Clinical Pharmacometrician in drug development

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Senior Scientist, PM, PS, Pharma Research & Early Development (pRED),

F. Hoffmann-La Roche Ltd

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Agenda

- My path from university to industry
- What is modeling?
- What is Modeling and Simulation (pharmacometrics)?
- What is the role of pharmacometrics in drug development?
- Case studies, applying pharmacometrics to:
  - Formulation development, accelerated drug development
- Summary & conclusions

Some basic terminology

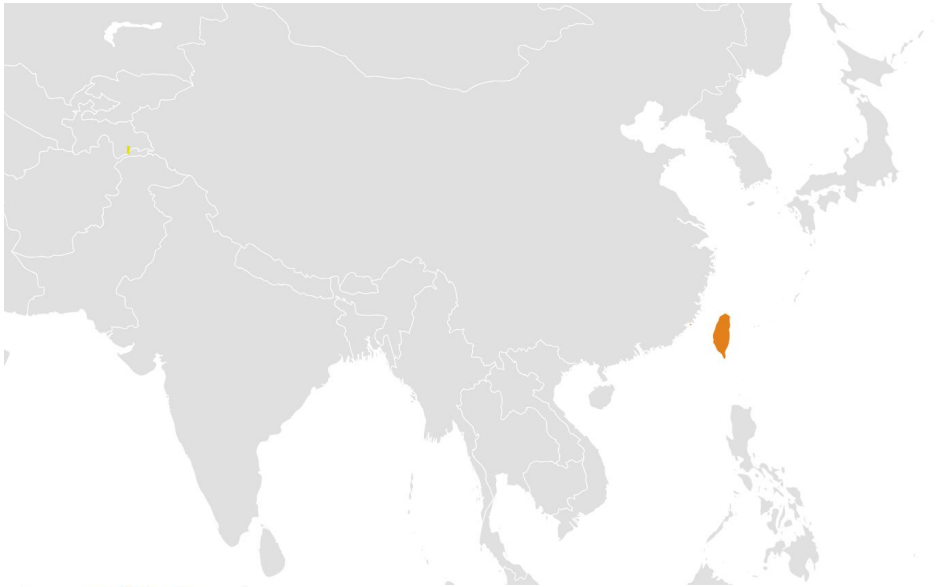
Different companies & institutions use different terms:

- Modeling and Simulation Scientist
- (Clinical) Pharmacometrician
- Model-informed Drug Development (MIDD) Modeler
- And others…

From university to industry

Trained as a Clinical Pharmacist

Bachelor in Pharmacy, Taipei Medical University, Taiwan



- Guest student of the International Pharmaceutical Student Federation (IPSF) Two months internship at University of Düsseldorf
- Research assistant at Institute of Pharmacognosy

Expertises:

Licensed Pharmacist in Taiwan

Focused on preclinical pharmacology research from medicinal plants

Delving deeper into bioanalytical techniques

Master in Focus Pharmacy, University of Würzburg, Germany

- Focused on pharmaceutical biology
- Master thesis focused on the expression of heat shock proteins in *Arabidopsis*
- Research assistant at Chair of Pharmaceutical Biology

Expertises:

Bioanalytical analysis (LC-MS/MS)

Optimizing immunoblot method in house

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

First contact with Pharmacometrics

PhD in Clinical Pharmacology, University of Cologne, Germany

- Bayer Graduate Program in Pharmacology and Experimental Therapeutics
- PhD thesis focused on major human membrane transporter mediated-DDI *in vitro* and *in vivo*

Expertises:

PK/PD modeling

Regulatory bioanalytical analysis (LC-MS/MS)

Cell-based assays

Transporter-mediated DDI

Clinical studies (operation aspect)

Board overview of PK/PD modeling in drug development

Certificate in Pharmacometrics, University of North Texas, online, in the cloud

- Deeper understanding and boarding overview of PK/PD modeling in drug development
- Strengthen statistic knowledge

Expertise:

PK/PD modeling in different disease areas

PK/PD modeling in pediatric programs

Concentration-QT modeling

hsc

THE UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at FORT WORTH

Modeling and Simulation Scientist in Clinical Pharmacology

Idorsia Pharmaceuticals Ltd, Switzerland

- Working closely with clinical pharmacologists on projects from Phase 1 to Phase 3

Expertise:

PK/PD modeling in cardiovascular disease, immunology and neuroscience

Concentration-QT modeling to investigate the QT liability of new compounds

idorsia

Clinical Pharmacometrician in Predictive Modeling

F. Hoffmann-La Roche AG, Switzerland

- Clinical Pharmacometrician in PM since January 2024

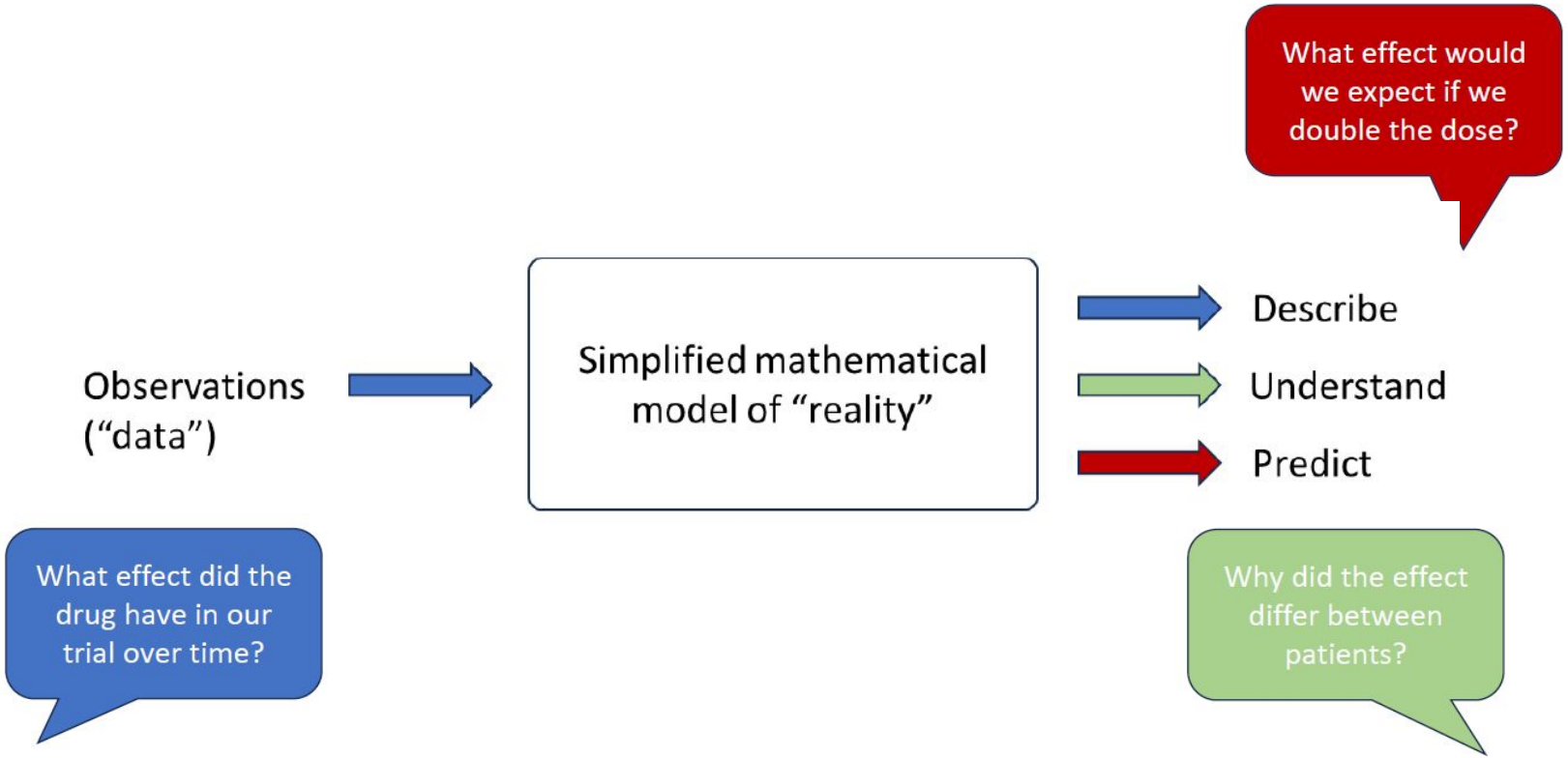
Expertise:

PK/PD modeling in Cardiovascular, Renal & Metabolism disease and neuroscience

Roche

What is modeling?

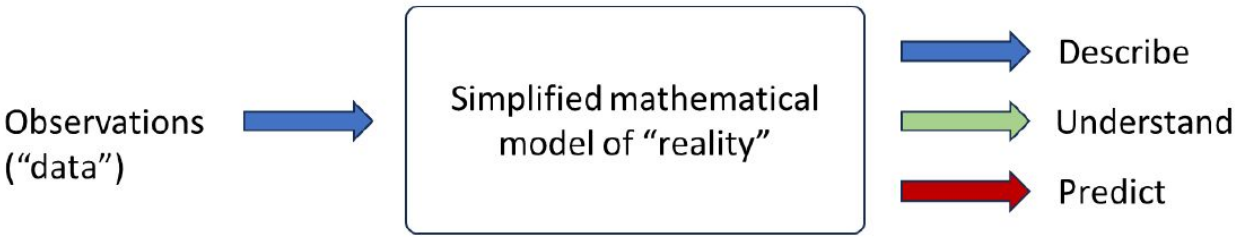
What is modeling?



What is pharmacometrics?

Broadly, pharmacometrics comprises:

- Application of quantitative models in drug development to facilitate decision making
- Based on mathematical models that dynamically describe the PK/PD of a drug
- Integrating diverse data sources, from in vitro to (pre-)clinical in vivo data
- Providing the means to extrapolate, e.g., to new dosing regimens, to alternative patient collectives, to patients with specific characteristics (genotype, BMI, …)



Wang et al. Clin Pharmacol Ther. 2019;105(4):899-911.

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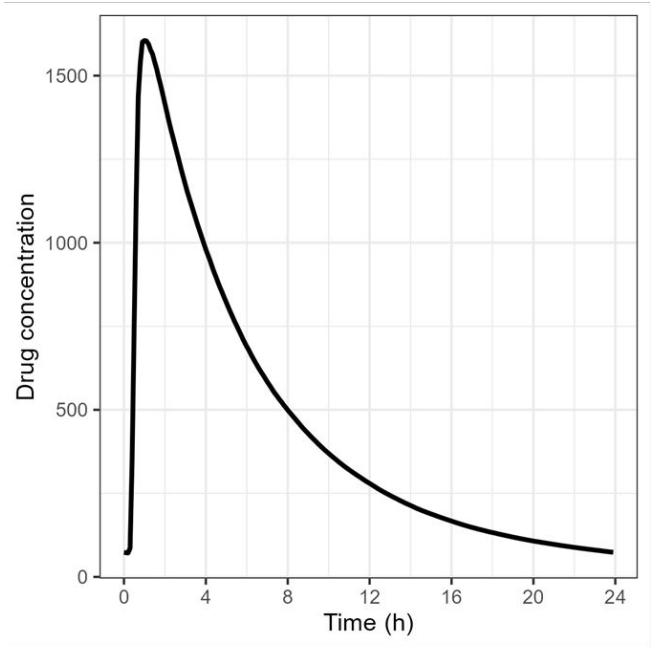
Pharmacometrics requires:

- Expertise in (clinical) pharmacology, programming & statistics
- Exciting for those interested in learning and applying quantitative methods

