

Principles of modeling and simulations

François Bouzom

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EUFEMED conference – Lyon - FRANCE



Louisa, living with epilepsy

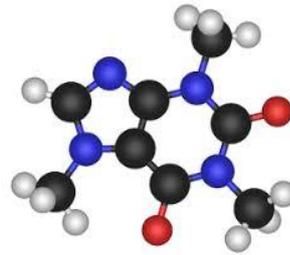
Setting the scene

| Medicines objectives



The Right patient(s)

The Right drug(s)



The Right dose (regimen)

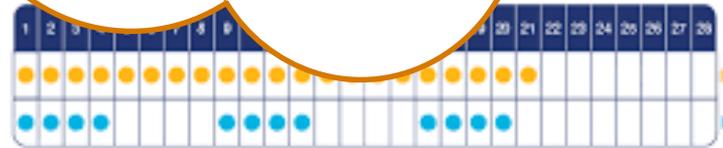
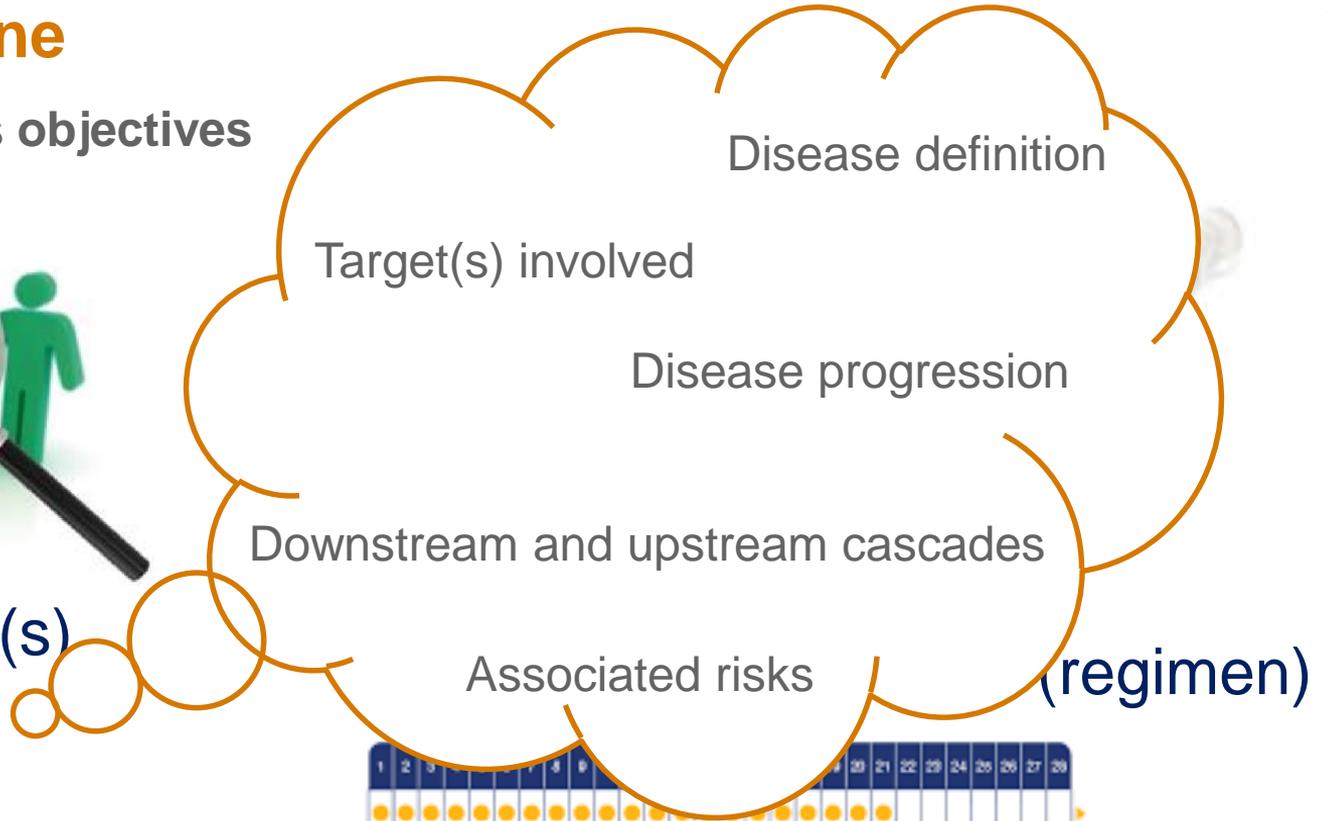


