

Development of paediatric formulations - points to consider

Workshop on Paediatric Formulations II London, 8 November 2011

Presented by: Ann Marie Kaukonen Scientific Administrator, Paediatric Medicines, EMA (Fimea)



Timing of paediatric formulation development



Timing of paediatric formulation development







4 Development of paediatric formulations - points to consider









6 Development of paediatric formulations - points to consider



7 Development of paediatric formulations - points to consider



Rationale and justification for planned formulation strategy in (early) PIP's

- Paediatric subset(s) targeted
- Condition to be treated
- Proposed dosing, need for normalised dosing (criticality)
- API pharmaceutical and biopharmaceutical properties
 - solubility limitations vs dose physico-chemical basis
 - permeability properties physico-chemical limitations and/or efflux/active transport, GI first pass components
 - stability issues limiting choice of formulation approach (chemical and physical)
 - taste issues, need for taste masking
 - food effects, differences in exposure between formulations used in pre-clinical or Phase I trials
 - \rightarrow (likely) excipients, function and safety considerations
 - → differences in approach across age sub-sets and/or during development
- → Feasibility of formulation strategy and identification of risks
 - → Target formulation and/or formulation performance
- Development of paediatric formulations points to consider

Considerations on dosing needs

Appropriateness of dosage form and formulation related to dosing needs Depending on metabolic pathway, dose in certain paediatric subsets may be lower, same or even higher than in adults

- higher clearance most common in children 2 6 10 years
- if dose is higher in children and the same formulation or API/excipient ratio used in adults & children
 - → excipient dose higher in children (mg/kg/day)
 - \rightarrow bulk and volume of dose higher in children
 - potential issue both for oral and parenteral products
 - also excipient concentration related (local) effects may be more pronounced
- dosing needs during clinical trials may differ from needs for marketed product
 - for initial PK/PD higher need for precision and accuracy (mg/kg or mg/m2)
 - after established safety and efficacy, dose banding (fixed dose) may be possible → possibility to use unit dose dosage forms
- 9 Development of paediatric formulations points to consider

Dosing flexibility Challenges for solid dosage forms

Risk of dosing errors – uniformity of content and user errors

Parts of tablets

_

- uniform distribution of active across tablet
- functioning score line → breakability
- Need for content uniformity to be confirmed depending on dose criticality
- Multiple units of 'mini-tablets' or pellets
 - how to dose or count device, packed in unit-dose capsules or sachets?
- Proportion on sachet content of multi-particulate system (mini-tablets, pellets, granules)
 - dose uniformity across units of multi-particulate systems
 - number/amount of particles to be dosed and amount of active/particle
 - means of measuring the dose?
 - potential to disperse multi-particulate system (taste, dosage form, stability)?
 - if solution or dispersion dosing accuracy when sub-sampling?

Concerns especially relevant for potent drugs with low drug content

Dosing flexibility - Challenges for liquid systems

Risk of dosing errors - dosage form performance and user error

Suspensions (multidose)

- Ease/reproducibility of reconstitution and re-dispersibility
- Viscosity and wetting properties → effects on sedimentation and formation of froth (entrapment of air)
- Dosing accuracy vs dose criticality (possibility for dose banding)
- Dedicated measuring device (syringe) to ensure appropriate dosing
- Dispersible solid formulations (tablets, granules, powders)
 - Less risk if entire dose unit is taken after dispersion in liquid
 - If a solution of active is formed, risk related more to user error
 - High risk if part (volume fraction) of a dispersion is to be taken!
 - Same concerns as for multidose suspension to obtain well dispersed system
 - May be acceptable, but dosing accuracy needs to be shown
 - Clarity of steps for preparation critical in addition to confirmed dosing accuracy

Especially relevant for potent drugs – low drug content in suspension

Oral administration through feeding tubes

- an option for oral administration when patient is unable to swallow due to their age or the condition to be treated
- prerequisite that intestinal absorption is functioning
- risk for dosing inaccuracy and blockage of feeding tube
- volume, density, viscosity and particle size (active or dosage form) affect ease of administration and dosing accuracy after extrusion through tube
- also potential compatibility issues with feeding tube material
 - Active substance adsorption (esp. lipophilic API's)
 - Excipients (lipids, surfactants)

Dose recovery needs to be shown after extrusion through feeding tube

- doses and rinse volumes relevant to the target age group!
- and relevant feeding tube (sizes)

Changes in the formulation during development

Different formulation technology and/or excipient(s) levels may lead to

- different exposure and PK (e.g. Cmax)
- potentially also different PD and/or safety
- different palatability and acceptability \rightarrow compliance
- risk assessment based on critical parameters of API and adult formulation compared to likely final paediatric formulation
 - → NEED FOR BRIDGING STUDIES!!
 - Manipulated adult dosage forms
 - may be justifiable for use in clinical trial but may be risky
 - validation of method of preparation and formulation performance
 - physico-chemical stability and compatibility
 - dosing accuracy and reproducibility
 - BA PK (- PD?)
- 13 Development of paediatric formulations points to consider

