

Concepts of Pharmacometric Model- Based Decision Making

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Outline

- Model-Based Decision Making in Pharmacometrics
- Modeling and Simulation
- General Framework

Outline

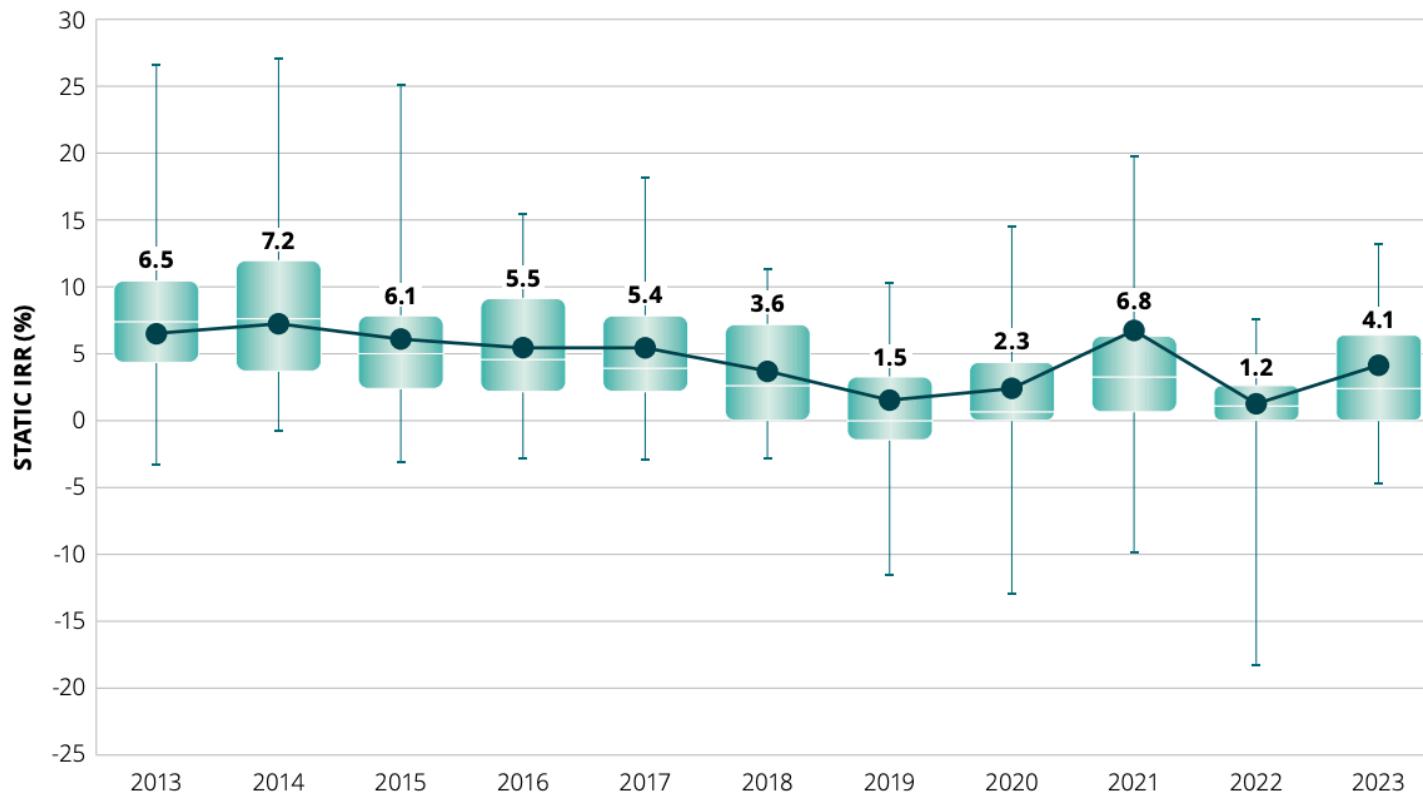
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Developing a New Drug is Increasingly Expansive and Time-Consuming

- The median capitalized R&D investment to bring a new drug to the market was \$985.3 million.¹
- The median clinical development time for FDA-approved drugs from 2010-2020 was reported to be 8.3 years.²

Deloitte: Measuring the return from pharmaceutical innovation

Figure 1. Return on late-stage pipeline, 2013-2023



Note: 2013-2022 calculated from GlobalData dataset, 2023 data point calculated from Evaluate dataset

Source: Deloitte analysis, 2024.

