Pharmacometric Modelling to Support Extrapolation in Regulatory Submissions

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PSI One Day Extrapolation Workshop

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MPA or EMA.

Outline

- Introduction to pharmacometrics and extrapolation
- Why population analysis
- What are population models used for in support for extrapolation from adults to children
- Design and modelling considerations
- How to assess exposure similarity between adults and children
- Conclusion

Pharmacometrics

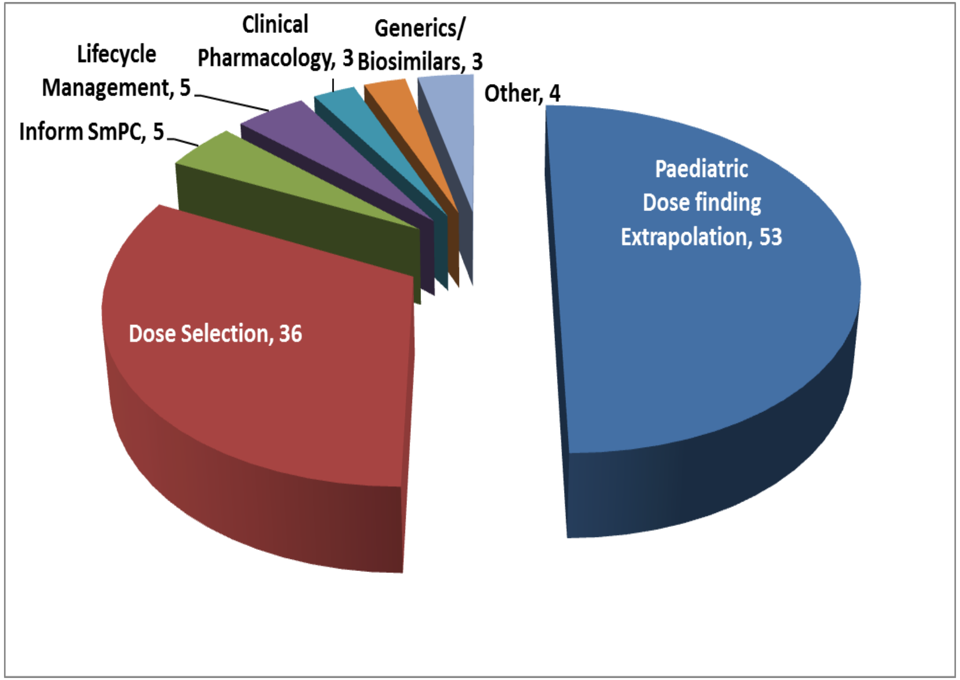
"the science of developing and applying mathematical and statistical models to characterize, understand and predict a drug's pharmacokinetics, pharmacodynamics and biomarker-outcome behavior, data visualization, statistics, stochastic simulations and computer programming" [1]

- **Pharmacokinetics**
  "what the body does to the drug"
- **Pharmacodynamics (=Response)**
  "what the drug does to the body"
- **Biomarker-outcome behavior**
  disease progression, relationship between biomarkers and clinical endpoints etc.

[1] Ette, E.I. and P.J. Williams, Pharmacometrics: **The Science of Quantitative Pharmacology.** 2007: John Wiley & Sons.

EMA Modelling and Simulation Working Group 2016 Activity Report

- **105 product related procedures**
  - **41 from Paediatric committee,**
  - **62 from Scientific advise working party,**
  - **2 from CHMP**
  - **7 Guidelines**
- A breakdown of the **scope** of questions addressed by M&S is shown in the pie chart



