Formulations for clinical trials in children: possibilities and pitfalls?

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Formulation – two meanings

- Process in which different ingredients, including the active substance, are combined to produce a medicinal product.
- Dosage form (the way in which a medicinal product is manufactured and presented) – e.g. tablets, capsules, oral drops, oral solution etc.

Formulation information in CTs reported

- (Standing JF, Khaki ZF, Wong IC, Pediatrics. 2005;116:e559-62)
- 76 papers (from 3992 reviewed):
  - 37% - adequate information
  - 26% did not state the formulation used
  - 49% used a “pediatric formulation” (liquid, chewable tablet, granules
- Catherine Tuleu, S. Pandit et al., 2010 (same methodology)
  - No improvements, even worse

Two possibilities/options

- Same formulation with the one intended to be marketed (adult formulation or specifically developed)
  - Clinical data directly linked to the formulation
  - May imply additional delay to complete development
- Different from the formulation intended to be marketed
  - BE (or comparability) demonstration likely to be needed (not in children)
  - Save time (more rapid assessment of effects in paediatric patients)
  - May avoid unnecessary development work if product inefficacious or unsafe
  - If bioinequivalence shown ⇨ additional delays

Final commercial formulation used in CTs

- Theoretically preferable
- Appropriate for uncomplicated substances, where formulation is relatively simple (e.g. no solubility, stability, absorption etc issues)
- Less likely usable when there are multiple formulation issues and clinical efficacy/safety (at best) uncertain
- In a staggered approach, usable for older children, when adult formulation may be appropriate

Interim formulation used in CTs

- Various reasons, e.g.:
  - multiple formulation issues, needing additional time to sort out
  - important diseases (e.g. oncology, unmet medical needs) – CTs are often initiated before a pediatric formulation is developed
  - instability of the proposed formulation discovered during CT (e.g. change in polymorphism - embarrassing, rare, but possible)
  - tolerability issues, high variability found in CT, needing reformulation (e.g. Abdel-Rahman SM et al. 2010, quoting a case where the suspension – unlike the tablet – was associated with a high incidence of vomiting ⇨ reformulation ⇨ delay)
- It may be an industrial formulation, “industry-verified” or an extemporaneous one

Adult formulations used in children

- Enrolment limited to older children
- Skewed distribution to older children
- Dose titration difficulties

Industry-verified preparation

- superior extemporaneous preparations
- explicit instructions for preparation, information about concentration and stability data supporting the shelf life of the constituted product
- considerations of microbial stability in case of solutions, suspensions
- Example: lisinopril (FDA: PK information in adults and children, + clinical efficacy data; CMC data – stability, dissolution, microbiological assessments; multiple preparers and multiple lots of raw materials)
- Oseltamivir (“pharmacy compounding” and “home preparation”- see SmPC)

Industry-verified preparation

"*Add 10 mL of Purified Water USP to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets of Lisinopril and shake for at least one minute. Add 30 mL of Bicitra® [Alza Corporation] diluent and 160 mL of Ora Sweet SF™ [Paddock Laboratories, Inc.] to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients. The suspension should be stored at or below 25ºC (77ºF) and can be stored for up to 4 weeks. Shake the suspension before each use*." (FDA approved product information)