Setting the scene

Medicines objectives

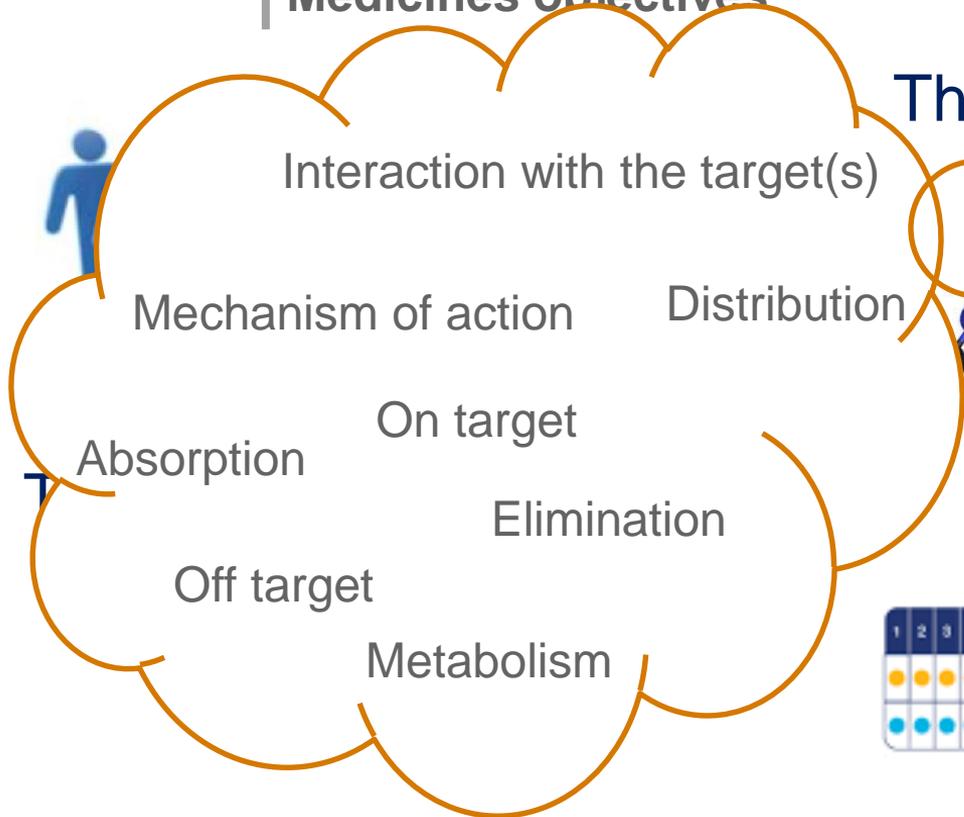


The Right patient(s)

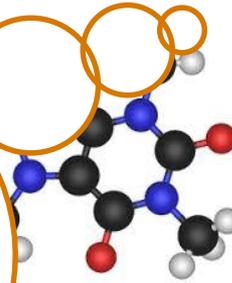


Setting the scene

Medicines objectives



The Right drug(s)

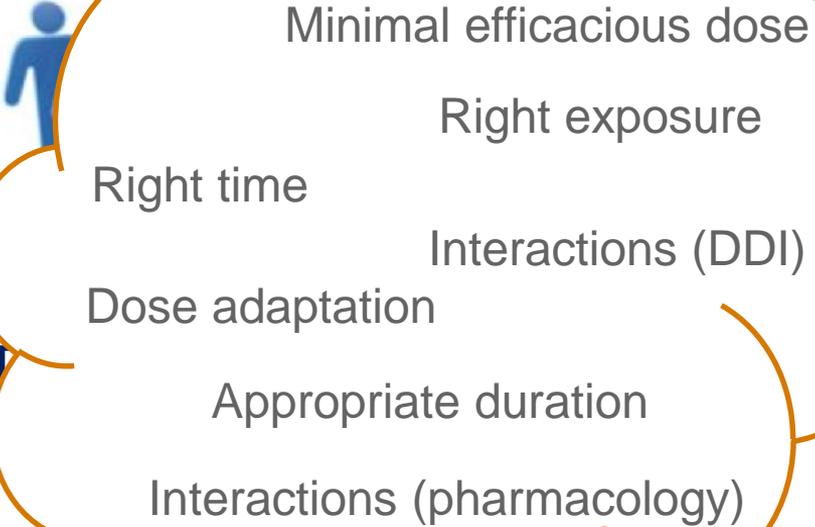


The Right dose (regimen)