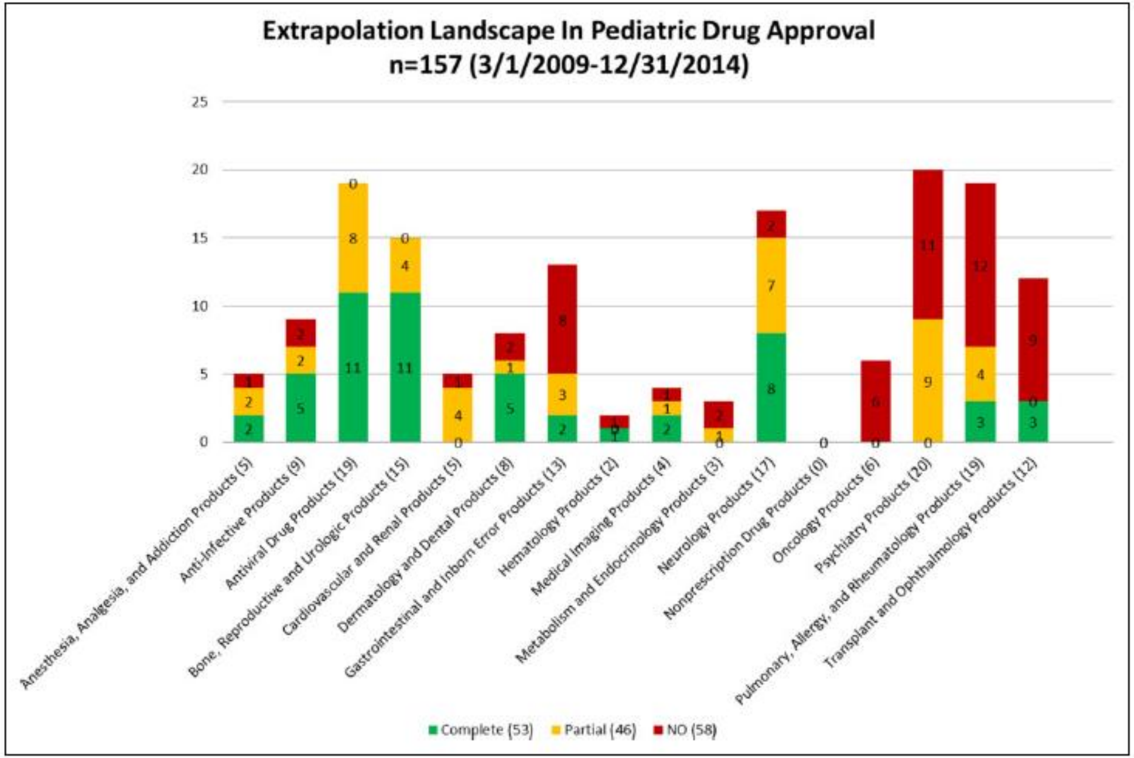
Courtesy of Efthymios Manolis

FDA publication 2017

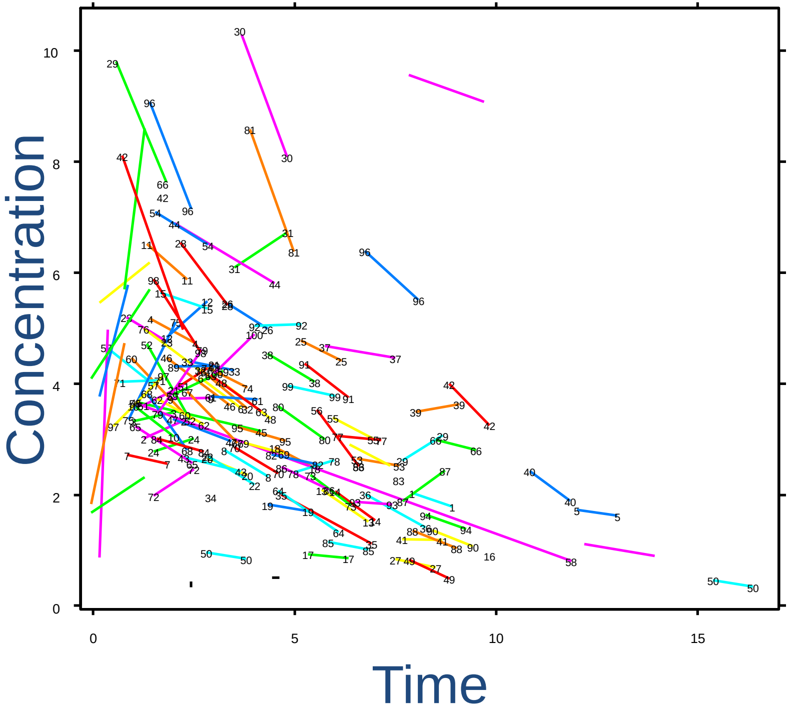
Extrapolation of Efficacy in Pediatric Drug Development and Evidence-based Medicine: Progress and Lessons Learned. Sun *et al.* Therapeutic Innovation and Regulatory Science, 2017

