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Regulatory Perspectives for Reliable Model Informed Drug Development (MIDD)

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MIDD Definition

The application of a wide range of quantitative models in drug development to facilitate the decision-making process *

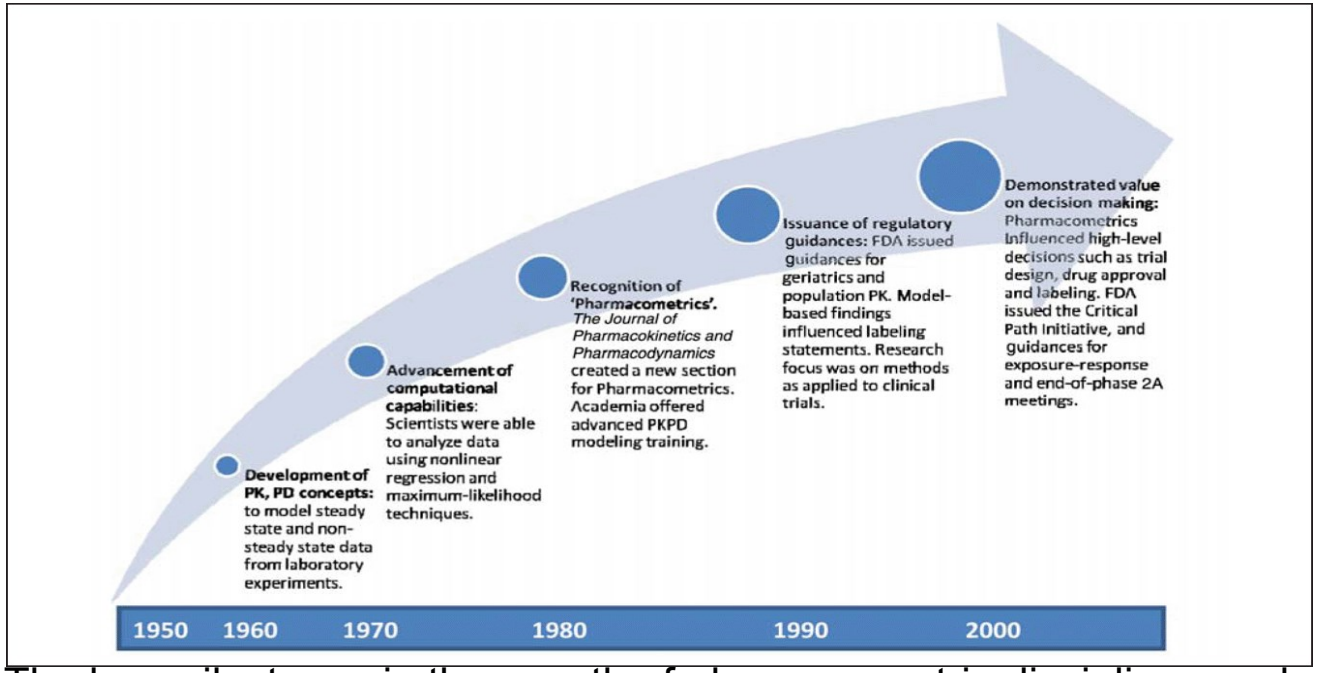
The science of using quantitative analysis and modelling and simulation (M&S) approaches to inform and enhance drug development and regulatory review **

MIDD ⇔ Pharmacometrics ⇔ M&S approaches

*Wang et al. Clinical pharmacology and therapeutics, 2019
**Pharmacometrics working group/Health Canada

MIDD Applications

- Pharmacometric reviews had approval or labelling impacts on about 65% off the 198 received submissions between 2000-2008 by FDA*



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The key milestones in the growth of pharmacometric discipline are depicted, adapted from "Journal of Clinical Pharmacology" by Gobburu, Jogarao V. S. 2013, *Pharmacometrics 2020*

*Lee et al, Clin Pharmacokinet. 2011

Common MIDD Applications for Regulatory Submissions

- Support design of clinical trials
- Identify clinically relevant covariates, ex. age, weight, race …
- Exposure-response analysis
- Investigate/estimate Drug-Drug Interactions
- Characterize pharmacokinetics:
  - Population PK vs. limited non-compartmental PK data
  - Evaluate exposure in subpopulations such as hepatic and renal impairment patients
- Support alternative dosing recommendations
- Extrapolate efficacy to special populations, ex. pediatrics
- Leverage available information and knowledge when data is very limited, ex. rare diseases