Setting the scene

Medicines objectives



Minimal efficacious dose

Right exposure

Right time

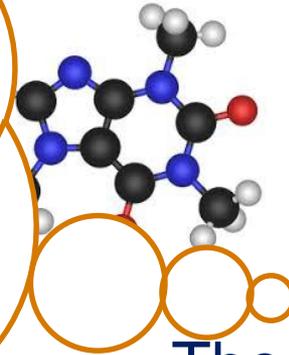
Interactions (DDI)

Dose adaptation

Appropriate duration

Interactions (pharmacology)

The Right drug(s)



The Right dose (regimen)

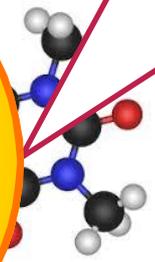


Setting the scene

Medicines objectives

The Right

Is there any way to get a simpler and integrated view?...



The Right patient(s)

The Right dose (regimen)



Setting the scene

Medicines objectives



The Right patient(



MODELLING?!!!

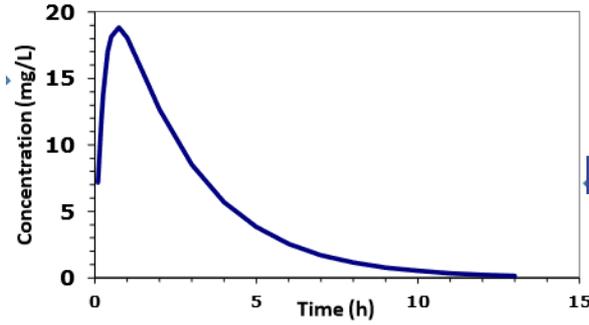
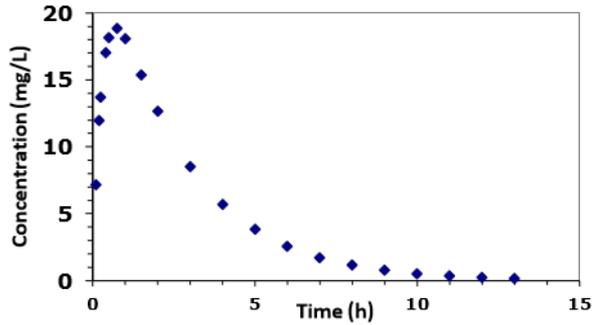
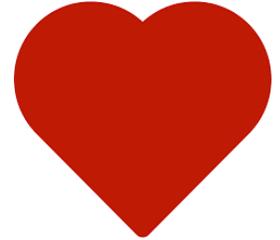
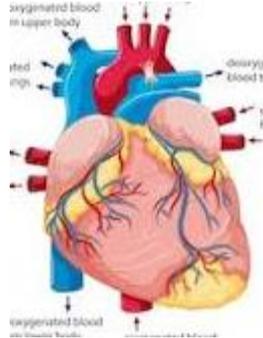
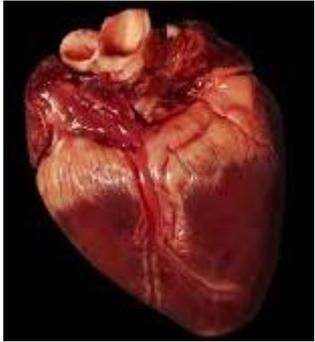


Right dose (regimen)