PK/PD data

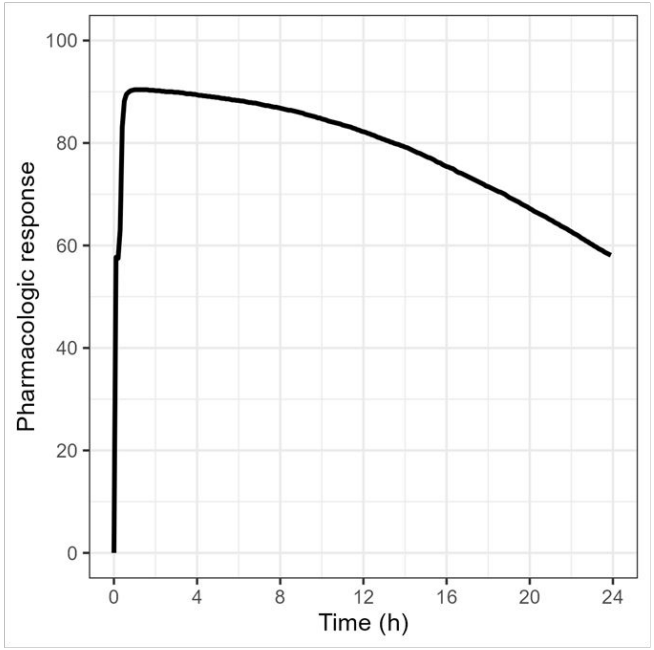
Collected from clinical data

Pharmacokinetics (PK)



What body does to the drug

Pharmacodynamics (PD)



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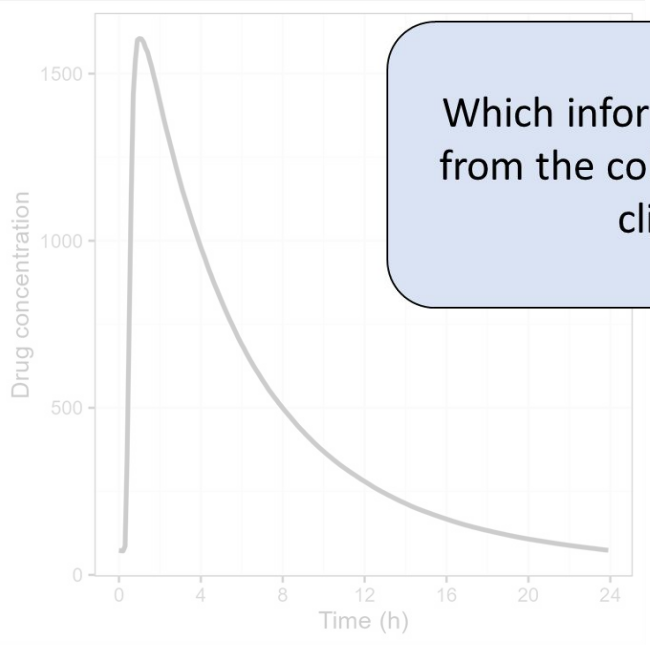
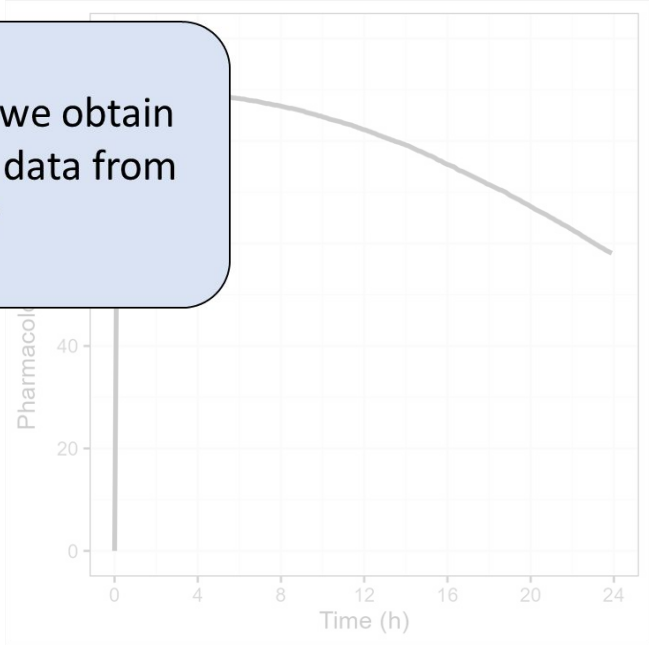


What body does to the drug

Which information could we obtain from the collected PK/PD data from clinical studies?

Pharmacodynamics (PD)

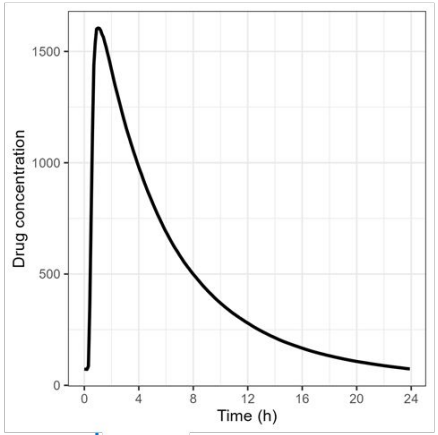


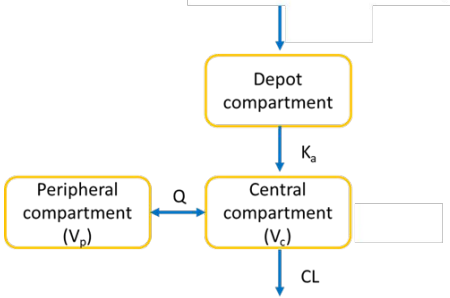
What drug does to the body

PK-PD Analysis

Fit-for-purpose model (empirical model)

Pharmacokinetics (PK)



