

Challenges Associated with Developing Medicines for Children – An Industry Perspective

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Wikihow.com excerpt – ‘How to administer medicine to a resistant child’

"Lay the child on the floor (this may require two people once the child gets wind of what's coming) with their head between your knees and their legs facing in front and away from you.

*Use your knees to hold the child's head still. **Be careful**, do not squeeze, just hold. This gives you both hands to administer the medication.*

Pinch the child's nose closed with one hand and squirt the medication into the mouth with the other. Don't let go until they swallow. When you pinch the nose, they will have to open their mouth to breath, no choice. With the nose plugged, they have to swallow or choke. Again, this is a last resort, temporary until better arrangements can be made.

Do not praise the child after using this technique - make it a non-plus situation. Giving it any credit will only encourage a repeat episode."

Perspective

Pharmaceutical scientists in industry and academia have a responsibility to design and develop age appropriate formulations



Developing global medicines designed for children using most appropriate pharmaceutical and analytical technologies.

Designing and Developing a Pharmaceutical Product Intended for Paediatric Use

- There are a number of challenges associated with developing a pharmaceutical product intended for paediatric use and these have been recently well published e.g. Ernest et al 2007.
 - provide dose flexibility
 - provide dose accuracy
 - overcome dysphagia
 - meet the needs of a population with a wide range in physiological size and maturity
 - ensure patient adherence i.e. need for taste masking etc.
- This presentation aims to highlight potential strategies and areas where additional research may help overcome some of these challenges.

Know your patient



Know your patient - physiology

- The paediatric population is highly homologous and includes the following age groups as defined by ICH:
 - preterm newborn infants
 - term newborn infants (0 to 27 days)
 - infants and toddlers (28 days to 23 months)
 - children (2 to 11 years) Note: the EMA define age 2 to 6 as 'Pre-School' and 6 to 12 as 'School Children'
 - adolescents (12 to 16-18 years (dependent on region))
- The difference in physiological maturity between these groups can be significant and relevant data associated with healthy subjects is sparse and contradictory as illustrated by Bowles (2010) and Kaye (2011).
- Funk (2012) suggests that an understanding of the anatomic and physiologic changes during development is paramount in predicting age-appropriate changes in drug disposition.

Know your patient - physiology

Table 2 Summary GI tract pH data in patients of different age groups in the fasted state

Organ	Neonate (0–27 days)	Infant (1–23 months)	Child (2–11 years)	Adolescent (12–18 years)	Adult (>18 years)
Mouth	7 [14]	–	7.1 [15]	7.4 [16]	6–7.4 [17]
Oesophagus	–	>5 [18]	>5 [18]	>5 [18]	5–6 [5]
Stomach	6–8 [7]*	1.4 [19]	1.5 [12]	1.5 [12]	1–2.5 [5, 19]
Duodenum	–	–	6.4 [2]	6.3–6.4 [12, 20]	5–6.5 [21–23]
Small intestine	–	–	6.4–7.4 [12]	6.4–7.4 [12]	6–7.5 [5, 24, 25]
Caecum	–	–	5.9 [12]	5.9 [12]	6–6.5 [5, 11]
Colon	–	–	5.9–6.5 [12]	5.9–6.5 [12]	7–7.5 [5, 24, 25]
Rectum/faecal matter	4.4–7.2 [13]	5.9–10.9 [26, 27]	6.5–12.1 [12, 26, 27]	6.5 [12]	6.7–7.8 [23, 28]

* Falls to 1.5–3 several hours after birth, then raises again to pH 6–7 [6–9]

Review Article. Review of paediatric gastrointestinal physiology data relevant to oral drug delivery

Jonathan L. Kaye, Int J Clin Pharm (2011) 33:20–24

DOI 10.1007/s11096-010-9455-0

Know your patient - territory

- Do the children in all intended territories have similar access to clean water? What impact does this have on products designed to require reconstitution prior to use?



- What dosage forms are children in the intended territories more familiar with? Oral solutions in the US or dry syrups in Japan for example.
- Are multi-use packs more convenient for the patient than single use packs?

Know your patient - preferences

- ‘Voice of the customer’ intelligence is absolutely critical to developing medicines for children.
- Children are far less tolerant than adults. If a child tries something once and doesn’t like it there often is no going back!
- More research is required to define acceptable dosage form presentations across the sub populations with an emphasis on the patient and not necessarily the care giver.

Know your patient - Summary

- Be sure to understand the physiology of the targeted patient group or groups and consider how this may affect the performance of the formulation and subsequent bioavailability. Consider the impact of disease state on this physiology too.
- If developing a global product consider the impact of lifestyle differences and any potential impact on access or administering the medicine in the way that is intended.
- Gain intelligence for patient preferences in the intended territories and seek to develop a product with generic acceptability across intended territories.
- Packaging may be used to present a similar formulation in different ways e.g. a granule may be filled into a sachet and be presented as a 'dry syrup' or compressed into a small tablet.