Model Informed Drug Development (MIDD)

- Innovative approach are needed to reduce the overall time and cost of drug development.
 - EMA: “*...quantitative framework... aimed at improving the quality, efficiency and cost effectiveness of decision making.*”
 - FDA: “*...approach that has been recognized as critical to streamline and accelerate the development of new medical products and enable more informed decision-making, and reduce uncertainty.*”

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 416–417; doi:10.1002/psp.412223
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COMMENTARY
Commentary on the MID3 Good Practices Paper

Efthymios Manolis^{1,2*}, Jacob Brogren^{2,3}, Susan Cole^{2,4}, Justin L. Hay^{2,4}, Anna Nordmark^{2,3}, Kristin E. Karlsson^{2,3}, Frederike Lentz^{2,5}, Norbert Benda^{2,5}, Gaby Wangorsch^{2,6}, Gerard Pons^{2,7}, Wei Zhao^{2,8,9}, Valeria Gigante^{2,10}, Francesca Serone^{2,10}, Joseph F. Standing^{2,11}, Aris Dokoumetzidis^{2,12}, Juha Vakkilainen^{2,13}, Michiel van den Heuvel^{2,14}, Victor Mangas Sanjuan^{2,15}, Johannes Taminiau^{2,16}, Essam Kerwash^{2,4}, David Khan^{2,3}, Flora Tshinanu Musuamba^{2,17} and Ine Skottheim Rusten^{2,18}: on behalf of the EMA Modelling and Simulation Working Group

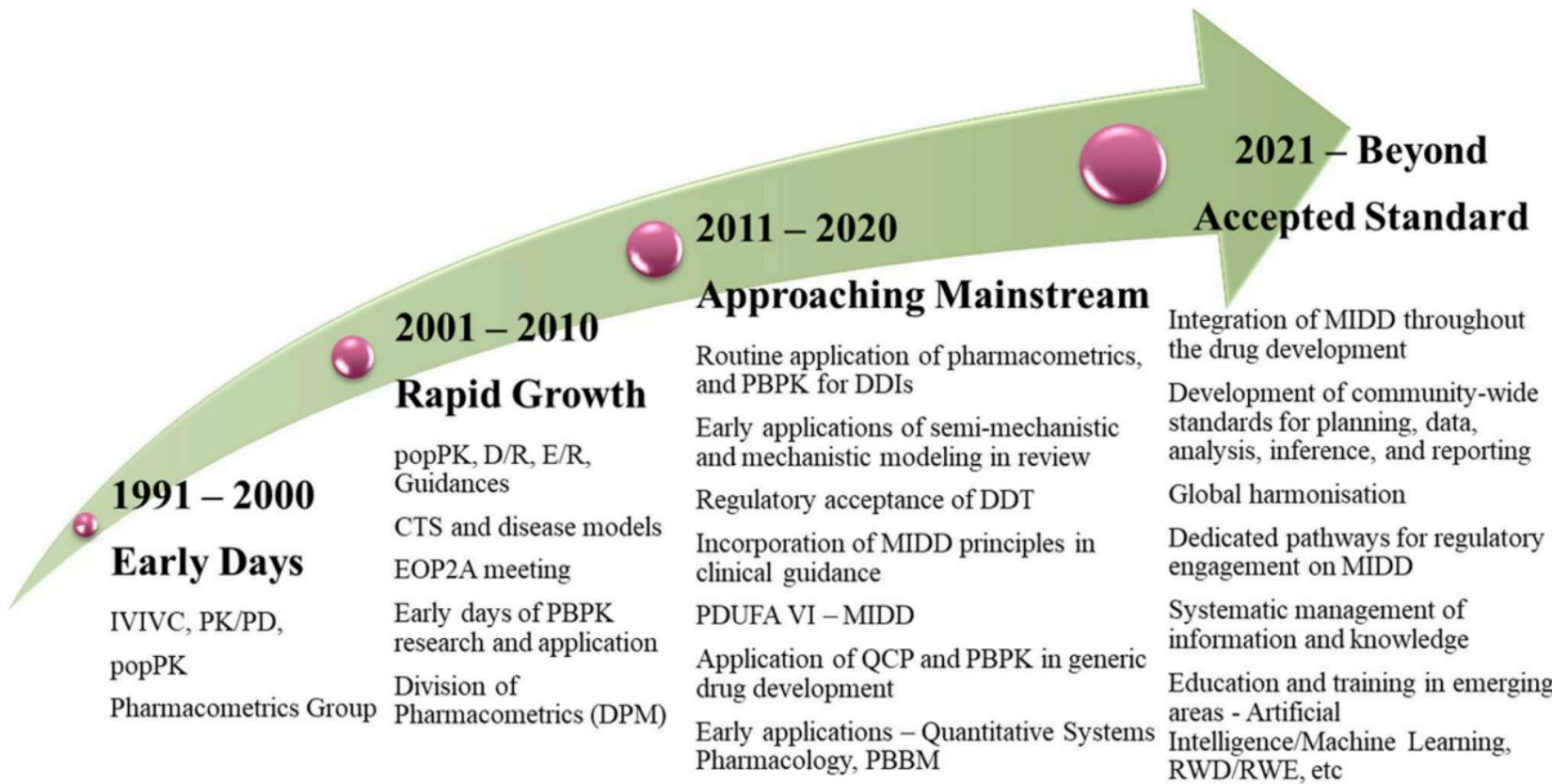
Pharmaceutical Research (2022) 39:1669–1680
<https://doi.org/10.1007/s11095-022-03288-w>