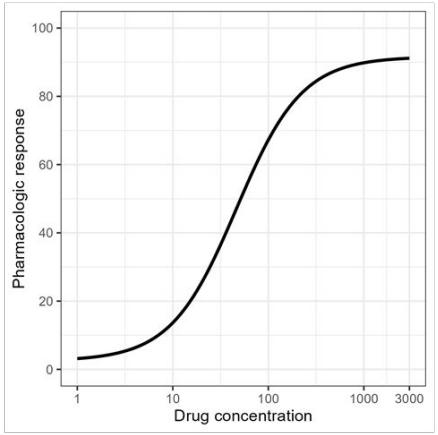


$$\frac{dA1}{dt} = -K_a * A1$$

$$\frac{dA2}{dt} = K_a * A1 - K * A2 - K_{12} * A2 + K_{21} * A3$$

$$\frac{dA3}{dt} = K_{12} * A2 - K_{21} * A3$$

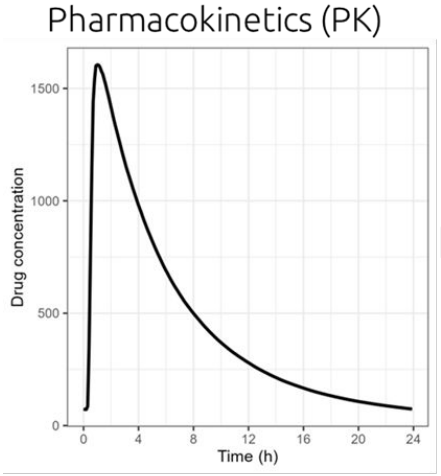
Exposure-response

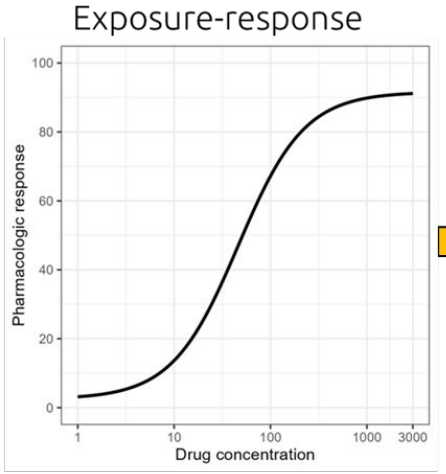


$$E = \frac{E_{max} * Conc}{EC_{50} + Conc}$$

PK-PD Analysis

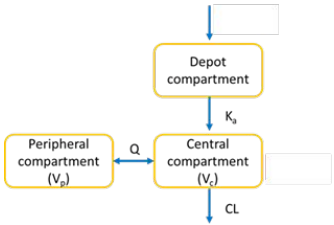
Fit-for-purpose model (empirical model)





Covariates

- Body weight
- Age
- Liver function
- Renal function
- And more…



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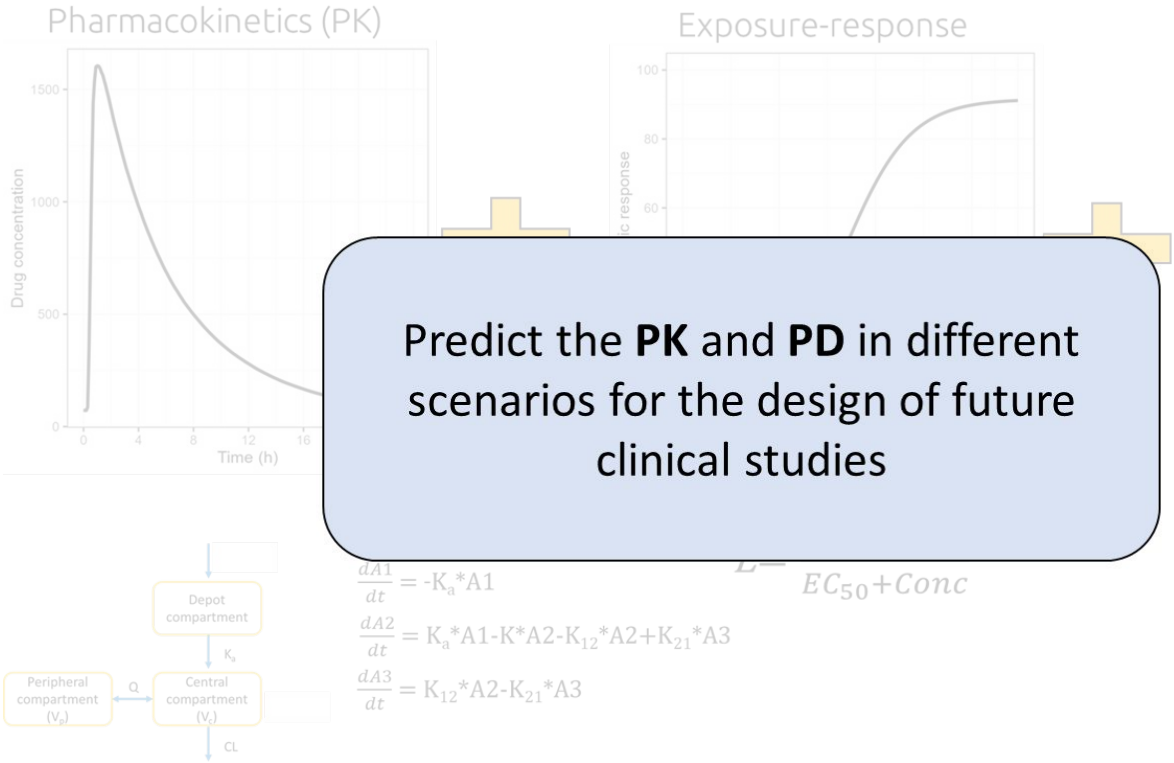
PK-PD Analysis

Fit-for-purpose model (empirical model)



Predict the **PK** and **PD** in different scenarios for the design of future clinical studies