Selecting the Most Appropriate Dosage Form Type

- A number of factors will influence the selection of the most appropriate dosage form type for the paediatric medicine.
- It is unlikely that one dosage form type will fit all requirements and therefore analytically based risk/benefit approach is recommended to help select the most appropriate dosage form design.

Ref. Sam, T. et al, A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – An application for paediatric dosage form selection, International Journal of Pharmaceutics 435 (2012) 115 - 123

Table 3

Case study 3: multiple dose oral liquid containing preservative versus a single unit dose non-preserved oral liquid (treatment group 2–6 years).

Benefit/risk	Criterion for drug product	Liquid solution (2–6 years)	Non dispersible tablet (6–12 years)	Sprinkle (2–12 years)
1. Efficacy/ease of use	1.1 Dosage: – Dose flexibility – Acceptable dose size/dose volume	High dose flexibility provided by volume administered	Minimal dose flexibility, but a range of unit doses could be prepared	Moderate dose flexibility but a range of unit doses could be prepared. Or the quantity of sprinkle administered could be adjusted according to the dose required Risk mitigation A dispensing device would be required to enable sprinkles to be 'sub dispensed' by volume according to dose required Portable
	1.2 Dose preparation and administration: – Easy and convenient handling – Correct use		Portable A breakline could be used	
	1.3 Compliance: – Minimal impact on life style – Acceptable colour and taste – Minimal administration frequency	Taste masking/flavouring of solution may be required	Tablet would need to be suitably small to avoid swallowing difficulties in the age group	Mouthfeel would need to be considered but taste per se could be masked by administering with food for example or by coating
	2.1 Drug substance/drug product: – Acceptable and consistent bioavailability	Potential for precipitation upon administration or increased exposure to be considered Risk mitigation A relative bioavailability study may need to be considered if significantly different formulations are to be used across age groups Solubility enhancing, flavouring or sweetening excipients may be required	Acceptable biorelevant dissolution profile required	Acceptable biorelevant dissolution profile required. If taken with food the impact of the food on bioavailability would need to be considered Risk mitigation Testing with food might need to be conducted
2. Patient Safety	2.2 Excipients: – Minimal number and levels needed for acceptable formulation – Acceptable tolerability and safety	Risk mitigation Paed tolerability of such excipients would need to be considered Preservatives may be required for long term storage		Foodstuff could impact drug product or API stability Risk mitigation Stability/compatibility of drug product in a range of foodstuffs would need to be considered If sprinkled on food all food would need to be consumed for complete dose to be administered
	2.3 Stability: (chemical/physical/microbial stability in the relevant environments and climates) – Stable during shelf life – Stable in use	Risk mitigation Single use or multi use packs of solution could be prepared		
	2.4 Dosing precision and accuracy: – Minimal risk of medication error/dosing error – Minimal manipulation by health professionals or caregivers prior to use	A suitable device for dose measurement required		
	3. Patient Access	3.1 Manufacturability: – Robust manufacturing process – Commercial viability	Conventional manufacturing process	Conventional manufacturing process
3.2 Affordable: – Acceptable cost to patient or health care provider – Easily transported and stored e.g. need for cold chain – low environmental impact e.g. consider packaging and disposal costs		May require specialized storage conditions if preservatives are not used. May require 'clean' manufacturing conditions if non preserved		Sachet packaging costs could be high.
3.3 Speed: – Easily developed and produced		Depends on need for solubility enhancement and taste masking. Could be complex development	Could be derived from adult dosage form if available	Fastest approach as only one dosage form is required. However taste masking efforts may be required. Sprinkle formulation could be derived from adult dosage form if available. Requires specialized manufacturing

Table 6
Score card to evaluate the most appropriate paediatric dosage form.

Scale and criteria for selecting an appropriate drug product		Score card to evaluate the most appropriate paediatric drug product (Compound X, Children 2–6 years, chronic treatment at home, volume per dose 5 mL, 14 days supply of medication required)																	
1 Equal	Two products contribute equally to the objective	Multiple dose oral liquid containing preservative (150 mL bottle plus syringe)									Single unit dose non-preserved oral liquid (5 mL sachets)								
3 Moderate	Experience and judgement slightly favours one product over the other																		
5 Strong	Experience and judgement strongly favours one product over the other																		
7 Very strong	One product is strongly favoured and its dominance demonstrated in practice																		
9 Extreme	The evidence favouring one product over the other is of the highest possible order of affirmation																		
2,4,6,8 Intermediate values – compromise is needed																			
Efficacy/ease of use	Dosage	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Dose flexibility																		
	Acceptability of dose size/dose volume																		
	Dose preparation & administration	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Easy and convenient handling																		
Patient safety	Compliance	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Minimal impact on lifestyle																		
	Acceptable colour and taste																		
	Minimal administration frequency																		
	Drug substance/drug product	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Acceptable and consistent bioavailability	9	8	7	6	5	4	3	2	1	2	3 ²	4	5	6	7	8	9	
	Excipients																		
	Minimal number & levels needed for acceptable formulation																		
	Acceptable tolerability & safety																		
	Stability	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
Patient access	Stable during shelf life																		
	Stable in-use																		
	Medication errors	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Minimal risk of dosing error																		
	Manufacturability	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Robust manufacturing process																		
	Commercial viability																		
	Affordable	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9	
	Acceptable cost to patient or health care provider																		
	Easily transported and stored																		
Low environmental impact																			
Speed	9	8	7	6	5	4	3	2	1	2	3	4	5	6	7	8	9		
Easily developed and produced																			