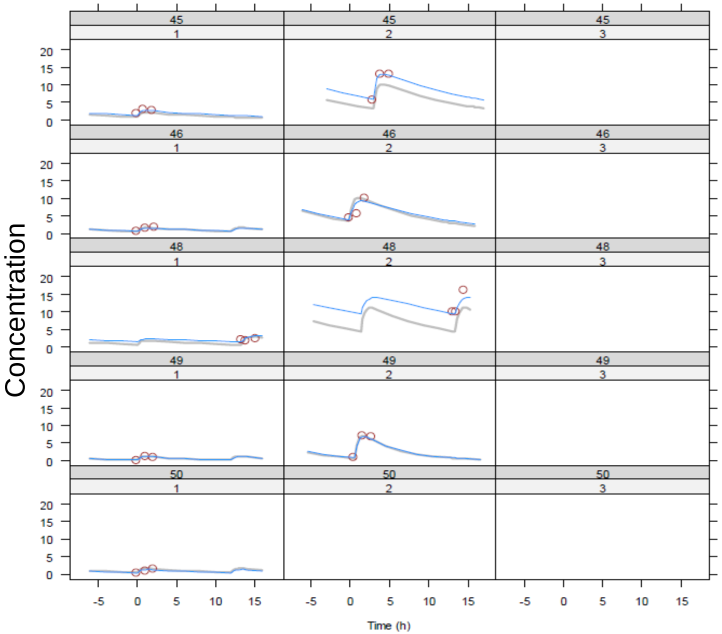
Table 1. Overview of Extrapolation Assessment Changes.

Extrapolation Category	Current Data Numbers of Products (%) 2009-2014	Dunne's Reference Numbers of Products (%) 1998-2009
Complete	53 (34)	24 (14)
Partial	46 (29)	113 (68)
No	58 (37)	29 (18)



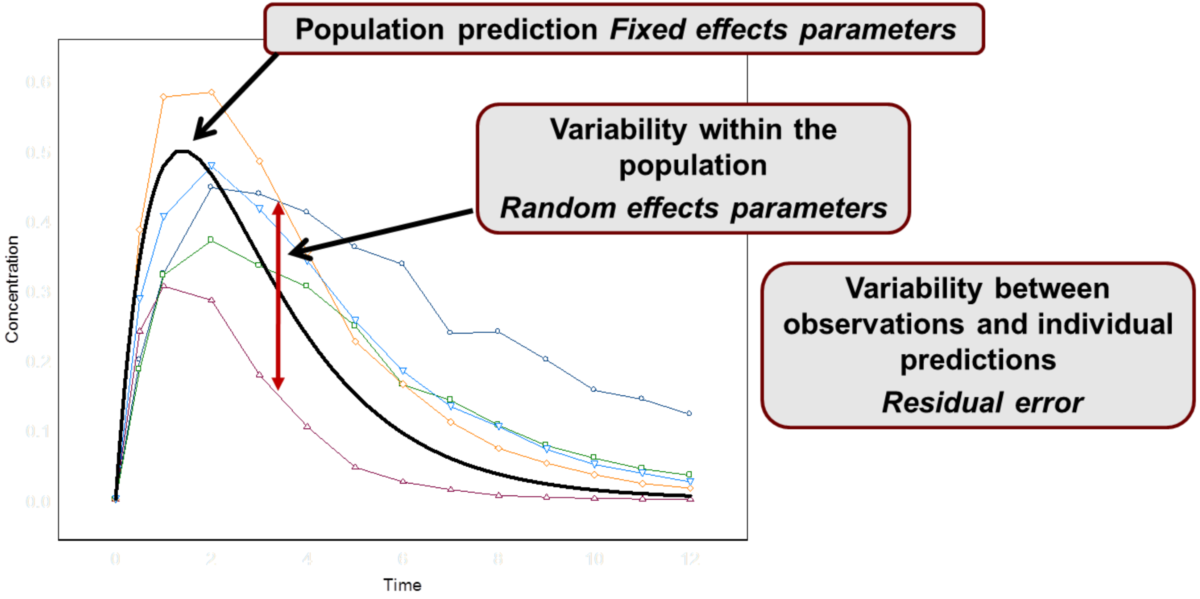
Sparse data





Blue lines: individual predictions, red circles: observations, gray lines: population predictions. Dark gray panel headers indicate individuals, light gray panel headers PK assessment days.