More can be done

MIDD can further enhance:

- Efficiency of the drug development process by simulating complex and diverse data to:

  Ex. **DDI** dose recommendations for the different **2D6 genotypes** in patients with different stages of **hepatic impairments** for a drug that is mainly metabolized by 2D6

- Drug information for populations or clinical scenarios that are difficult to test for practical or ethical reasons

  Ex. optimizing pediatric dose regimen for different age and weight subgroups

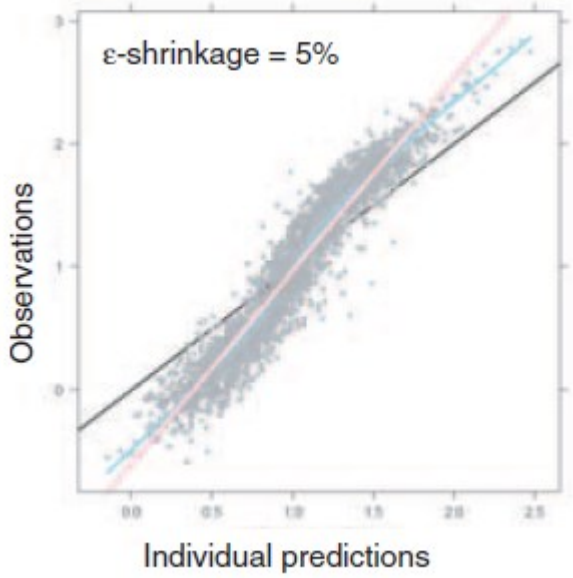
What should guide the use of MIDD during drug discovery and development?

- To better understand the benefits and risks of a drug for an intended use and patient population
- To minimize health risks and optimize therapeutic outcomes for patients and clinical trial subjects
- To provide new therapies to patients faster in cost-effective manners while maintaining high standard of efficacy and safety

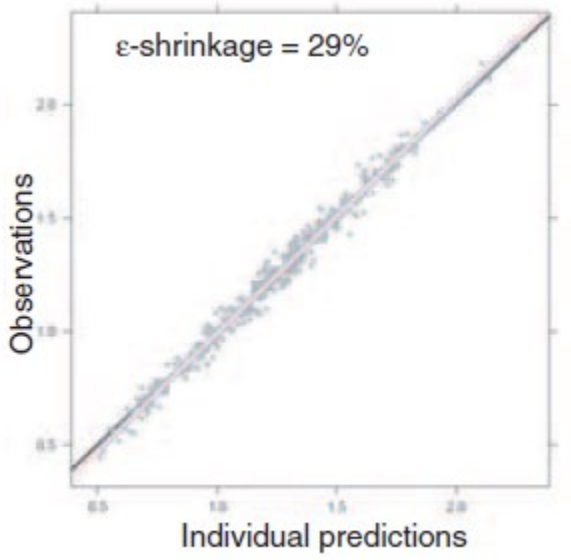
Main Considerations in Reviewing MIDD Application

- Quality of the data and analyses
- Strengths and limitations associated with their use
- Availability and feasibility of alternative conventional approaches