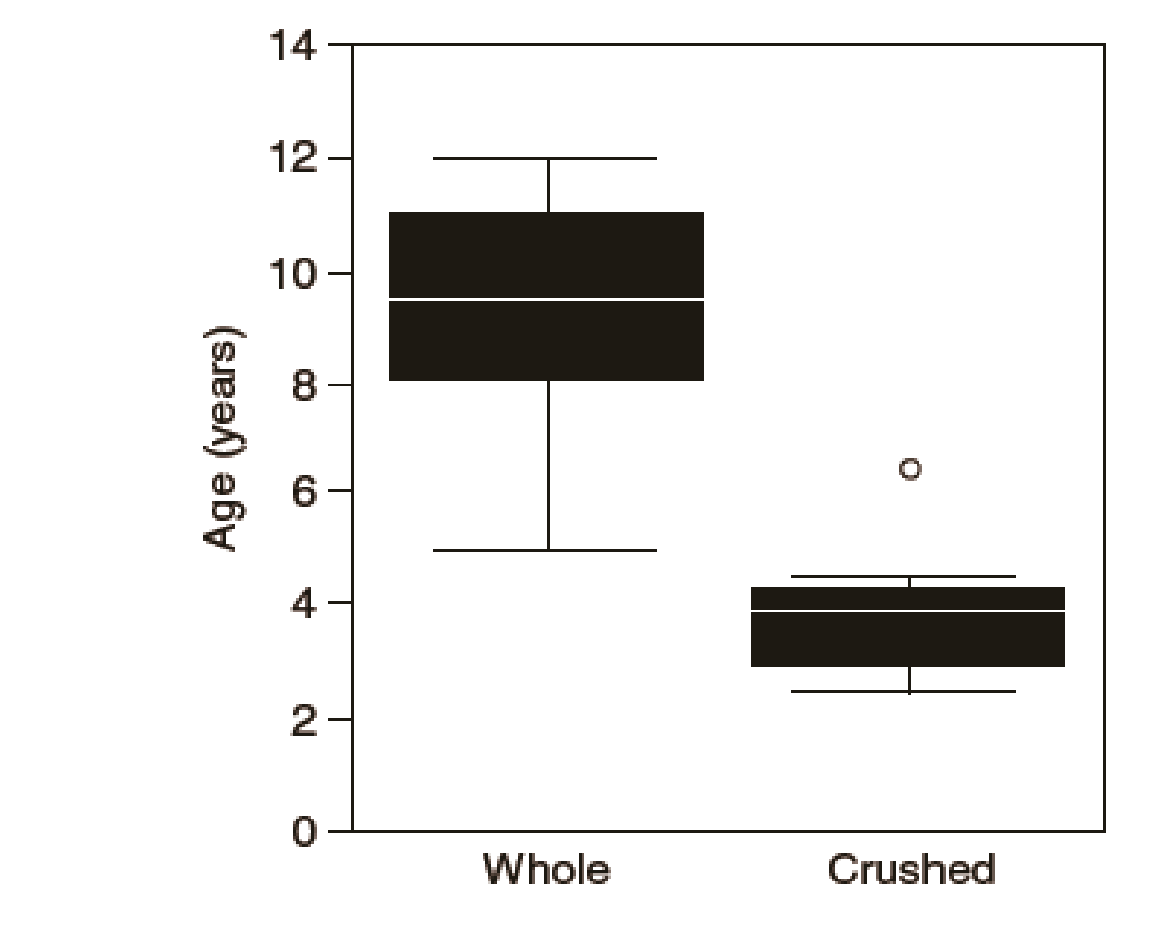
Extemporanous formulations in CTs

- Difficulties to ensure uniformity, especially in multi-center studies
- Particle size affects BE and it is important to have it controlled and ensure accurate dosing
- In mixing with food/beverages - dose accuracy, reproducibility and physicochemical stability
- Short-term stability data - necessary
- PK of extemporaneous formulation may be different from PK of intact tablets

Extemporanous formulations in CTs (cont.)

- Quality assurance of the compounding process (e.g. appropriate cleaning of the mortars – often same mortar is used for oncological and other products) – GMP principles should be followed
- (C. Tuleu et al., 2010) - almost 70% of the studies using tablets/capsules involved children under 6 years old
  - Investigators seem unaware of many of these issues