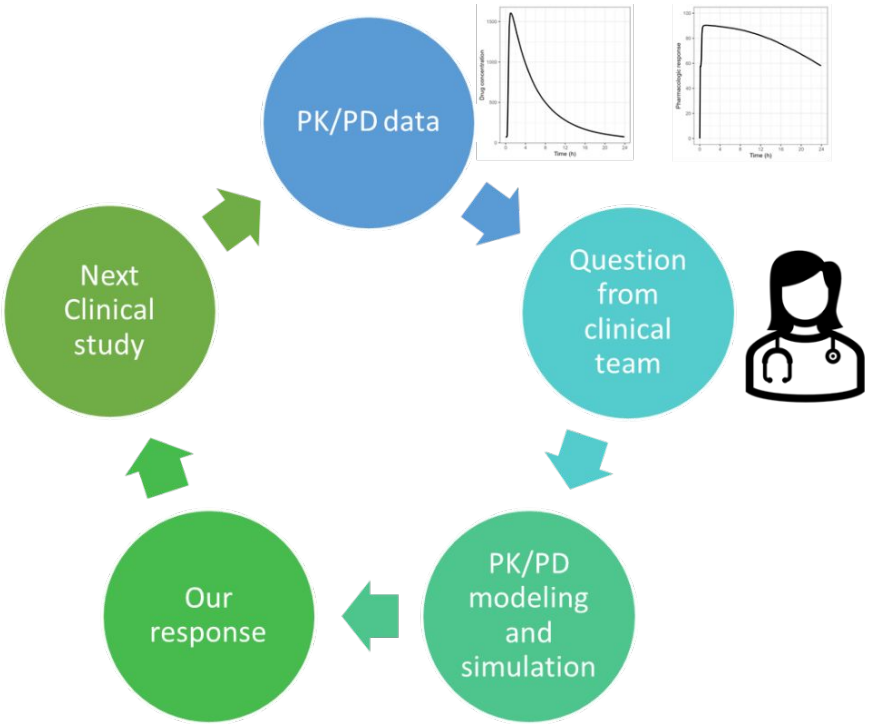
Covariates

- Body weight
- Age
- Liver function
- Renal function
- And more…

Role of pharmacometrics in drug development

Daily life as a Clinical Pharmacometrician

Answering clinical questions using PK/PD modeling

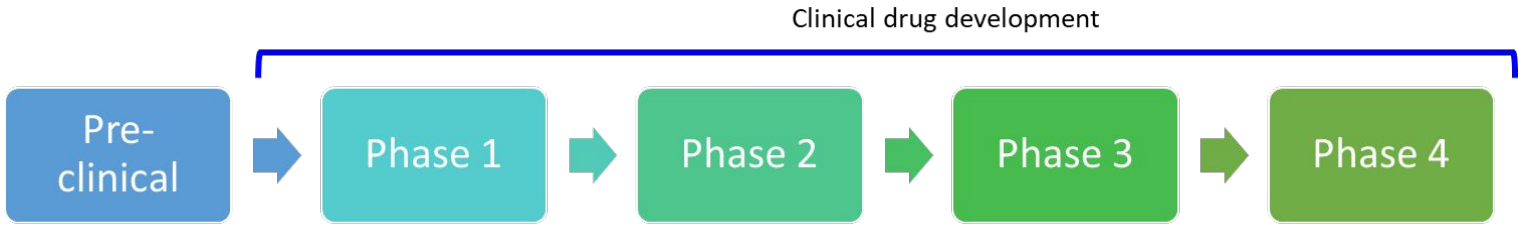


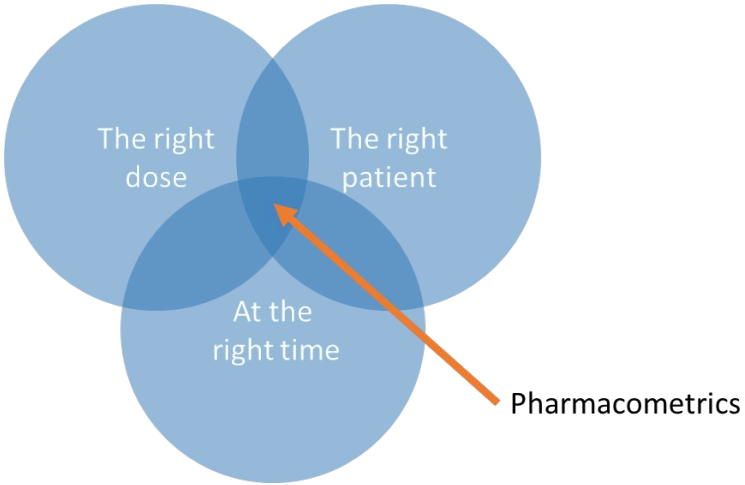
Prediction of response over time for:

- Different dosing regimens (Once or twice daily? Which dose?)
- Specific populations (Hepatic impairment, renal impairment, pediatrics)
- Specific patient characteristics (High/low body weight, genotypes)
- Targeted clinical efficacy
- Safety issue
- & more…

Drug development

Role of Pharmacometrics





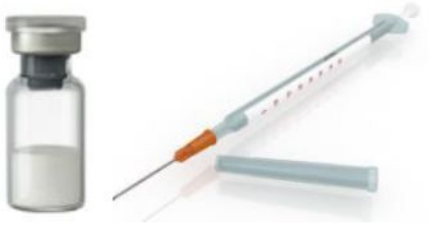
Case study - Formulation development

Compound UB-001 was developed for the emergency treatment of heart attacks

Status of the compound:

- Several Phase 1 clinical studies were conducted to investigate the safety, efficacy (biomarker), and pharmacokinetics in healthy volunteers.
- One Phase 2 clinical studies were conducted to investigate the therapeutic dose level, safety, efficacy, and pharmacokinetics in the target patient population.
- The compound is progressing to a Phase 3 clinical study in the target patient population, which will include a large number of patients.