Reliable conclusions require Good Data + Good Model+ Good Analysis



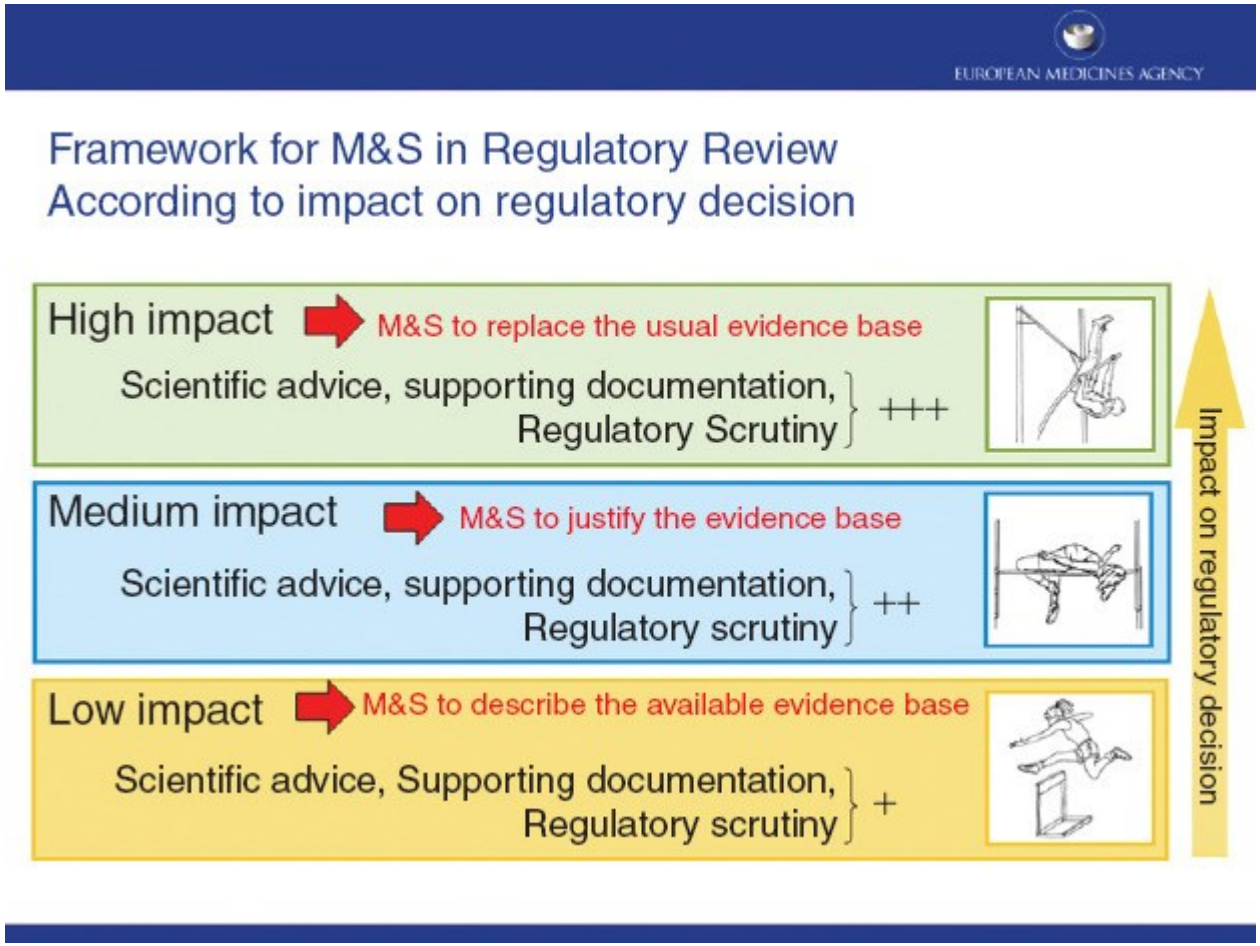
Good Data + Poor model
⇨ **Useful diagnostic plot**