Principles of modelling

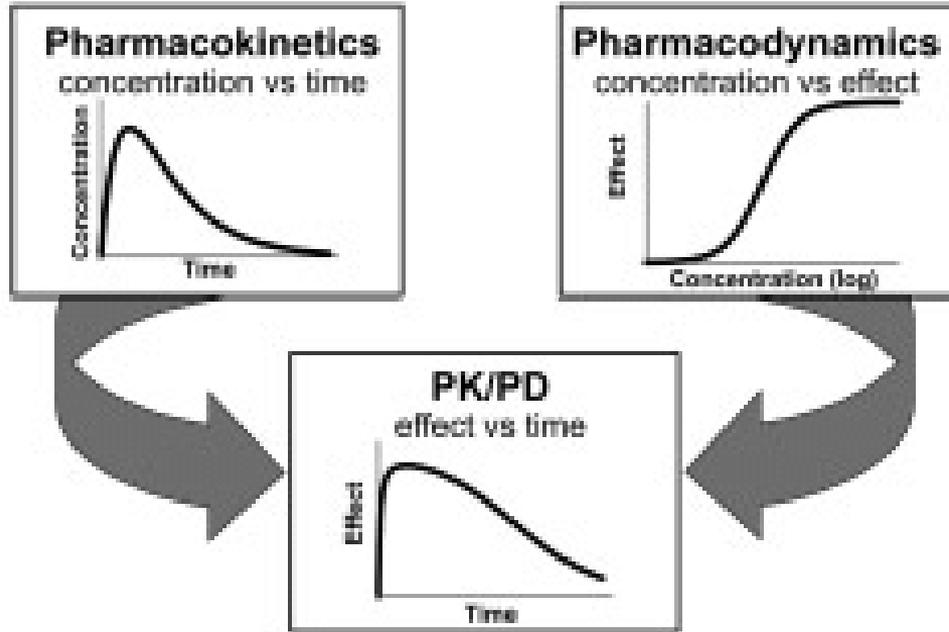
Simplified representation of a system



$$C_t = f(t, \text{dose}, \text{route})$$

Principles of modelling

| Simplified representation of a system



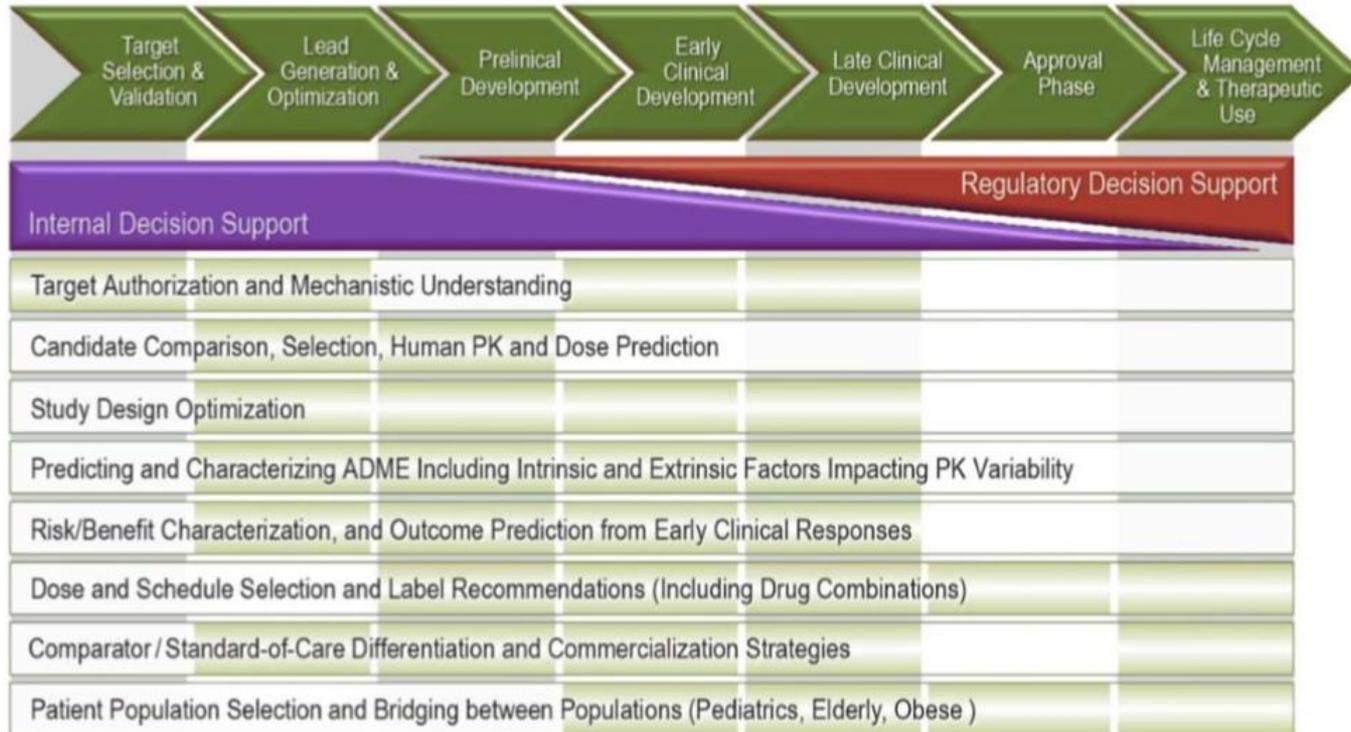
Principles of modelling

Simplified representation of a system

- Fit for purpose
- Able to accurately describe the observed data
- Able to include the most important features of the data
- As simple as possible
- Logically consistent, plausible
- Appropriate levels of precision and detail
- Validation/qualification with external dataset