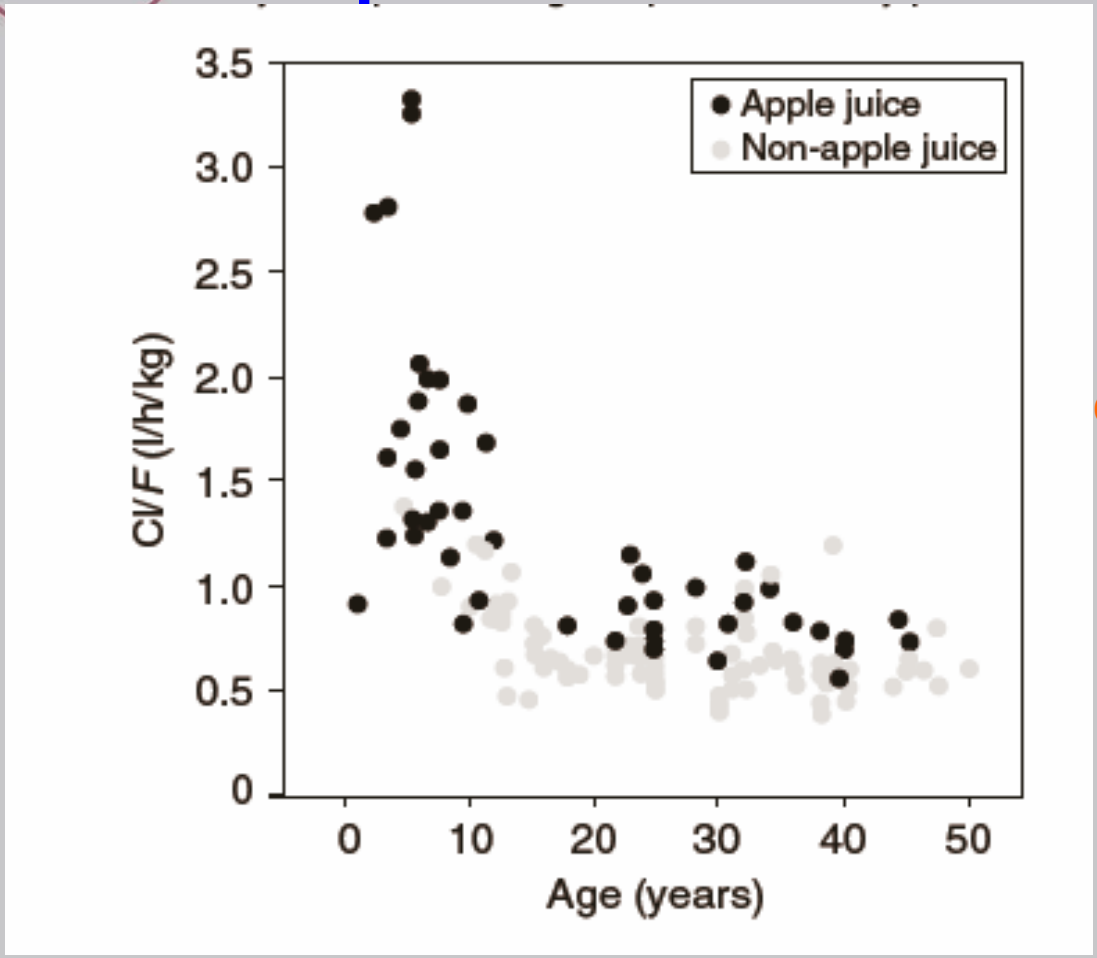
Difficulties with extemporaneous formulations



Difficult to segregate age influence on PK from formulation influence

A phase II trial (from Abdel Rahman SM et al, 2010)