Poor Data + Poor model
⇨ **Misleading diagnostic plot**

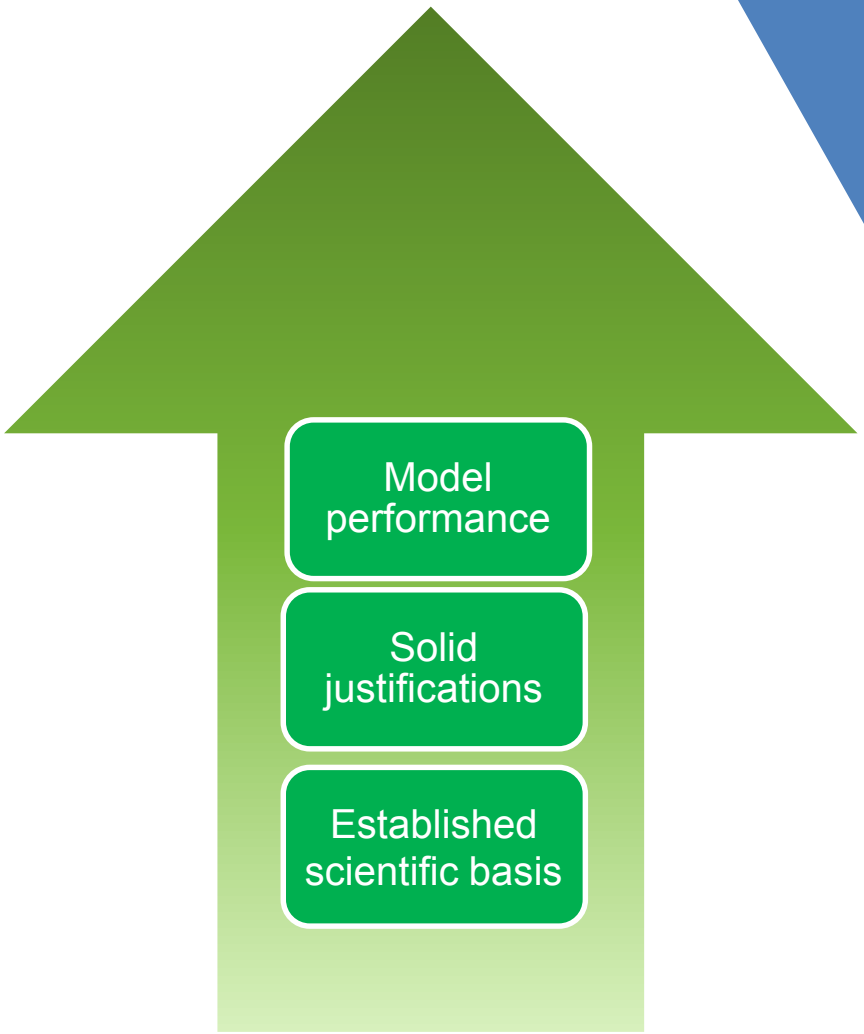
Figures adapted from Karlsson et al. Clin Pharmacol Ther 2007

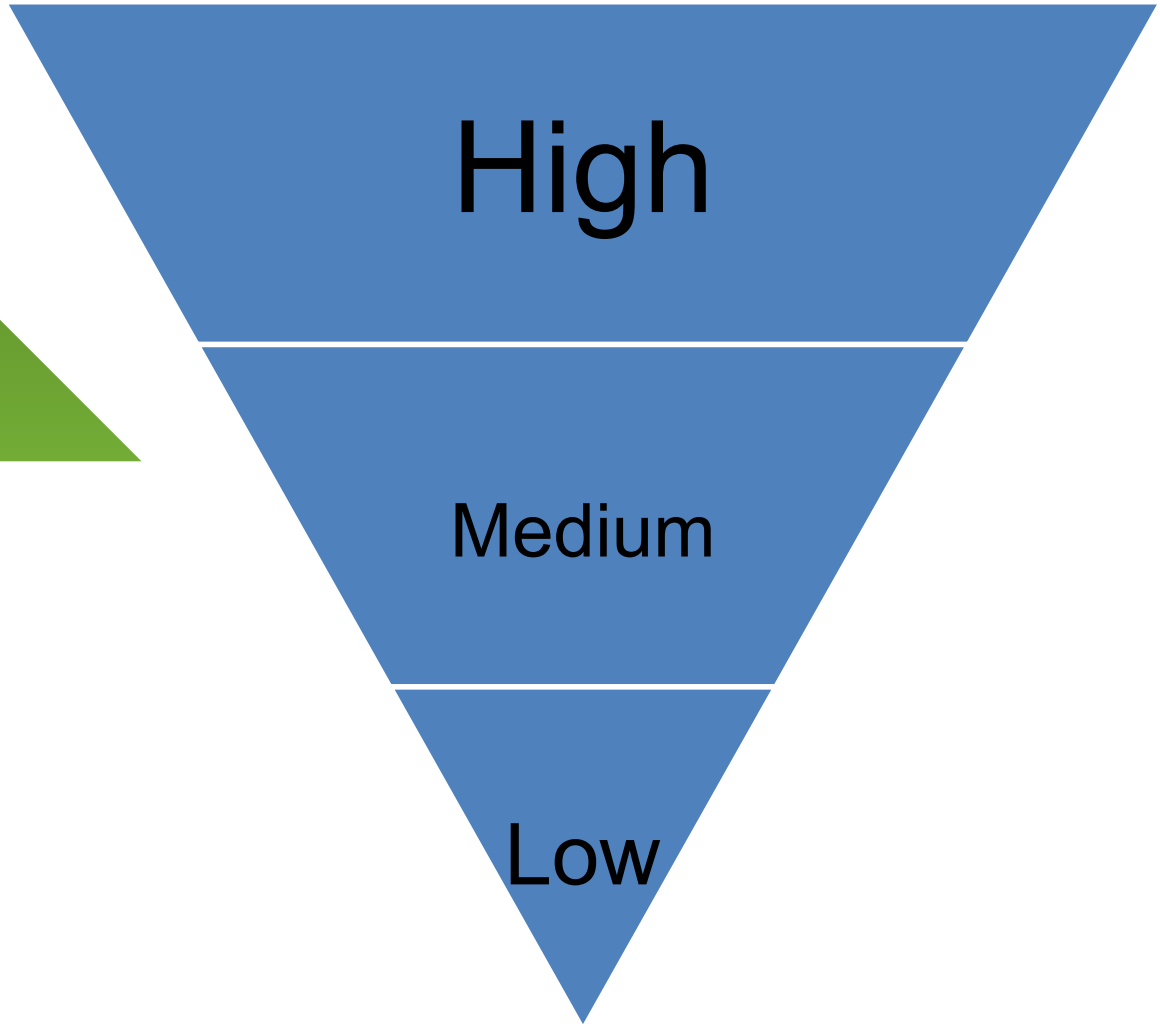
Main Considerations in Reviewing MIDD Application