EXPERT REVIEW

Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making

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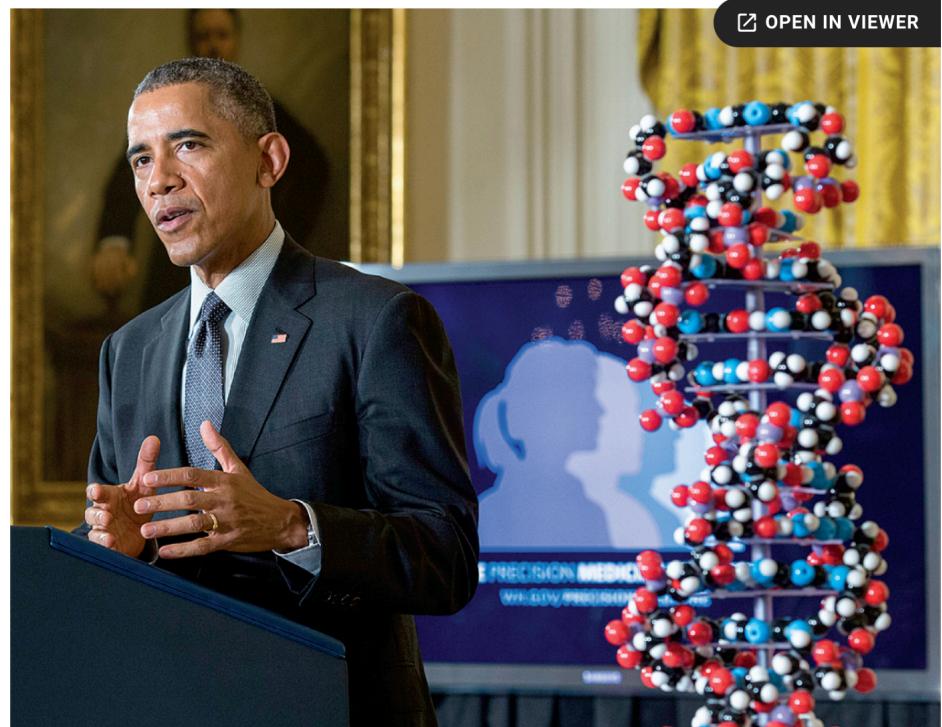
Model Informed Drug Development (MIDD)



Precision Medicine

“In 2015, President Barack Obama launched the Precision Medicine Initiative that outlined efforts to move beyond the “one-size-fits-all” approach of modern medicine and into the realm of individualized, tailored dosing.

“1



NIH now has a plan for carrying out the study of more than a million Americans that President Obama called for in January as part of his Precision Medicine Initiative.

PHOTO: PETE SOUZA

Model Informed Precision Dosing (MIPD)

- A “state-of-the art” science fall under the umbrella of precision medicine.
- Aim to optimize the drug treatment outcome using a model-based approach.
- Clinical Decision Support (CDS) platforms



Model-Based Decision Making in Pharmacometrics

- Model-Informed Drug Development (MIDD)
- Model-Informed Precision Dosing (MIPD)

Outline

- Model-Based Decision Making in Pharmacometrics
- **Modeling and Simulation**
- General Framework

Models?