Note: Scores are for illustrative purposes only. Scoring should be made on a case-by-case basis.

² Preservative selected considered acceptable for this age group.

Selecting Safe Excipients at Appropriately Safe Levels

- Excipients are fundamental to any dosage form design but historically the tolerability of excipients has often been overlooked.
- Langley (2012) recently demonstrated that one multi-syndrome infant was receiving five times the WHO recommended maximum daily amount of propylene glycol a day from one medicinal product.
- Breitzkreutz and Boos in 2007 also demonstrated a number of excipients which may result in adverse events in children when used at particular concentrations. For example, an article in the European Industrial Pharmacy (Issue 8, February 2011) suggests that microcrystalline cellulose should not be used in children ≤ 2 years. However, this excipient is one of most commonly used excipients in adult tablet formulations.
- However, it is essential that the 'formulators toolbox' contains as many functional excipients as possible to help ensure that the dosage form can be appropriately designed.

Enabling the Safe Use of Excipients

- What are the solutions?
 - Can pre-clinical juvenile toxicity studies help ensure that the ‘formulators tool box’ retains the tools required to develop medicines for children.
 - If so and when performed, can these data be shared within the industry to prevent the need for individual companies performing duplicate testing on the similar excipients.
 - Improvements in consistent and haphazard reporting of **potential** issues.
 - The EuPFI are compiling a database of associated literature references (STEP database) associated with toxicity of excipients

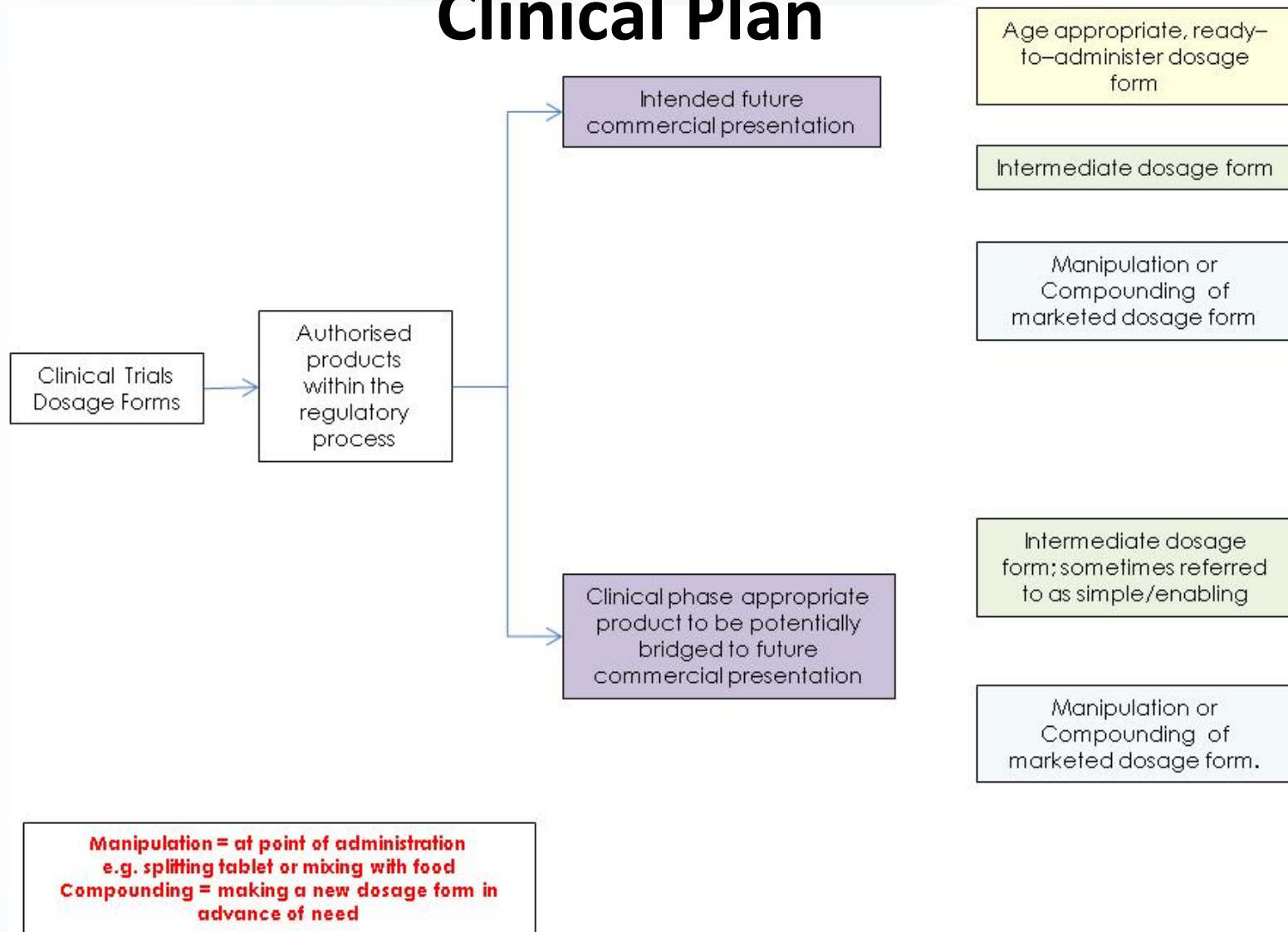
Selecting Appropriate In-vitro Techniques

