric QTPP

- **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* (pQTPP)

Attribute	Targets ^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 compared 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

Focus	Attributes	Targets	Comments
Age of Drug	Age appropriate; early in development set direction for oral solid vs oral liquid (or both, when needed)	Age appropriate; early in development set direction for oral solid vs oral liquid (or both, when needed)	Dosage form must be suitable for use in proposed age group; define terminology for consistency
Route of administration	Route depends on indication (disease state), drug properties and age	Route depends on indication (disease state), drug properties and age	Indication can be different from adult indication
Age range	0–18 y	0–18 y	Adolescents can be included in original adult clinical studies and original submission, where justified
Age groups	Preterm and term newborn infants (0–27 d); neonates (28d–12mo); Infants (13mo–23mo); Children (2y–11y); Adolescents (12y–18y(18y))	Preterm and term newborn infants (0–27 d); neonates (28d–12mo); Infants (13mo–23mo); Children (2y–11y); Adolescents (12y–18y(18y))	Dosage forms may be different for different age groups; it is critically important to set targets to guide CMC development work. Consider two subcategories for “Children”: preschool and school-aged children, where appropriate
Drug, dose, potency	Paediatric dose range; dose increments Consider dose banding by weight or age	Paediatric dose range; dose increments Consider dose banding by weight or age	Higher dose flexibility may be needed during clinical studies; major driver for resulting number of SKUs
Acceptability	Acceptable for the proposed patient population & care giver(s); appropriate for disease state	Acceptable for the proposed patient population & care giver(s); appropriate for disease state	“Acceptability” is a recovery “soft target”; critical evidence of “acceptability” needs to be generated. Consider healthy adult taste panels.
Drug release profile (PK)	Cmax, AUC, t1/2	Cmax, AUC, t1/2	
Adult vs pediatric formulation	“Closeness” of pediatric PK with adult PK	“Closeness” of pediatric PK with adult PK	Depends on development strategy e.g., fully pediatric clinical program vs. modeling and extrapolation strategy. Close collaboration of CMC with Clinical Pharmacology and Clinical needed
Comparator drug	Yes/no	Yes/no	For clinical studies; open-label vs blinded; need for over-encapsulation. Could become time-critical activity
Excipients selected for clinical studies	Yes/no	Yes/no	For clinical studies
Quality of excipients	Tox qualified for intended age-group	Tox qualified for intended age-group	Attention to novel excipients with potential need for additional toxicology
Additional Toxicology	Juvenile toxic studies	Juvenile toxic studies	Gap assessment to identify need for additional studies; requirements for AP/Pharmaceutical
Drug characteristics	Morphology, particle size distribution, wettability, etc.	Morphology, particle size distribution, wettability, etc.	Specify targets if API characteristics different from API used for adult product
Age Form	Patent protection/freedom to operate Synergies with adult dosage forms?	Patent protection/freedom to operate Synergies with adult dosage forms?	Assess potential for patent protection, if innovative formulation concept Existing knowledge (e.g., stability of adult formulation) vs starting fresh with new dosage form
Dose strengths (if dosage forms)	Meeting requirements for dosing flexibility	Meeting requirements for dosing flexibility	Typically, more strengths, more concentrations/different volumes needed during clinical studies
Administration of dosage form	To enable instructions given in product label	To enable instructions given in product label	There is also value in generating data to exclude certain manipulations.
Administration aids (devices)	E.g., indicate if application via nasogastric and gastric tubes required	E.g., indicate if application via nasogastric and gastric tubes required	
Dosing devices	Clearly establish upfront and identify need for user requirements	Clearly establish upfront and identify need for user requirements	
Stabilizers	Yes/no	Yes/no	If “yes”, specify
Preservatives	Yes/no	Yes/no	
Compatibility	When administration with specific food recommended	When administration with specific food recommended	Good practice to identify food that should not be used for administration, e.g., for pH sensitive formulation
Purity/Degradation products	Anything requiring special attention?	Anything requiring special attention?	As good or better than adult product?
Dilution	Tied to desired PK profile	Tied to desired PK profile	Comparison with adult formulation
Age conditions	Commercially viable, noncomplex supply chain	Commercially viable, noncomplex supply chain	Stable for early/infant use timelines
Stability (shelf life)	Commercially viable, noncomplex supply chain	Commercially viable, noncomplex supply chain	Different during clinical chain
Primary packaging material	Easy to manufacture, freedom to operate, noncomplex supply chain	Easy to manufacture, freedom to operate, noncomplex supply chain	In particular for clinical studies
Stability (in-use)	Consider best practice for pharmaceuticals; consider stability, e.g., time between preparation and administration	Consider best practice for pharmaceuticals; consider stability, e.g., time between preparation and administration	Stability to be administered within clinical timelines; e.g., time between preparation and administration
Access	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	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