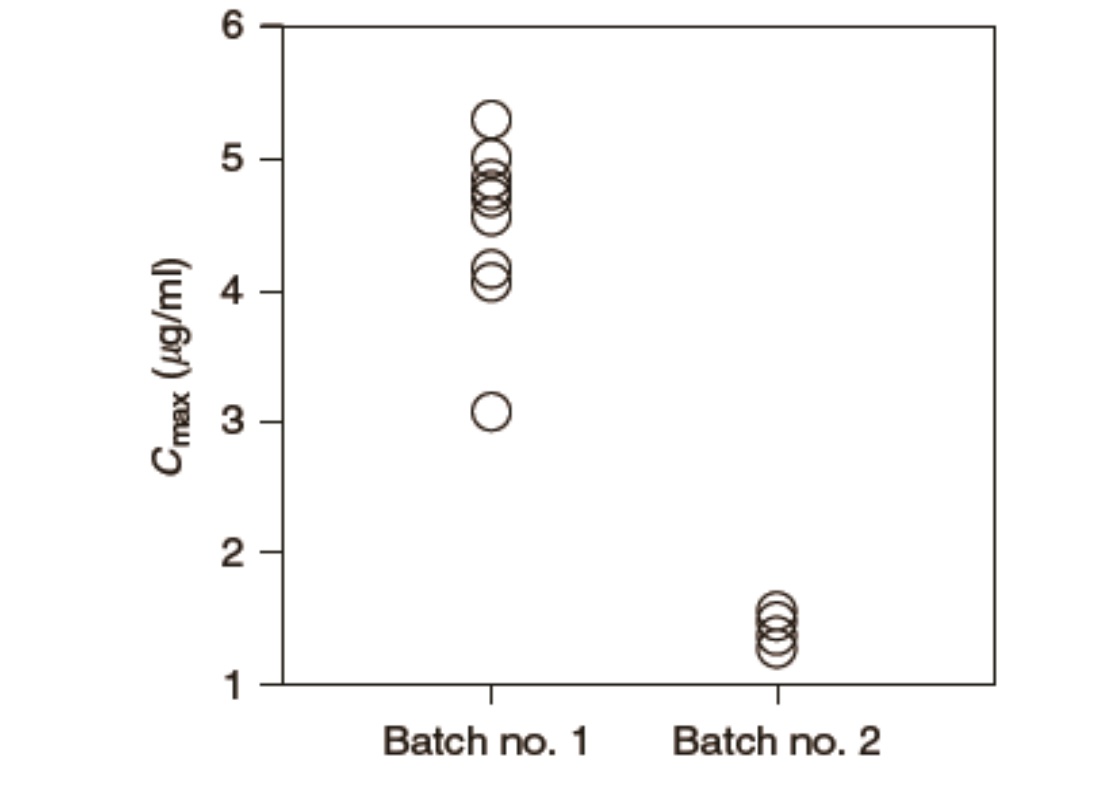
Difficulties with extemporaneous formulations



Apple juice increased oral clearance, when compared with non-apple juice

A phase II trial (from Abdel Rahman SM et al, 2010)

Difficulties with extemporaneous formulations



2nd batch (extemporaneous) – 33% of the nominal dose (HPLC)

A phase II trial (from Abdel Rahman SM et al, 2010)

Points to consider

- Formulations have considerable influence on compliance
- Staggered approach, with initial eligibility for children old enough to be able to swallow tablets probably preferable to an all-inclusive study, if formulation not available for young children
- Formulations successful in CT may present difficulties in scaling-up for industrial manufacturing (⇨ such formulation will become “interimar”)
- Dose flexibility and accuracy, stability, compatibility (with packaging and dosing devices), ease of use, reliability of the manufacturing process

Blinding

- Same principles and means as for adult trials
- Higher proportion of less common formulations (i.e. other than tablets/capsules)
- For tablets/capsules: film coating, gel coating, de-inking/removing of markings, overencapsulation
- For liquids: repackaging, change in color, clarity, viscosity, taste, and smell (difficult!)
- For orodispersable tablets, minitablets?

Blinding (cont.)

- For metered dose inhalers: challenging (change in packaging/labeling + placebo matching if necessary)
- For creams and ointments: repackaging, overlabelling
- When blinding impossible, double-dummy technique may be an option (but compliance more difficult)
- For a good practical example of multiple issues involved – see Witham D. et al., PJ, 2009.

Thank you!