Regulatory experience of paediatric data - focusing on modelling aspects

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Outline

- Experience of paediatric data
- Methodological aspects
  - Aspects to consider when adult data available
  - Developmental effects on PK (growth, maturation)
- Regulatory assessment of PK and PKPD analyses

PK and PKPD modelling in submitted paediatric files

- PKPD analyses paediatric data rare
  - if at all included - simple exposure response relations

  No mechanistic PKPD models applied to paediatric data so far
- Population PK models often included
  - data often very sparse
  - models for influence of growth and maturation on PK vary
  - varying quality of analyses and reports

Aspects to consider if adult data available

Disease model

Present/Estimated?
Valid?

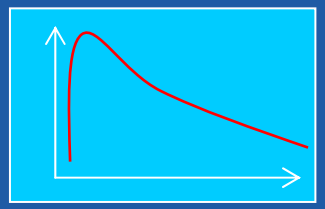
Clinical endpoint

Disease dependent?

PK

PKPD

Dose



Biomarkers

Efficacy

Safety

Developmental dependent

Developmental dependent?
or Similar?

Allometric scaling?

Physiology-based simulations?

CPMP/ICH/2711/99. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population

CHMP/EWP/147013/04 Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population

Tolterodin
EU Worksharing in Paediatric Assessment

- Over active bladder syndrome (Adults)
- Assumption: similar exposure - effective in urinary urge incontinence suggestive of detrusor instability
- PK characterised in children 1 month – 15 years
  - traditional PK studies and population PK analyses
- Weight-based dose in children 5-10 years
  - 2 mg qd < 35 kg and 4 mg qd > 35 kg => similar exposure as in adults

Tolterodin
EU Worksharing in Paediatric Assessment

- Two studies in children 5-10 years
  - 2 mg qd used in all children
  - no convincing results in primary endpoint (frequency of incontinence)
  - no clinically meaningful effect

Why? – different disease? different PKPD expected? too low dose?

Recommendation: Clinical condition should be carefully described and well defined e.g. neurologic bladder disorder, urogenital malformations or other and studied separately

Aspects on modelling of growth and maturation effects on PK

Size: BW, FFM, BMI, BSA, HT etc
- Allometric scaling, fixed or estimated coefficients?
- A priori inclusion or tested for significance?

Organ maturation: postmenstrual, gestational, postconceptual or postnatal age?

Puberty onset?

Age classification in current guidelines:

Preterm or Term newborn infants	Infants and toddlers	Children	Adolescents
0-27 days	28 days-23months	2-11 years	12-17 years

Modelling approach: Empirical PBPK

AGE

Meibohm et al AAPS J 2005, Population pharmacokinetic studies in pediatrics: issues in design ….
Anderson & Holford Ann. Rev. Pharamcol. Toxicol. 2008 Mechanism-based concepts of size and maturity..

Example 1 Model parameterisation

- Parameterised as V1and k_e
- V1 dependent on size as:

$$TVV1=X+Y(BSA-Median)$$

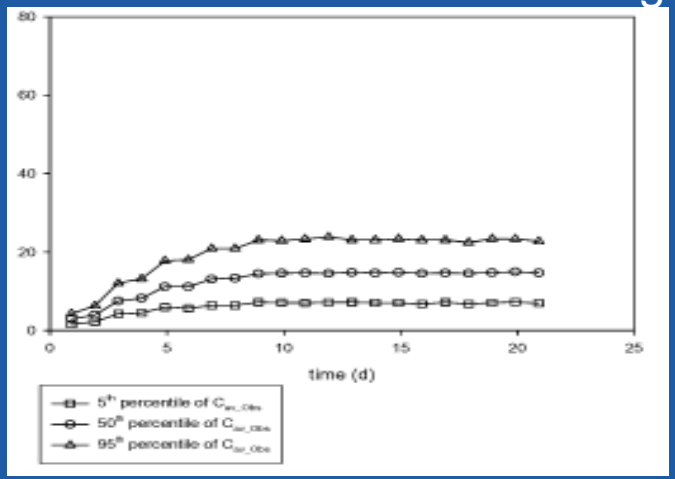
- k_e included no covariate relation

More easily interpretable if size effects are modelled on Clearance and Volume

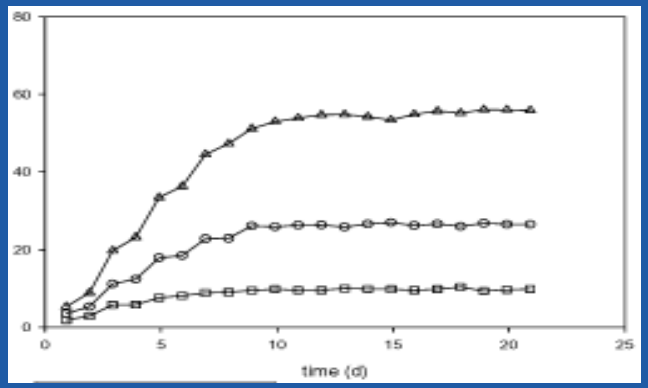
Example 2 Multiple covariates

- Pop PK model based on adult and paediatric data
- Covariate relation modelled as additive covariate effects
- Subjects with low body size - simulations:

Without co-administered drug

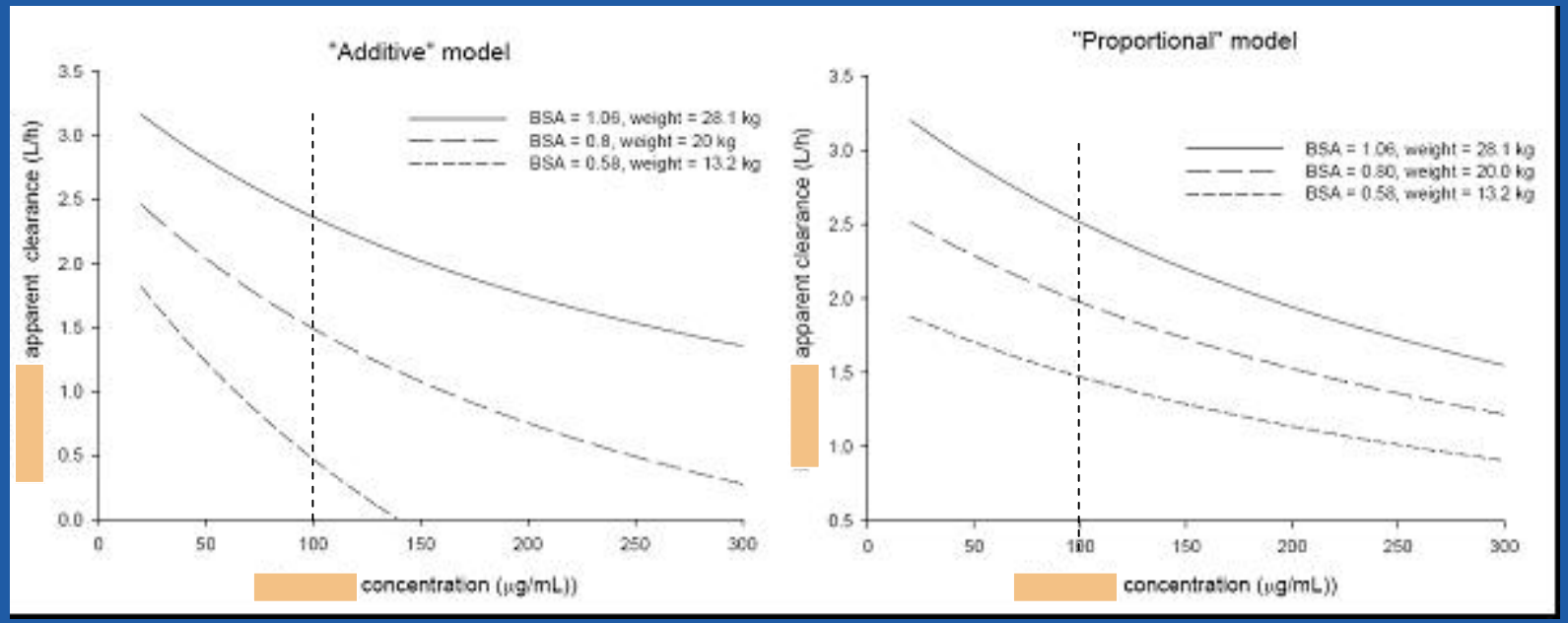


With co-administered drug



Likely or model induced?