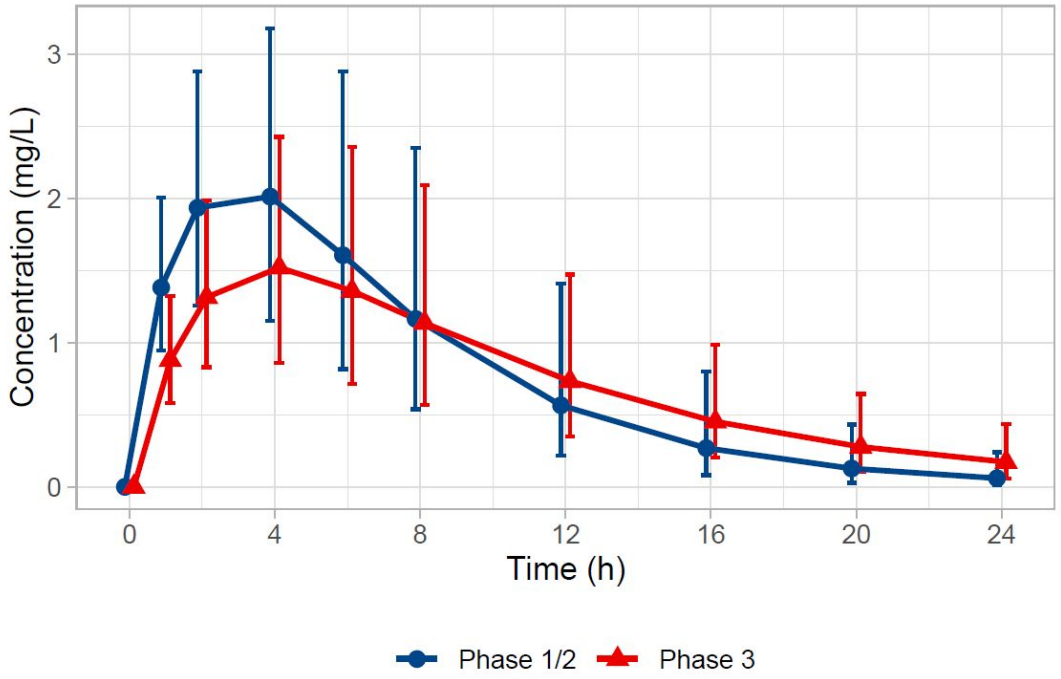
A refined formulation was required for Phase 3 due to the use of an auto-injector device



Phase 1/2 formulation

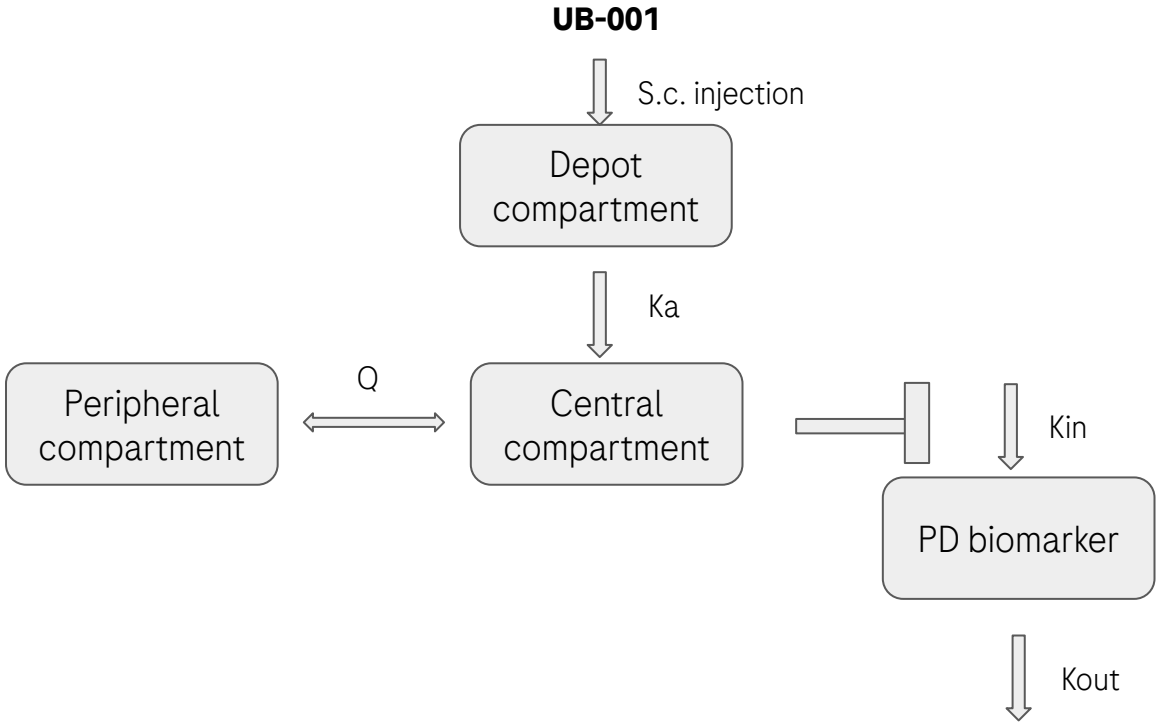
Phase 3 formulation

The absorption was slightly slower and with a lower C_{max} when using the new Phase 3 formulation