Population modelling view
(Nonlinear Mixed Effects Modelling)



Fit one model to the data from all individuals while retaining the notion of individuals

PK model equations

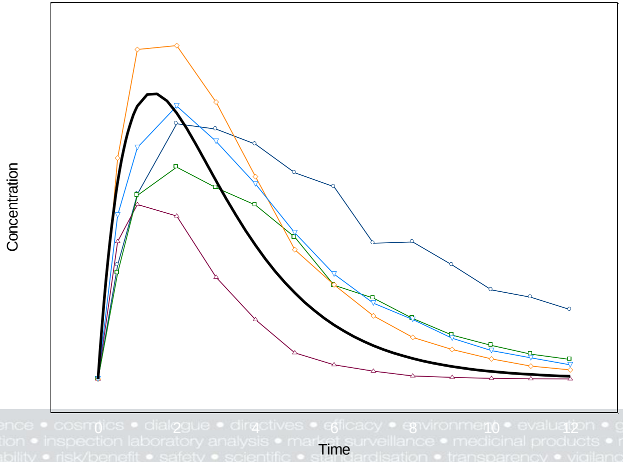
General structure of a mixed-effects model:

$$y_{ij} = f(X_{ij}, P_i) + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2)$$

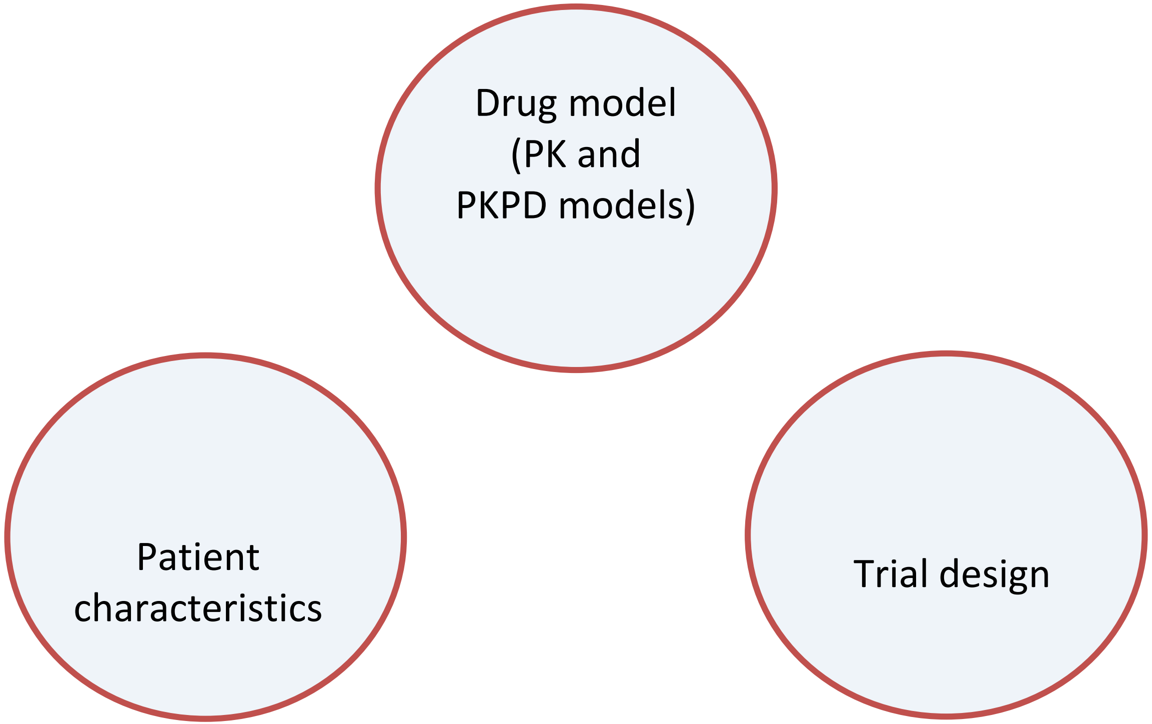
Individual parameter P_i:

$$P_i = \theta \cdot e^{\eta_i}, \qquad \eta_i \sim N(0, \omega^2)$$

$$C = \frac{F \cdot ka \cdot Dose}{V \cdot \left(ka - \frac{CL}{V}\right)} \cdot \left(e^{-ka \cdot t} - e^{-\frac{CL}{V} \cdot t}\right)$$



Pharmacometric non-linear mixed effects models



Nonlinear mixed-effect modelling software

- NONMEM
- …
- Phoenix
- Monolix
- S-ADAPT
- SAS (PROC NLMIXED)
- R (LME)

Extrapolation of Efficacy

Based on knowledge of clinical pharmacology and disease etiology

PIP
Scientific Advice

No

Same dose as in adults/adolescents

Establish new dose in children by exposure similarity (PK bridge)

PK bridge + Additional support for efficacy in children

No study	Pivotal PK study	Pivotal PKPD study
In reality:	*Pivotal PopPK analysis*	*Pivotal PopPK analysis* *Supportiv PKPD analysis*

What are pharmacometric models used for in support for extrapolation from adults to children

- PK model in adults
  - Reliable description of PK based on patients and/or HV
- Exposure-response (PKPD) model(s) in adults

- PK model in children
  - Pivotal to establish dosing recommendations in children
  - Often pooled analysis with adult or adolescent data
- Exposure-response model in children
  - Often based on effect data collected in PK study
  - Supportive for the extrapolation concept

How to develop and apply pharmacometric models?

- Understand the clinical pharmacology of the drug (PK and PKPD)
- Understand the structure of the data
- Choose adequate analysis method
- Evaluate the performance of the model
- Apply the pharmacometric model for quantitative and/or predictive purposes

What are the considerations to make when planning and performing PK(PD) analyses?

- **What is the question to be addressed?**
  - **Is the proposed dose in children adequate?**
  - **What is the quantitative exposure-response relationship in children**

- What is known about the clinical pharmacology?
  - Pre-specify structure models and covariates to be tested
  - Does the sample size and number of observations allow for covariate testing?
  - Avoid testing correlated covariates such as weight, BMI, height and age

Evaluate the performance of the model

- **Termination messages** (successful estimation?)
- **Simulation based diagnostics**
  - Visual predictive checks
  - Numerical predictive checks
  - Posterior predictive checks
- **Parameter uncertainty**
  - Fisher information matrix (covariance step)
  - Non-parametric bootstrap
  - Sampling importance resampling (SIR)
  - Likelihood profiling
  - Cross-validation
- **Goodness-of-fit diagnostics**
  - Observations vs population/individual predictions
  - Residual plots

Pivotal PK study in children – design and modelling considerations

- Main question to address: *Does the dose recommendation provide similar exposure as in adults, considering body size and age?*
  - The study must cover relevant body size and age range
  - Take advantage of known clinical pharmacology properties of the drug/class
  - Collect sufficient number of PK samples to estimate relevant PK parameters

Pivotal PK study in children – design and modelling considerations

- High demands on the quality of the model
- Required model adaptations:
  - Body size relations (allometric scaling)

    CL_i=(CL/70)**0.75; V_i=(V/70)**1.0
  - Maturation functions for small children (age limit depending on specific organ ontogeny)
- Provide a battery of model evaluation metrics

Pivotal PK study in children – what is exposure similarity?