- Able to make accurate and precise predictions (intrapolation)
- May allow for extrapolation outside the data range

Principles of modelling

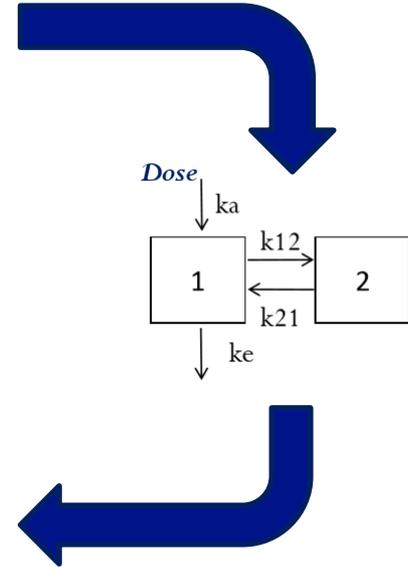
Simplified representation of a system - Fit for purpose



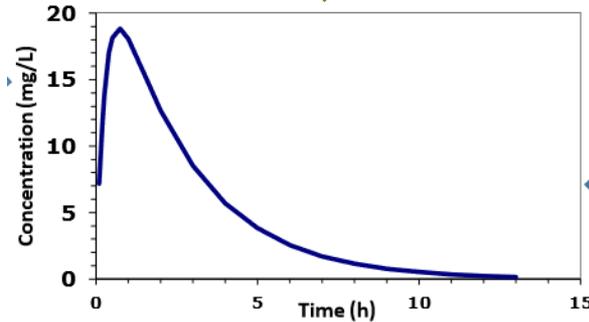
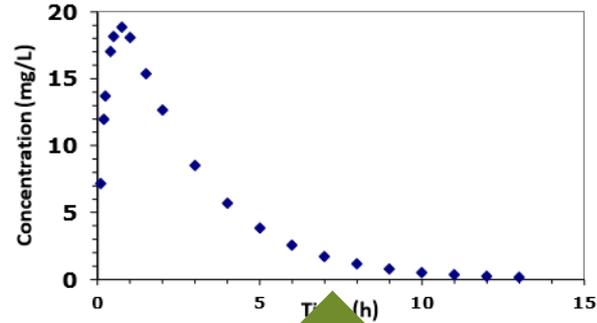
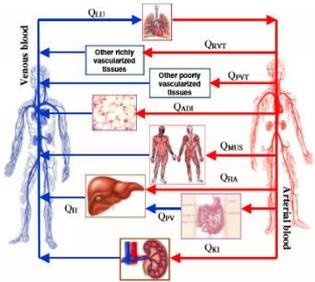
Principles of modelling

Different modelling approaches

TOP-DOWN



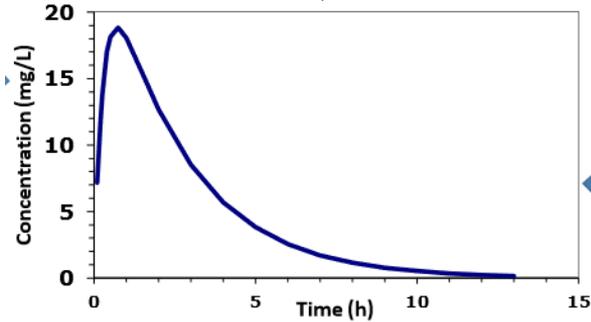
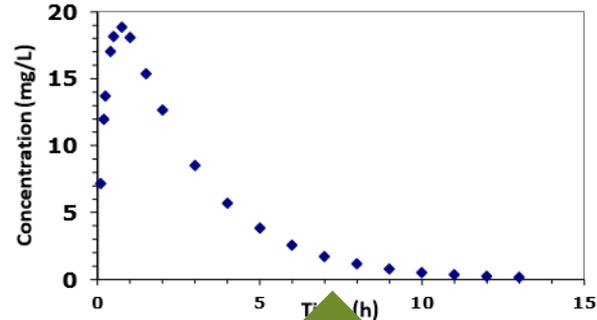
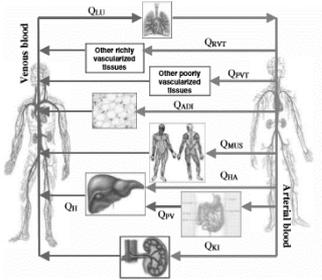
BOTTOM-UP