Manolis, E et al. Pharmacometrics & Systems Pharmacology, 2013

Expectations vs. Model Impact





Expectations **Model impact**

Examples

- Pop-PK model to evaluate differences between formulations
- Simulation/Analysis to provide supportive data
- Extrapolation for pediatric patients with rare disease

Examples

- Pop-PK model to evaluate differences between formulations
- Simulation/Analysis to provide Supportive data
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Pop-PK Model to Evaluate Differences Between Formulations

Background

- Two formulations were used in pivotal clinical studies
- No comparative bioavailability study
- Sponsor claimed “comparability” between the two formulations based on:
  - Comparability of observed steady-state plasma trough concentrations
  - Pop-PK analysis and simulation indicating exposure ratios within bioequivalence (BE) limits
- Was the use of the PK model to evaluate bioequivalence well-established?

Assessment

- The Pop-PK analysis has indicated that there is NO formulations effect on the bioavailability

- The no formulation effect on the bioavailability may be a valid finding however
  - Any possible formulation effect (which may have not been detected by the Pop-PK analysis) has not been taken into consideration in the simulations

- The used model was not validated for bioequivalence assessment (i.e. its discriminating capacity to evaluate bioequivalence has not been demonstrated)

The suggested use of the developed Pop-PK model to evaluate bioequivalence is NOT reliable/valid

Examples

- Pop-PK model to evaluate Differences between formulations
- Simulation/analysis to provide supportive data
- Extrapolation for pediatric patients with rare disease

Simulation/Analysis to Provide Supportive Data

Background

- In a previous analysis, the renal impairment categories were defined based on estimated Creatinine Clearance (CLCr)
- The product monograph dose recommendation for renal impairment categories was established based on Estimated CLCr
- For clinical reasons, the product monograph has to be updated to use renal impairment categories defined based on estimated GFR (eGFR)

Background

- PK data were not well distributed between eGFR renal impairment categories (only 2 subjects in the normal function category so the reliability of estimation of all the exposure rations is questionable)

Renal Impairment Category CLCr	Subject #	Renal Impairment Category eGFR	Subject #
Normal ≥80	6	Normal ≥90	2
Mild 50 to 80	6	Mild 60 to 90	5
Moderate 30 to 50	6	Moderate 30 to 60	8
Severe <30	6	Severe 15 to 30	6
ESRD Requiring hemodialysis	6	End Stage Renal Disease (ESRD) < 15	9

- Pop-PK model developed in more than 800 subjects (PK data from Phase 1 and 2 studies) was used to simulate exposure parameters and guide dose recommendations
- Are the simulated exposures for the different renal impairment categories reliable (are they more reliable than the observed ones)?