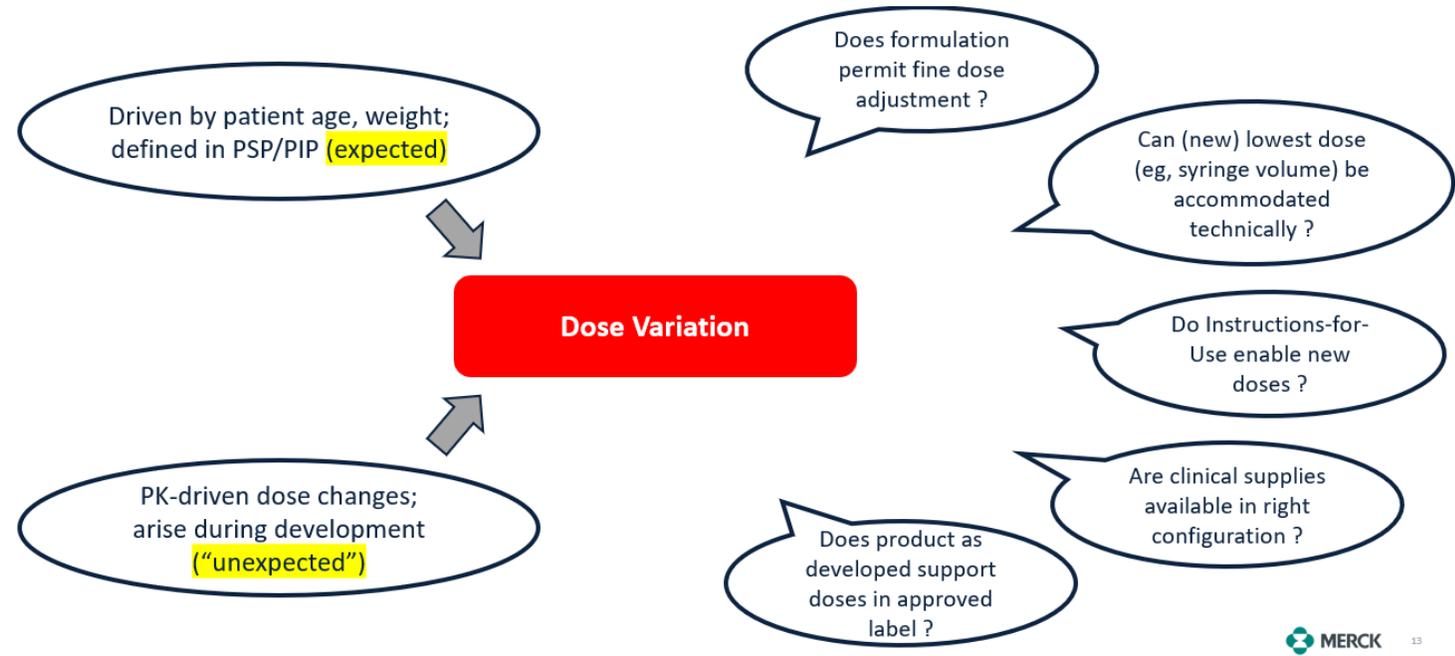
LIFE CYCLE MANAGEMENT/ POST-APPROVAL CHANGES

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



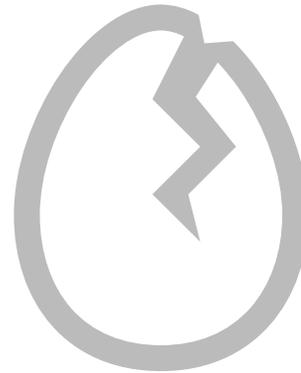
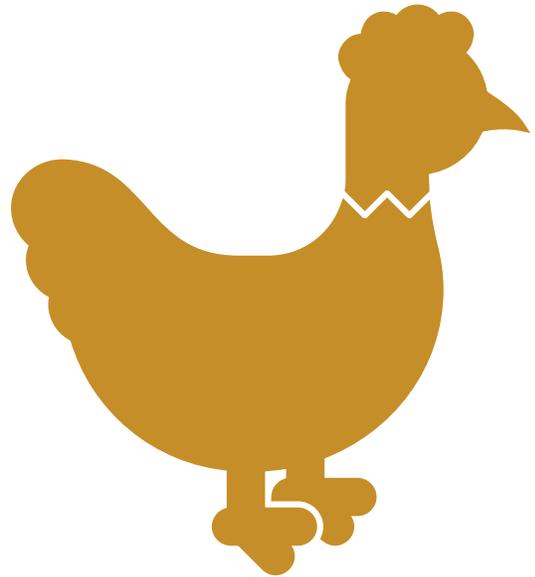
QTPP and Dose Selection

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





Dose & Strength – What Comes First?



Dosing Tables

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

Strength?
(Concentration/Volume)



Age-appropriate strength



Dose?



Right Dose?



Dose Selection – “The Wizard of Dose”

The Wizard
DOSE
Children's Medication Dosage
Made Easy



Start

www.wizardofdose.com

Tribeca Pediatrics

Your Child's Info

2 Months

Male Female

10lbs 8oz

Not sure about the weight?

Next

Choose Medication

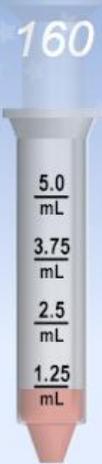
Infants' Acetaminophen
Suspensions Drops
Strength | 160 mg / 5 ml



Calculate Dose

Result

Infant's Acetaminophen
Strength: 160 mg / 5 ml



Dosage
1.25 mL

Back



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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