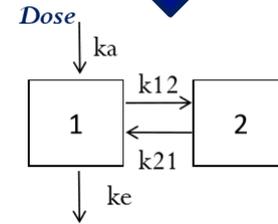
PK/PD modelling

Top-down approach

BOTTOM-UP



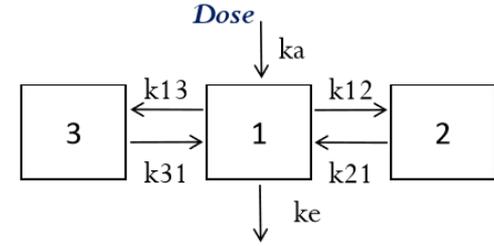
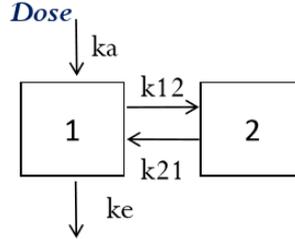
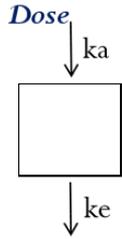
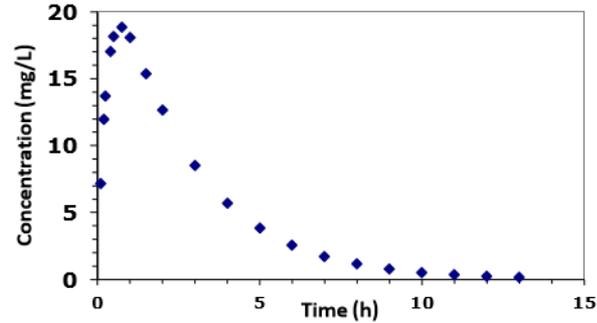
TOP-DOWN



PK/PD modelling

Top-down approach

Individual PK approach



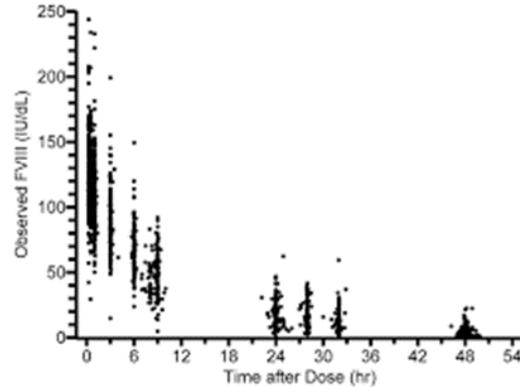
$$C_t = \frac{Dose}{Vd} \frac{ka}{ka - ke} (e^{-ket} - e^{-kat})$$