Assessment

The simulated exposures:

- based on limited sampling and Pop-PK model
  - The model was well established and includes renal function as a covariate
  - The model seems to adequately describe the data and to provide a good predictions for the deferent renal impairment subgroups
- the dataset included relatively large number of subjects over the deferent levels of renal impairment (total N=800, **100 Normal**, 600 Mild, 100. 6 Sever and ESRD)

The simulated data leveraged substantially more PK profiles and prior well-established PK knowledge (i.e. population model) and seems to be more reliable

Examples

- Pop-PK model to evaluate Differences between formulations
- Simulation/analysis to provide supportive data
- Extrapolation for pediatric patients with rare disease

Extrapolation for pediatric patients with rare disease (RUZURGITM) *

Background

- RUZURGITM (3,4-DAP) has been available for the treatment of a rare autoimmune disease Lambert-Eaton Myasthenic Syndrome (LEMS) under a compassionate use program since the 1990s
- Available data in a recent NDA
  - In adults:
    - Efficacy was supported by
      - randomized withdrawal, placebo controlled, study in 32 patients
      - supportive data from Phase II, randomized, double-blind, placebo-controlled, parallel-group study in 26 patients
    - Safety: total of 247 patients including the compassionate use experience
  - In pediatric population:
    - No pediatric clinical trial to establish efficacy
    - Safety: 22 pediatric patients (only 7 pediatric patients with LEMS) from the applicant's compassionate use program

* https://www.accessdata.fda.gov re: **Drug Approval Package: Ruzurgi / # 209321**

Background

Extrapolation was based on

- Disease similarity between adults and pediatrics for LEMS
- Available safety data and clinical experience reported in pediatric patients (with LEMS and CMS) from the compassionate use program
- Modeling and simulation approach to predict the exposures in this population based on the adult PK data (No PK data available in pediatric patients)

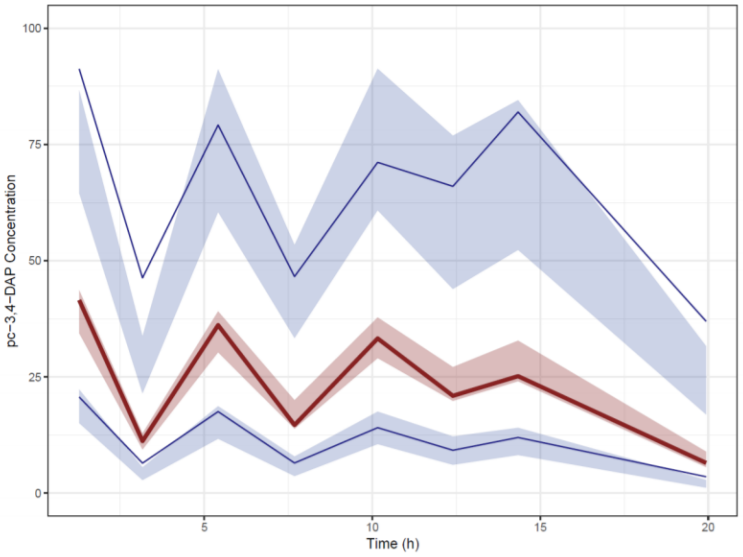
Background

- Dataset included a total of 2919 PK samples from 3 studies (healthy volunteers in PK1 and TQT studies and LEMS patients in DAPPER study)
- The Pop-PK final model included body weight, NAT2 phenotype and LEMS population as covariates
- No adequate data to confirm the adequacy of the assay validation for studies PK1 and DAPPER; thus FDA reviewers performed independent analysis using data only from the TQT study

Assessment

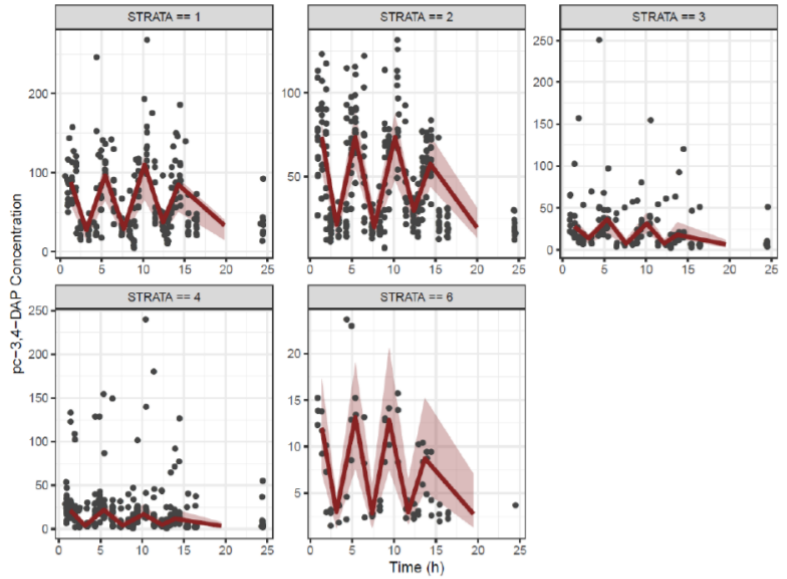
The model showed good performance and there was good agreement between observed and simulated data after stratification by weight and genotype

