Regulatory experience in application of modelling in dose selection

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Pediatric Applications based on M&S

- First in pediatrics:
- Search for therapeutic window: PK-PD models, empiric models (interactions)
- Target range extrapolated from adults: e.g anti-infective agents

- Extension of an approved age-range

- Changes in formulation (strength)

  Combivir example

  Telzir example

*Example change in formulation: *Combivir®*

- Combivir:lamivudine + zidovudine (150/300 mg), BID
- Till September 2007, only available for adults and adolescents

- For pediatric patients, only oral solutions of the separate substances were available

Benefits: allow precise dosing, easy to swallow

Drawback: compliance ('pill-load', large volumes for older children), hygenics/storage conditions challenge in resource-poor settings.

PEG: even young children may prefer solid formulations

- On request of the WHO/EMEA (PEG) /FDA: development of a fixed combination product for children

- *For details see EPAR Combivir; www.emea.europe.eu

Challenges for developing fixed combination

- Similar age range: 3 months-12 years

Different dose recommendations:

- Zidovudine: 360-480 mg, divided over 3-4 doses day, based on BSA
- Lamivudine: 4 mg two times daily (BID), based on kg BW

Strategy

- Make use of the existent Combivir® tablet

- Twice daily schedule
- Zidovudine AUC/Cmax BID in same range as AUC/Cmax TID (N=6)
- PENTA trials: evidence that zidovudine BID works as well as TID
- Rather intracellular concentration than plasma levels relevant for efficacy

- Per kg BW range
- For convenience reasons (EMEA NfG HIV products)
- Fit BSA* range to kg BW, based on US general population database

- Simulation of different dosing regimens
- Based on PK model of TID regimen in pediatric patients (>300 patients)

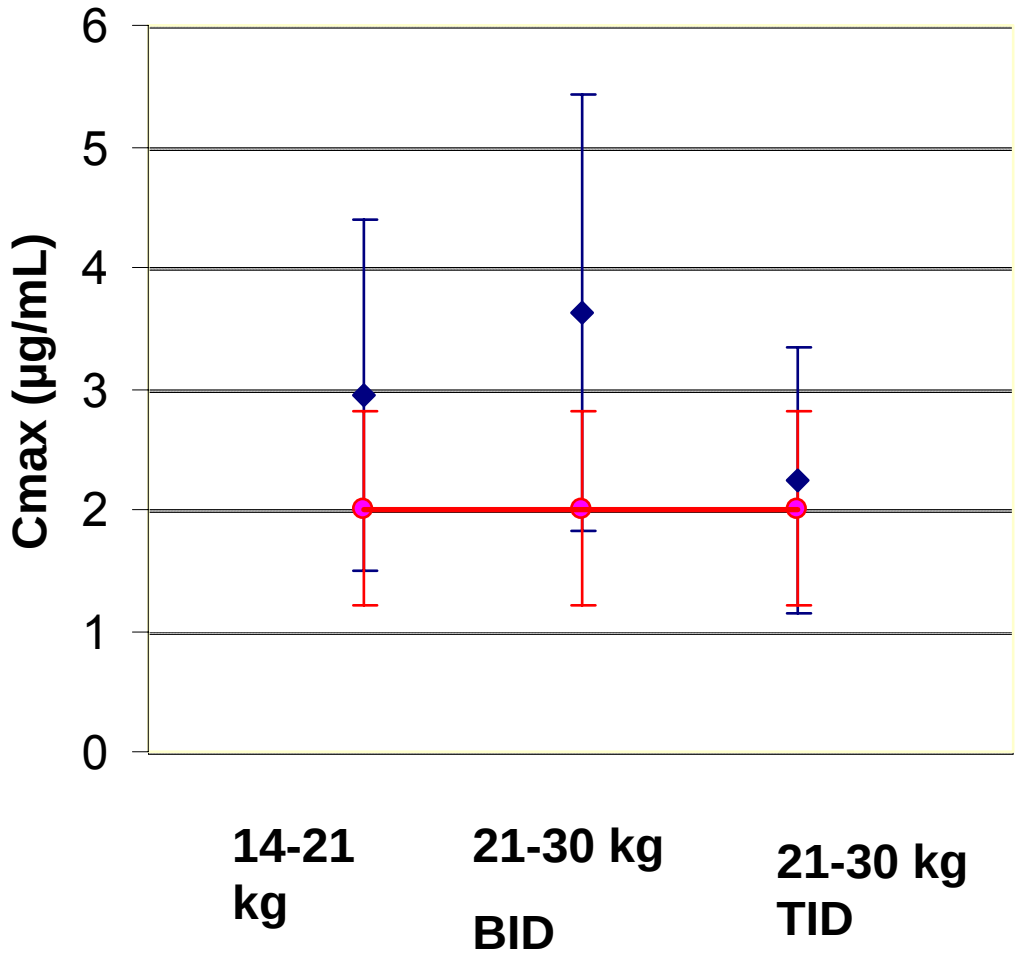
- *(Mosteller equation)

From flexible to fixed dose:

- Below 14 kg: fixed dose (LMV/ZDV 150/300 mg) not feasible, >> 33% overdose (7kg: 300% regular ZDV dose)
- Between 14-21 kg: 1 tablet a day (LMV fixed /kg: +33% to -7%)
- Between 21-30 kg: not feasible, either over- or underdose
- >30 kg (lowest 5% of 12 years old): like adolescents/adults, 1 tablet BID

- A scored tablet was developed:
- < 14 kg no tablets: agreed, typical 2-3 years old
- Between 14-21 kg: 0.5 tablet BID
- Between 21-30 kg: 0.5 tablet morning, 1 tablet evening