- Predefine what exposure metrics that should be used for comparison
  - Simulate exposure metrics from the model
    - Individual predictions generally not advised due to high shrinkage with sparse data

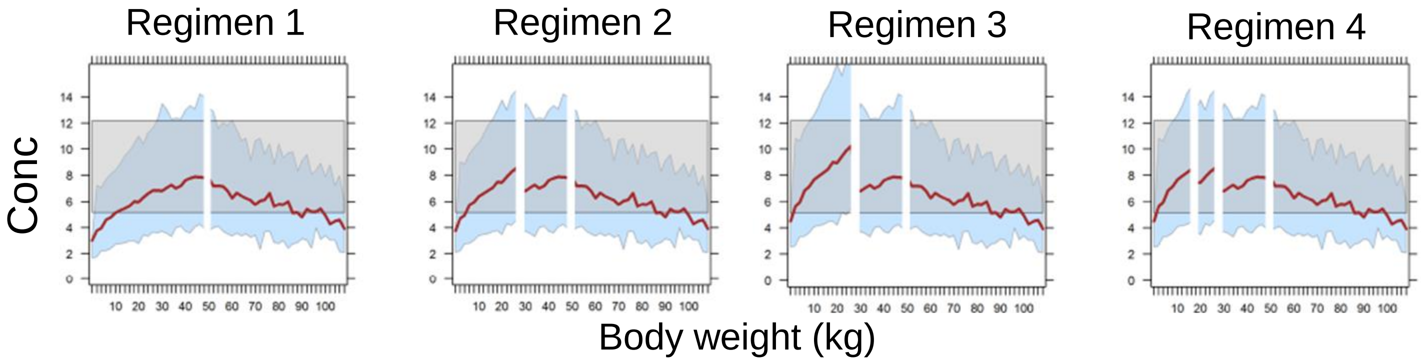
- **What is the success criteria for exposure similarity?**

Pivotal PK study in children – what is exposure similarity? *Comparison of predicted mean exposures*

Comparison of Mean (%CV) Exposures			
PK parameter Mean (%CV)	Adolescents (12 to < 18 Years Old) (N=50)	Adults Phase 2/3 Population (N=1695)	Adolescents vs Adults % GMR (90% CI)
AUC	1157 (50.6)	1027 (36.5)	109.7 (98.4,122.3)
Cmax	546 (53.0)	511 (32.5)	98.5 (86.7,111.9)

- Pros:
  - Easy to interpret the result
- Cons:
  - Individual predictions are often shrunk towards the population mean when the PK information is sparse
  - No information about the exposure in relation to body size

Pivotal PK study in children – what is exposure similarity? *Simulated exposure in children*



- Pros:
  - Good understanding of the exposure vs body weight, and in relation to the adult reference range
- Cons:
  - Subjective criteria for success
  - Can be difficult to simulate covariate distributions

Red line = median prediction
Blue area = 90% prediction interval
Gray area = adult reference region 90% prediction interval

Exposure-response (PKPD) analysis in children

- Often exploratory – a prospective analysis plan is still required
- Ideally a model established in adults could be used and the drug effect confirmed in children
- Model-based primary analysis could be used
  - Design the trial for the intended analysis
  - Use randomization test to assess actual significance level for parameter inclusion
  - Model-averaging techniques

Recent examples where population PK(PD) analyses have been pivotal in market authorization applications in children

- PK bridge to support dosing recommendations
  - Vimpat (partial onset seizures, ≥ 4 years)
  - Harvoni (HCV, ≥ 12 years)
  - Sovaldi (HCV, ≥ 12 years)
  - Mimpara (secondary hyperparathyroidism, ≥ 3 years)
  - Firazyr (acute attacks of hereditary angioedema, ≥ 2 years)

Conclusions

- Design studies for intended population PK and PKPD analyses
- Describe PK in relation to body size in children
- Prospectively decide on exposure similarity criteria
- Provide full documentation for model development
- Prepare the modelling and simulation reports such that assessors can review without access to data

References for good reporting standards (non exhaustive list)

- **Guideline on reporting the results of population pharmacokinetic analyses.** Committee for Medicinal Products for Human Use (2007)
- **Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation** EFPIA MID3 Workgroup, CPT:PSP, 2016
- **Reporting guidelines for population pharmacokinetic analyses.** Dykstra, K. et al. J. Pharmacokinet. Pharmacodyn. 2015
- **Guidelines for the quality control of population pharmacokineticpharmacodynamic analyses: an industry perspective.** Bonate, P.L. et al. AAPS J. 2012
- **Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models.** Bergstrand M et al. AAPS J. 2011