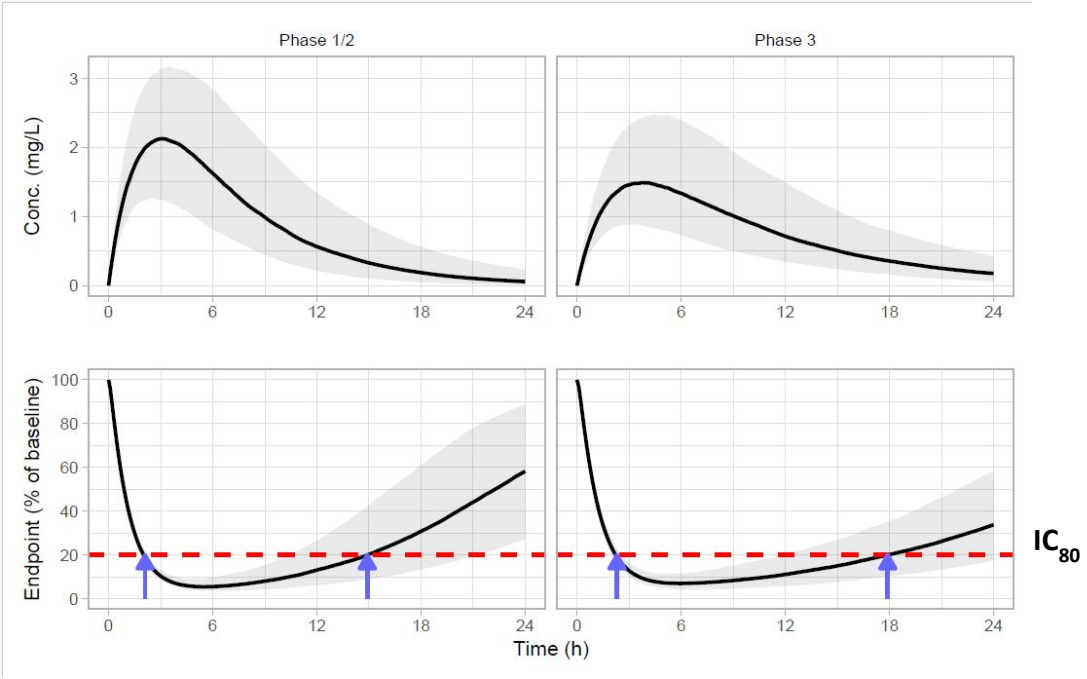


"Is the observed PK difference clinically relevant?"

Modeling & simulation provided the means to extrapolate the expected PD based on PK



Simulations indicated no clinically relevant impact on the clinical endpoint, supporting to proceed with new formulation



Median and 90% prediction interval up to 12 h

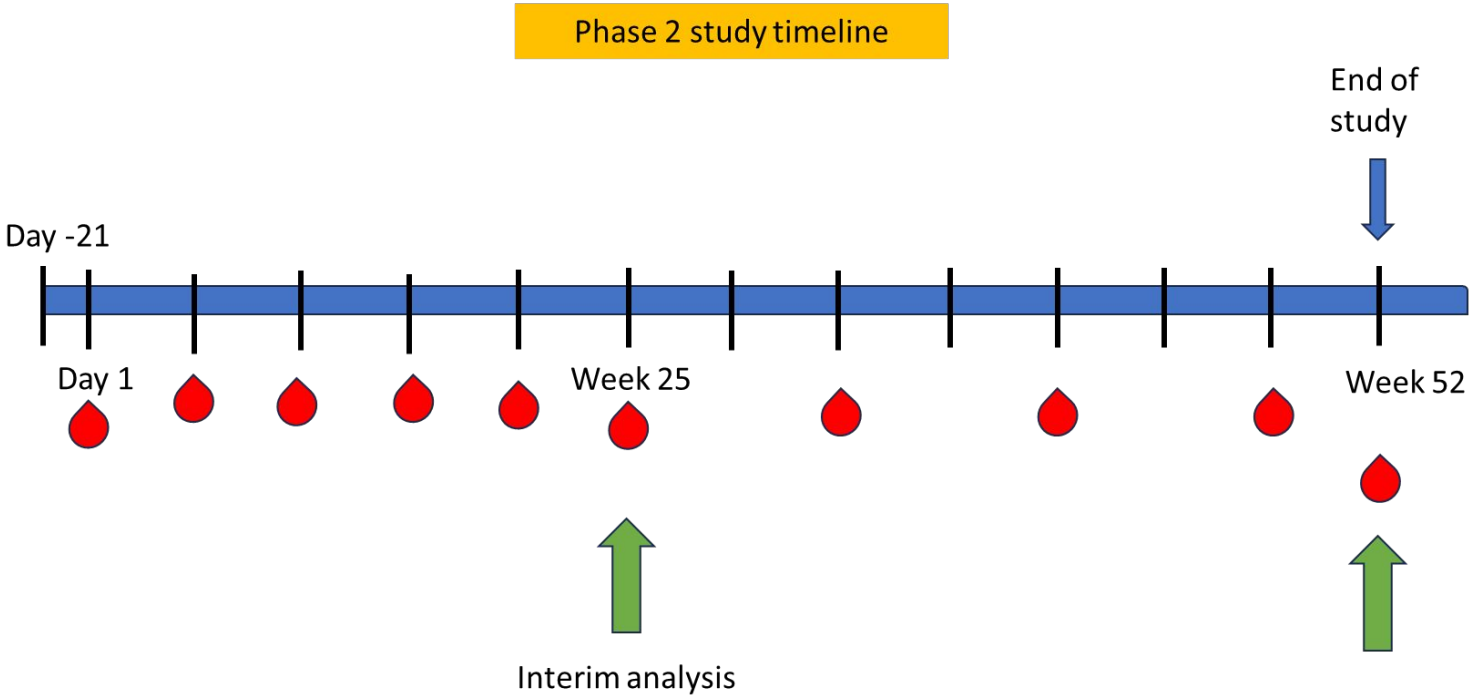
Case study – Accelerated drug development