Simulated Cmax (SD) zidovudine



Adult reference value

Labelling

- EMEA accepted the Combivir paediatric labelling September 2007 under conditions of:
- pro-active pharmacovigilance every 6 mths (choking, safety related high Cmax zidovudine)
- Reporting results of ARROW-study in Africa
- Education program considering inhomogeneous dosing

- LABELLING:
- This dose advice is merely based on PK modelling
- 14-30 kg: Overexposure of zidovudine may occur: safety monitoring
- 1 + ½ tablet: in case of gastrointestinal intolerance: ½ tablet TID

#Telzir (fosamprenavir)

- Pro-drug of amprenavir (protease inhibitor)
- Amprenavir not suitable for children < 4 years
- Fosamprenavir has considerable less volume, less propylene glycol, no vitamine E

- Request: dose development for children

#Data presented available on EMEA website, EPAR Telzir

Fosamprenavir: Dose finding studies:

- Stratified 3 different age groups: 2-5, 6-11,12-18 y

- 5 Different dose regimens:
  - low per kg (15 BID and 30 QD),
  - high per kg (18 BID),
  - fixed adult (700 BID and 1400 QD) > 40 kg BW

- Data-rich PK + sparse-sampling (Cmin) from clinical trial
- PK analyses: both non-compartmental (data rich) + population PK model (including all subjects)

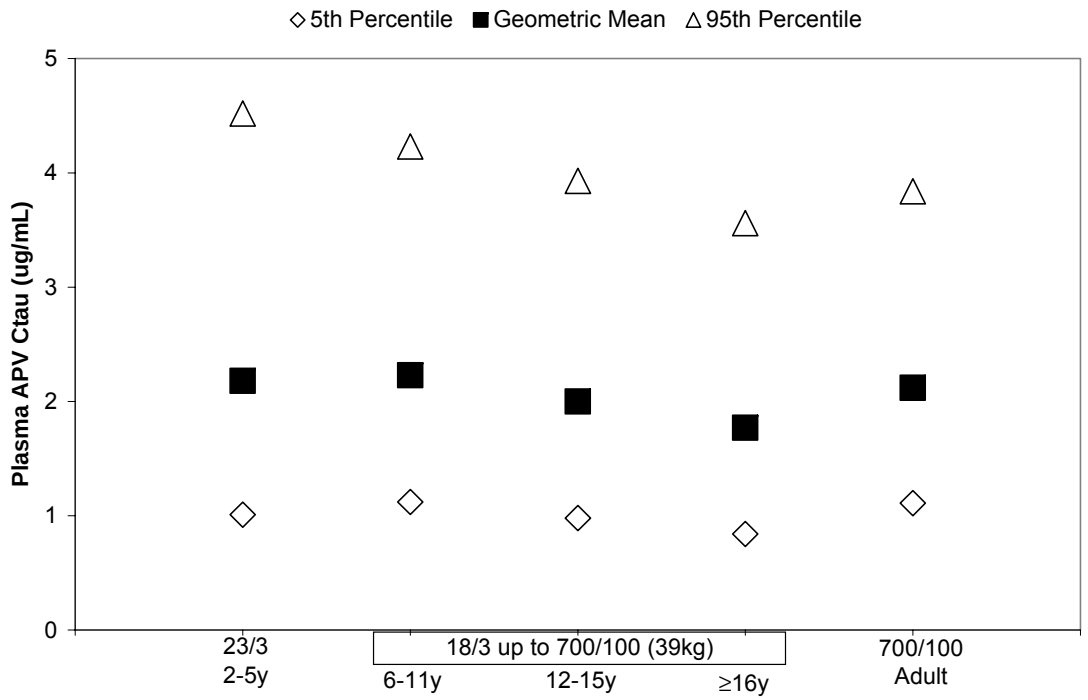
Participants

FPV/RTV Regimens (N=106)[1]						
FPV/RTV BID	**PK Profile[2]**			**Cτ[2]**		
	6 to 11y	**12 to 18y**		**6 to 11y**	**12 to 18y**	
FPV/RTV 15/3mg/kg BID	10	4		16	9	
FPV/RTV 18/3mg/kg BID	9	0		17	2	
FPV/RTV 700/100mg BID	3	8		4	24	
FPV/RTV QD	**PK Profile**			**Cτ**		
	2 to 5y	**6 to 11y**	**12 to 18y**	**2 to 5y**	**6 to 11y**	**12 to 18y**
FPV/RTV 30/6mg/kg QD	10	10	3	15	15	10
FPV/RTV 1400/200mg QD	NA	0	3	NA	1	19

Source: EPAR

Results

- Comparison with adult reference values:
- Best fit for children 6-11y: high BID dose level (18 mg/kg)
- Best for adolescents: adult dose (20% underexposure, but good clinical response



CBG-MEB

Fosamprenavir: children 2-6

- For children 2-5 year old, only limited PK data were available of single low dose (30 mg/kg): 30% underdosing, leading to clinical failures
- Best fit for children 2-5y according M&S: 23 mg/kg BID

- Proposed dose adjustment: 20 mg/kg (because of observed non-linear AUC increment after dose-step 15 to 18 mg in older children)
- Pilot study in infants < 2 years: dose finding failed, doses up to 45 mg/kg not sufficient!

- Dose proposal for 2-5 y not accepted, further studies awaited
- Recommendation:interim-analysis 20 mg/kg study or study-arm 23 mg/kg

Closing remarks

These examples show that

- Benefits of M&S in pediatrics are ackowledged by regulatories (Sparse sampling, flexible design, making optimal use of available data)

- Doses actually not tested could be accepted based on simulations (provided that model is well validated, the proposed dose adjustments seem reasonable, and there is sufficient evidence for safety/efficacy of the target levels)

- M&S can not solve everything (high variability, low absorption)