- Knowledge management tools¹
 - Knowledge of biological systems
 - Drug properties (e.g., potency, binding affinity, etc)
 - Disease mechanism (e.g., signaling pathways)
 - How a drug affects the human body (e.g., PK)
 - How a human body responds to the drug (e.g., PD)
 - Emerging data from diverse sources (e.g., *in vitro*, preclinical and clinical studies)

Models

$$\frac{dA}{dt} = -CL \times C; \quad A_{t=0} = 0$$

$$C = \frac{A}{V}$$

$$CL_i = TVCL \times e^{\eta_{1i}}$$

$$\eta_{1i} \in N(0, \omega_1^2)$$

$$V_i = TVV \times e^{\eta_{2i}}$$

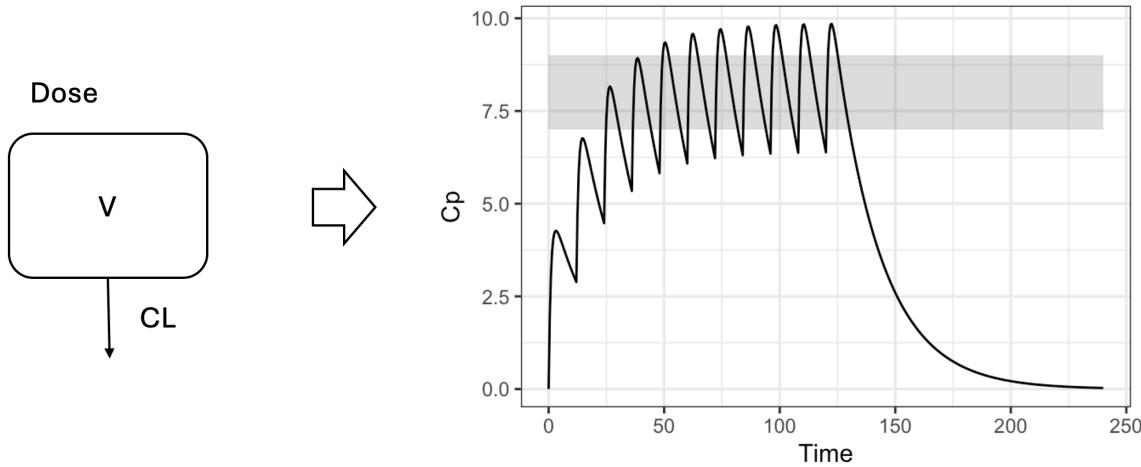
$$\eta_{2i} \in N(0, \omega_2^2)$$

$$OBS_{i,j} = C_{i,j} * (1 + \epsilon_{i,j})$$

$$\epsilon_{i,j} \in N(0, \sigma_1^2)$$

Simulations

- Allow us to extract information from models



- Allow us to answer drug development/clinical questions in a quantitative manner
 - Are dose adjustments needed in patients with a specific genotype?
 - Which dosing regimen provides a better efficacy/safety profiles?
 - What clinical effect might be observed if a metabolic inhibitor co-administered?
- Enables the decision-making in drug development / precision dosing

The Application of Simulations

- Analysis
 - Model evaluations (e.g., predictive checks)
- Illustration
 - Summarise and illustrate data/concepts
 - Integrate information across multiple sources
- Exploration
 - Interpolate between observed data
 - Extrapolate to new conditions
 - Express expected range of variability and/or uncertainty in response relationship
- Decision-making
 - Quantify the probability of outcome given decision path

Outline

- Model-Based Decision Making in Pharmacometrics
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General Framework¹

- Define the Questions
- Translate into Quantitative Terms
- Define Prior Knowledge, Assumptions, Constraints
- Model Development and Evaluations
- Plan and Execute Simulations
- Summarise and Present Results

Defining the Questions

- Guide model development and evaluation.
 - Which structural models?
 - Which statistical models?
- Guide simulation design.
 - Alternative dosing regimens?
 - Number of subjects, patient characteristics, duration of simulation.
 - Variability versus uncertainty?

Translate into Quantitative Terms

- The question must be translated into quantitative terms before simulations.
 - Question: How many subjects are needed in the upcoming pediatric PK study?
 - Quantitative translation: How many subjects needed to be enrolled to prospectively powered to target a 95% CI within **60% to 140% of the geometric mean estimate of CL** for Drug A in each pediatric group with **>80% power**.
- Defining the quantitative criteria is the **key** to formulate modeling and simulation strategies.