Compound UB-002 was developed for the chronic treatment of disease X

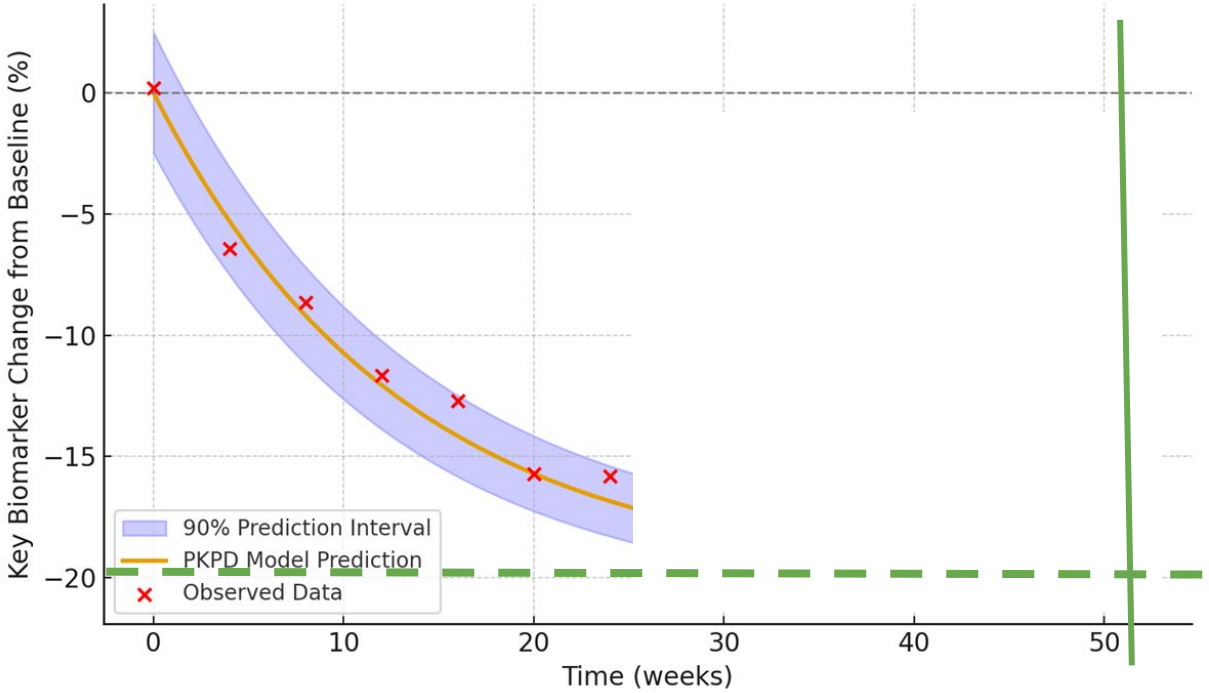
Status of the compound:

- Several Phase 1 clinical studies were conducted to investigate the safety, efficacy (PD biomarker), and pharmacokinetics in healthy volunteers.
- One Phase 2 clinical studies with a treatment duration of 1 year were conducted to investigate the therapeutic dose level, safety, efficacy, and pharmacokinetics in the target patient population.
- The clinical team would like to shorten the drug development duration and start the Phase 3 clinical study as soon as possible
- The decision to proceed the compound to Phase 3 would be based on the Phase 2 clinical data at week 25.

Accelerated the drug development duration



Simulations indicated the key predicted biomarker change from baseline at week 52 would meet the expectation



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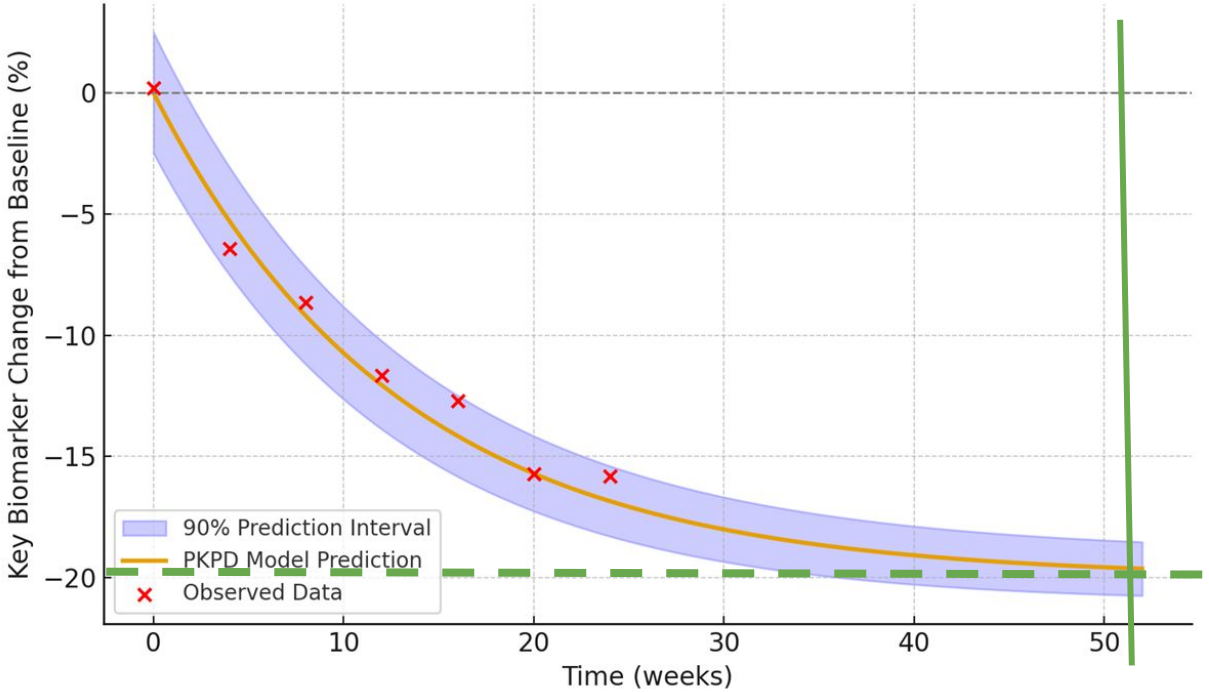

Doing now what patients need next