Compartmental analysis

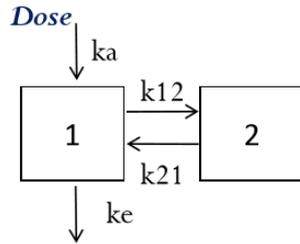
PK/PD modelling

Top-down approach

Population PK approach



Non-linear mixed
effect modelling
NONMEM



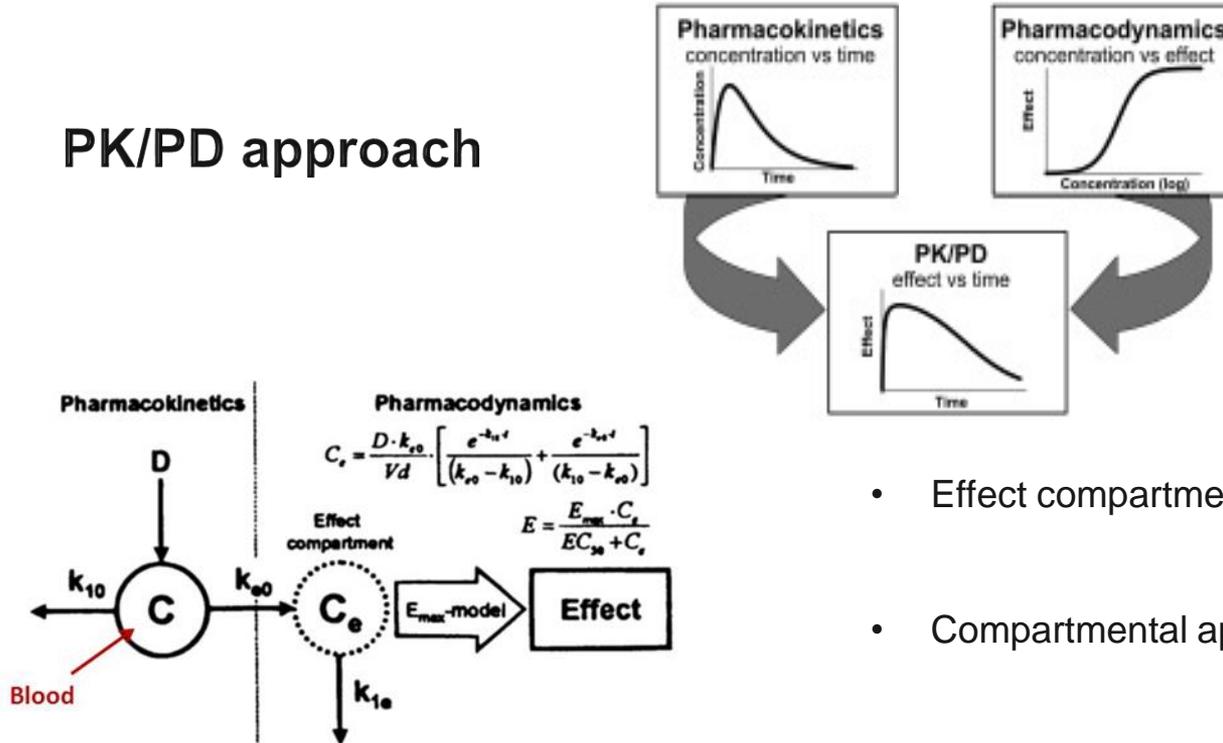
- fixed effects → PK population parameters
- Random effect parameters
 - Inter-individual variability
 - Intra-occasion variability
 - Residual variability
- Covariate analysis