Figure 9: Prediction-Corrected VPC



The solid red and blue lines present the median and 90th percentiles, respectively of the observed prediction-corrected concentrations. The shaded areas present the 90th prediction intervals for each percentile (i.e. 5th, 50th, and 95th percentiles) based on 200 simulated datasets.

Figure 10: Prediction and Variability Corrected VPC Stratified by Acetylation Phenotype and Weight Band

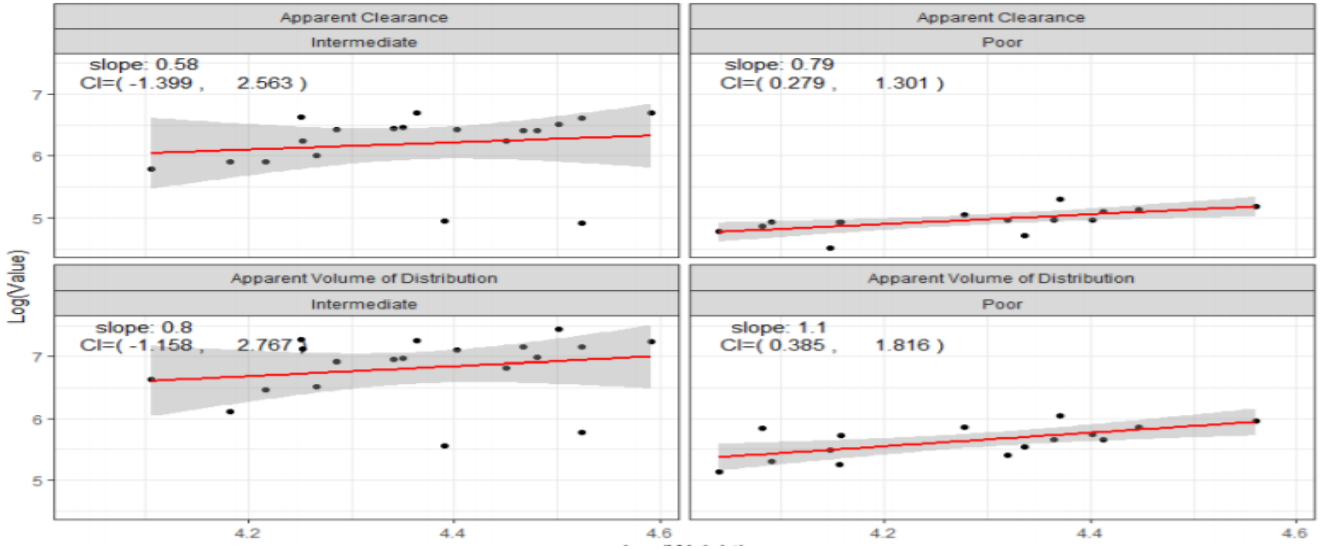


The solid red line presents the median of the observed concentrations. The shaded areas present the 90th prediction interval of the median based on 200 simulated datasets. The solid points are the observed prediction-corrected 3,4-DAP concentrations.

Assessment

- Adapting of the adult Pop-PK model for simulation in pediatric population needs to carefully consider potential differences ped vs. adults, ex. :
  - Maturation of the metabolism pathways: already achieved for the target pediatric population (> 6 year old)
  - Weight/size effects on the clearance and distribution parameters in the model: integrated based on allometric scaling

Figure 7: Relationship Between 3,4-DAP PK Parameters and Weight



Assessment

Simulation of exposure in pediatric patients

- The population choices used for simulation (healthy vs. LEMS patients, NAT2 phenotype and dose level) are not critical because dose proportional PK and the purpose of estimating relative PK

- Two relevant scenarios were simulated in health subjects
  - mg/kg dosing
  - Simplified dosing based on weigh vs. 45kg