Predicting performance of paediatric formulations

- BA/BE and PK of adult vs paediatric formulation in healthy volunteers
 - results obtained in adults are used as starting point for PK and dose extrapolation/modelling
 - relevant dose in adults if children receive higher dose (mg/kg)? (BCS II&IV)
- Preterms, neonates and (small) infants differ in gastric function
 - Gastric pH upto 2 years (gastro resistant)
 - Absorptive function (active/efflux transport)
 - Gastric emptying time (gastro resistant, modified release)
 - Intestinal transit time (modified release)
 - Bile flow (upto 2 years) (BCS II and IV)
 - Lipase activity (BCS II and IV; lipid formulations)
 - Food effect/Food composition
- Need for adjusted *in vitro* methods during pharmaceutical development?



Considerations on the BCS

Applicability of BCS in the paediatric population?

Class I	Class II
High solubility	Low solubility
High permeability	High permeability
Class III	Class IV
High solubility	Low solubility
Low permeability	Low permeability

Does the same BCS apply for a specific paediatric subset?

Difference in dose? Difference in volume available for dissolution? Difference in GI transit time? Difference in absorptive properties?

Special groups

- pre-terms, neonates and small infants
- Age groups where dose higher than in adults



Different formulations during development or between age groups

Compounds most at risk for effects on PK and exposure:



- compounds requiring control of solid state properties
- compounds requiring solubilising formulations or showing high (fatty) food effects
- substrates of efflux (and absorptive) transporters and/or metabolic enzymes
 - risk for effects by food or drink used to improve palatability (e.g. fruit juices)
- compounds sensitive to changes in transit time

Excipients - effects on intestinal wall processing

Lipid excipients/ surfactants	Examples	Comments	References
Polyoxyethylated/peg	ylated		
Polyoxyl 35 caster oil	Cremophor	CYP3A and P-gp inhibitors	[2,31,32,67,68]
PEG-15- hydroxystearate	Solutol HS-15	CYP3A and P-gp inhibitors	[2,67]
Medium chain glycerol and PEG esters	Labrasol, Softigen 767, Acconon	P-gp inhibitor	[2]
Polysorbates	Tween 80, Tween 20	CYP3A and P-gp inhibitors	[2,67,68,69]
Sucrose esters	Sucrose monolaurate	P-gp inhibitor	[2]
Tocopherol esters Polymers	Vitamin E-TPGS [*] Pluronic block copolymers	P-gp inhibitor CYP3A and P-gp inhibitors	[2,37,68,70] [2,71,72,73]

^a TPGS: D-alpha-tocopheryl polyethylene glycol 1000 succinate.

17 Development of paediatric formulations - points to consider



Excipients - effects on intestinal transit

Excipients used as sweeteners, stabilisers and/or solubilisers

Poorly absorbed excipients with osmotic effects (sugar alcohols, polyethylene glycol, others)

- GI disturbance, laxative and/or transit time effects
- Mannitol
- Sorbitol
- Xylitol and maltitol (?)
- PEG 400
- Effects vs dose similar in children and adults?
- Higher sensitivity to transit time effects than adults?
 - Diarrhea linked to carbohydrate mal-absorption common in infants and preschool children
- Major changes between level of excipient and/or use of different excipients (e.g. sucrose vs sorbitol) → potential effects on PK and BA



Excipients – safety considerations Benefit – risk considerations

- Pharmacological or physico-chemical basis for toxicity
- Age group to be treated
 - Sensitivity to potential toxic effect/mechanism of action
 - Metabolic capacity
 - Special groups: preterms, neonates, infants
- Dose of excipient (mg/kg/day) and length of treatment
- Condition to be treated
 - Acute or chronic
 - Severity of condition treatment needs
- Functionality and criticality of excipients and levels

Excipient justification – benefit - risk analysis

- EMEA/CHMP/SWP/146166/2007 CHMP Scientific Article 5(3) Opinion on the potential of carcinogens, mutagens and substances toxic to reproduction (CMR) when these substances are used as excipients of medicinal products for human use
- In addition to CMR toxicity, also a summary on the general justification on the use of excipients and risk-benefit analysis
- "Overall, the use of any excipient with a known potential toxicity, and which could not be avoided or replaced, would only be authorised if the safety profile was considered to be clinically acceptable in the conditions of use, taking into account the duration of treatment, the sensitivity of the target population and the benefit-risk ratio for the particular therapeutic indication."



Conclusions

Development of Paediatric Dosage Forms and Formulations

Requires an integrated approach

Lack of knowledge needs to be recognised and specified

More research is needed!

Collaboration between industry, academia and regulators