Prior Knowledge

- Prior (existing) models
 - Structural/statistical model
 - Parameter uncertainty
- Prior disease and physiology knowledge
 - Covariate (age, body weight, etc) distributions
 - Clinically important effect size
 - Expert opinions

Assumptions and Constraints

- Assumptions needed to implement M&S
 - Same exposure-response in adults and pediatrics?
 - Fixing parameter values because we have no data to estimate them?
 - Assuming a covariance matrix of random effects?
 - What is the clinically meaningful change in effect size? Subjective specification?
- Constraints
 - Limited sample size for trial design
 - Limited number of samples per subjects
 - Limited follow-up time

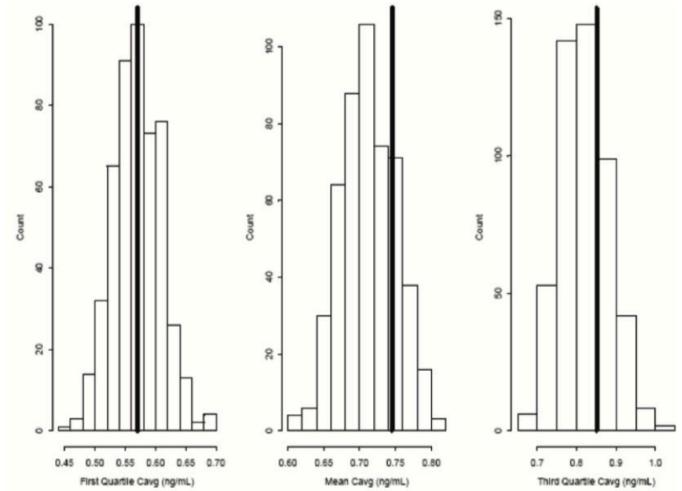
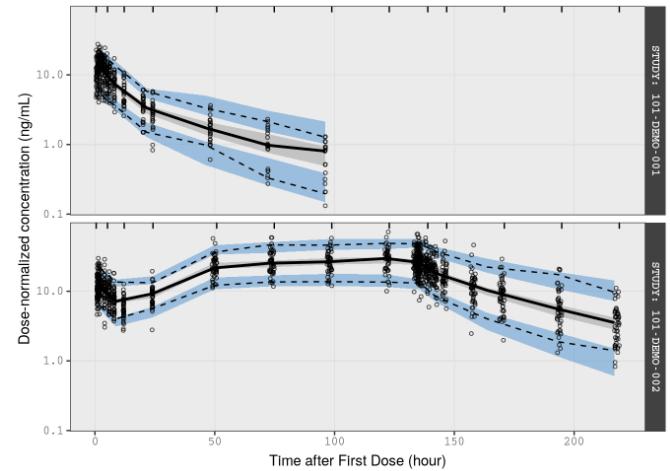
Model Development

Which model components are needed to implement a simulation to answer the question.

- Endpoints (PK/PD, clinical outcomes)
- Structure models (empirical versus mechanism-based)
- Covariate relationships (which covariates needed?)
- Random effects
 - Inter-individual, inter-occasion variability
 - Residual variability
 - Covariance among the random effects
- Parameter uncertainty (parameteric versus non-parameteric)

Model Evaluation

- Basic diagnostics
 - Plausibility of model structure and parameter estimates
 - Comparison with relevant literature models
 - Convergence, successful covariance step, stability
 - Goodness-of-fit plots
- Simulation-based
 - Predictive checks (longitudinal versus landmark)¹
- Parameter estimates
 - Precise enough?
 - Healthy variance-covariance matrices?



Plan and Execute Simulations

- Trial-related components
 - Drop-out, non-compliance, randomizations, duration
- Patients population (covariates)
 - Resample from previous studies
 - Resample from existing dataset ([NHANES](#))
 - Derive a joint distribution for resampling
- Statistical components
 - Deterministic versus stochastic simulations
 - Include inter-occasion variability?
 - With/without parameter uncertainty

Summarise and Present Results

- Re-state and answer the questions asked at the beginning.
- Be prepared to present to the audience with a diverse background.
 - Emphasize on important findings.
 - Focus on 1-2 key figures / tables that likely impacts the decision-making.
 - Usually not so useful to present P-values and model diagnostics.

The end