Table 15: Simulation Scenarios in Pediatric Population

Scenario	Initial Dose	Maximum Single dose	Maximum total daily dose
1*	0.07 mg/kg Q8h for the 1st day	0.3 mg/kg Q8h for 2 days	1.4 mg/kg Q24h for 2 days
2	2.5 mg for pediatric patients < 45 kg and 5 mg for pediatric patients ≥ 45 kg Q8h for the 1st day	15 mg for pediatric patients < 45 kg and 30 mg for pediatric patients ≥ 45 kg Q8h for 2 days	50 mg for pediatric patients <45 kg and 100 mg for pediatric patients ≥ 45 kg Q24h for 2 days

Simulation results

Scenario #2 was selected based on similarity to exposure in adults and clinical convenience

Figure 11: Comparison of Exposure ($AUC_{0-\infty}$: ng·h/mL and Cmax: ng/mL) in Pediatric and Adult Patients Following Scenario 1 Simulation Stratified by Weight Groups in Pediatric Population: Poor Metabolizers (TDD is total daily dose)

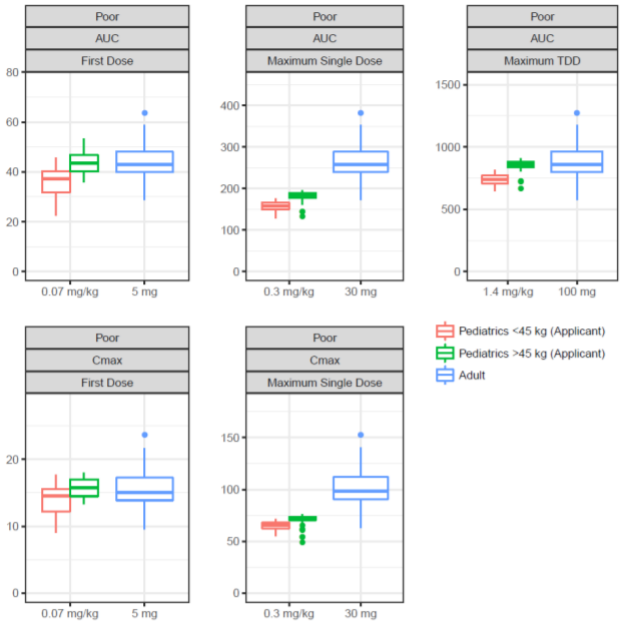
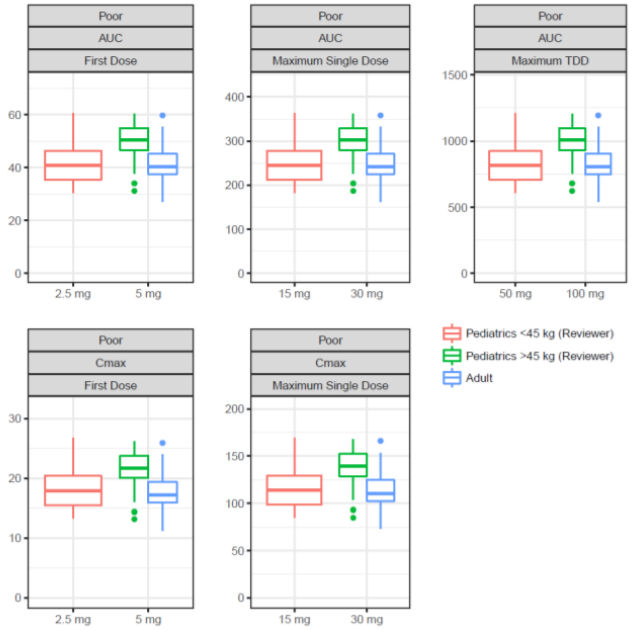


Figure 12: Comparison of Exposure ($AUC_{0-\infty}$: ng·h/mL and Cmax: ng/mL) in Pediatric and Adult Patients Following Scenario 2 Simulation Stratified by Weight Groups in Pediatric Population: Poor Metabolizers (TDD is total daily dose)



Within the context of rare disease and pediatric population the M&S provided critical support to leverage available data

Conclusions

- Reliable use of modeling and simulation in drug development and regulatory decisions requires verifying :
  - Fit-for-purpose of the data, model and analysis
  - Conclusions/claims are within the limitations of the data and model
- MIDD has a crucial role to leverage data for complex scenario and for populations that are difficult to test for practical or ethical reasons
- Appropriate use of MIDD can inform and enhance drug development and regulatory review


Questions