- As previously discussed the physiology of the paediatric subgroups requires greater definition to appropriately design paediatric formulations
 - For example, appropriate bio-relevant dissolution techniques require knowledge of GIT pH, relevant media volume and media composition (the volume of the stomach of a fasted neonate is 2.5mL).
- Development of suitable biopharmaceutical techniques e.g. solubility models, dissolution testing, permeability models to assist product development for paediatric patients is especially critical for the following reasons:
 - To enable development and refinement of a paediatric dosage form.
 - To minimise the number of in-vivo studies in children designed to evaluate product performance
 - To help avoid the need for bridging studies in children to support product development strategy whereby a different (enabling) formulation to the commercial formulation is employed for non pivotal studies.
- Purohit (2012) suggests strategic design of adult studies with paediatric formulation strategy in mind to help mitigate risks of bridging studies in children e.g. compare the use of a solution or suspension to a tablet in a relative biostudy in adults to gain an understanding of the biopharmaceutics of the compound and the formulation.

Evaluating Palatability

- Palatability testing is critical in the development of children's medicines.
- Palatability may be assessed using in-vitro test methods such as the electronic tongue, using adults in a taste panel or using other techniques as the rat lickometer model.
- The draft EMA guideline indicates the importance of testing palatability in patient acceptability studies.
- A taste strategy may be appropriate whereby taste is assessed (where possible) using an adult sensory panel followed by assessing taste acceptability in subsequent clinical studies conducted in children. A simple protocol can be designed and used in a clinical setting to gain feedback on the taste of the product administered in the target patient population.

Developing a Formulation Strategy to Support a Clinical Plan



Use of the Product in Practice

- Though difficult to anticipate, the potential manipulation of the final product in practice should be considered by industry e.g.
 - the stability of a product reconstituted in an alternative liquid to water should be considered.
 - the use of food to administer the product should be considered both in terms of impact on bioavailability but also in terms of stability.
 - the potential for only part of the medication to be administered for example tablet splitting or sub dosing, and formulation design or an appropriate packaging strategy should be used to mitigate these risks.
 - where proven feasible and supported by industry data, such manipulations should be registered and the method of manipulation detailed in the product SmPC.

EuPFI Workstreams

- Pharmaceutical Excipients
- Taste Masking and Taste Assessment Methods
- Extemporaneous Formulations and Dispensing
- Administration Devices
- Age Appropriateness of Formulations

Concluding Remarks

- Focus on your patient
- Consider a risk based approach when selecting an appropriate dosage form or to help select suitable excipients.
- Do not assume that tolerable safe excipient levels in adults are directly applicable to tolerable safe levels in pediatrics.
- If excipient juvenile toxicity testing for excipients is required consider how this may be shared to prevent unnecessary duplication and delay to providing medicines to children.
- Further research is required to understand healthy paediatric GI physiology and to translate this information into developing and validating *in-vitro* models to assist product development and to prevent the need for bridging studies.

Concluding Remarks

- Develop a strategy to assess palatability to help ensure adherence in children.
- Develop a formulation strategy that minimises risk and delay to clinical plans by considering the use of adult studies to gain an understanding of biopharmaceutics and the use of enabling paediatric formulations.
- Think about how the commercial product may be used in practice and consider mitigation to avoid misuse or unsafe application.