Example 2 Multiple covariates



- **"Additive" model (left graph)**

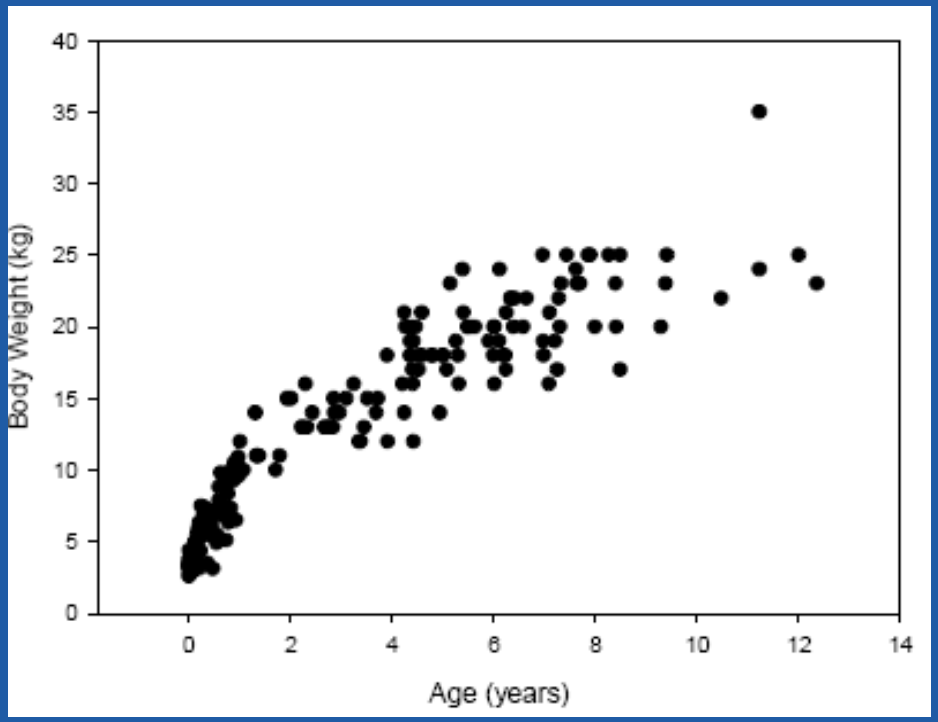
$CL = \theta1 + \theta2*(BSA - 1.77) + \theta3*CAT + \theta4*C_{INH}/(\theta5 + C_{INH})$……

- **"Proportional" model (right graph)**

$CL = (\theta1 + \theta2*(BSA - 1.77))*(1 + \theta3*CAT + \theta4*C_{INH}/(\theta5 + C_{INH})$……

Example 3 Influence of size and age

BW



$$P = (\Theta_{std} \cdot (BW/70)^{\Theta_{BW}}) \cdot (1 - \Theta_{AGE} \cdot e^{-AGE \cdot \ln 2/\Theta_{t1/2}})$$

Θ_{BW} =0.75 for CL and =1 for V

$\Theta_{t1/2}$ = half life of maturation

Regulatory assessment of PK and PKPD Modelling and Simulation

- Model development methodology in general
- Model adequate for it's intended use?

???

Assessment and demands vary within EU – composes 30 EU and EFTA countries – Swedish view presented here

Regulatory assessment of M &S

- What is acceptable?
  - evolving science
  - no European guideline defining what is acceptable

  Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)
  - requirements on a case by case basis
    - intended use
    - relative importance
  - demands on model evaluation ↑ with ↑ importance

Regulatory assessment of M &S

- Model evaluation issues
  - paediatric data + (rich) adult data

    predictive for the paediatric population?
    - use stratified model evaluation
  - sparse data - shrinkage towards the mean
    - Empirical Bayes estimate based diagnostics may be of limited value (perfect fit!)
    - Graphs of Empirical Bayes estimates versus e.g. weight or age - trends may be highly dependent on the model

Regulatory Assessment of M & S

- Limited resources
- Requires hands on experience
- Continuous education needed
- Current situation:
  - Not all submitted population analyses are assessed in detail (depends on relative importance)
  - No questions on the models ≠ full acceptance of the model for later use
  - The more valuable the model the more questions asked

Conclusions

- PKPD modelling rare (simple relations if any)
- PK-Efficacy
  - extrapolate efficacy from the adult population
- PK-Safety
  - adequate exposure entire age span?
  - identify risk groups
- Population PK analyses of varying quality
  - Divergent handling of size and maturation effects

Conclusions

- Model-based drug development highly appreciated
  - Avoid unnecessary studies!
- Reports should be sufficiently detailed
  - Show that the model is predictive!