PK/PD modelling

Top-down approach

PK/PD approach

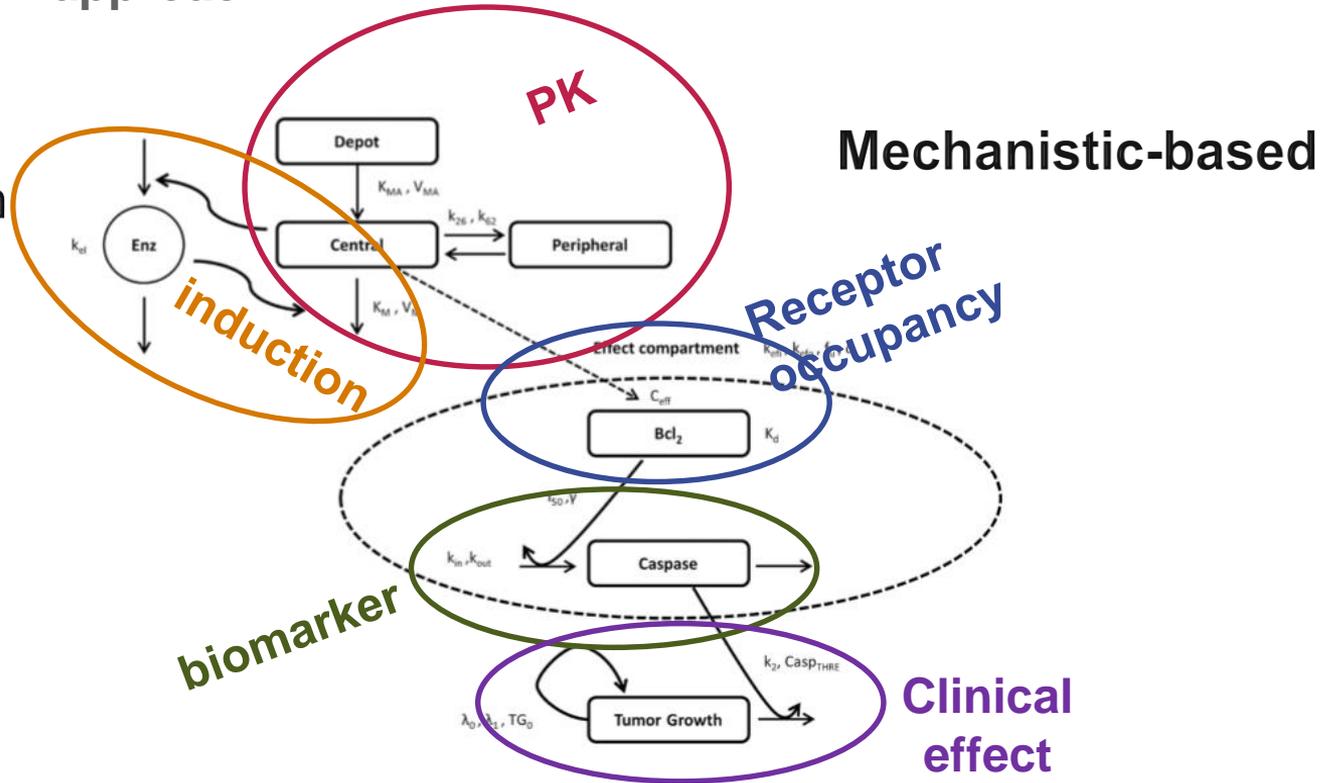
Empirical and descriptive



PK/PD modelling

Top-down approach

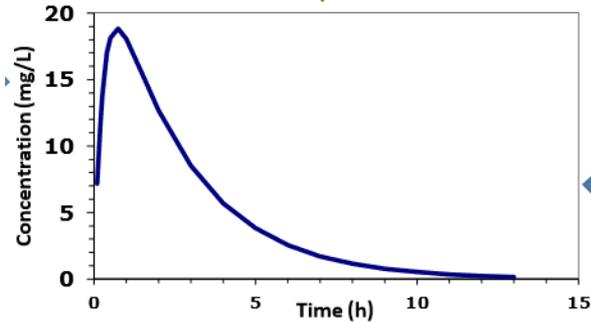
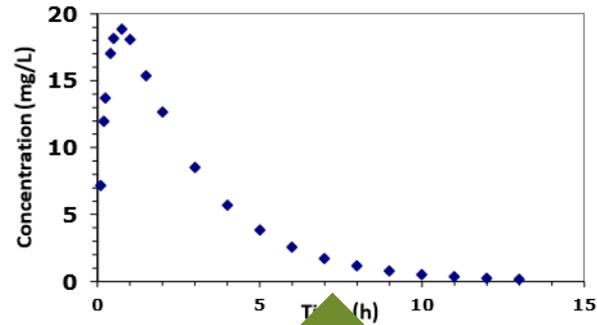
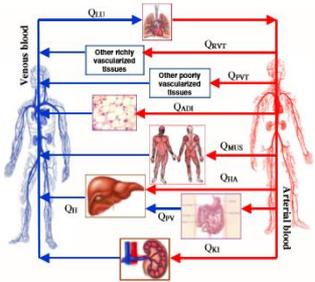
PK/PD approach



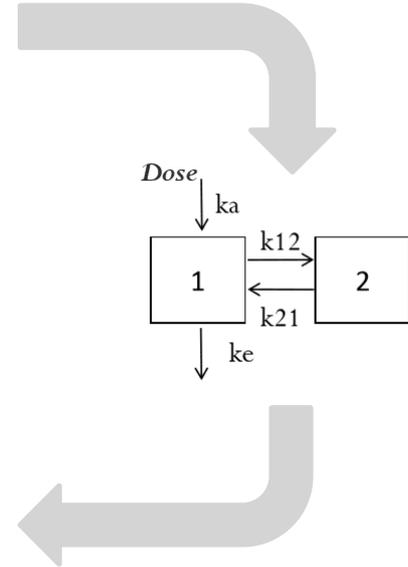
PK/PD modelling

Bottom-up approach

BOTTOM-UP



TOP-DOWN



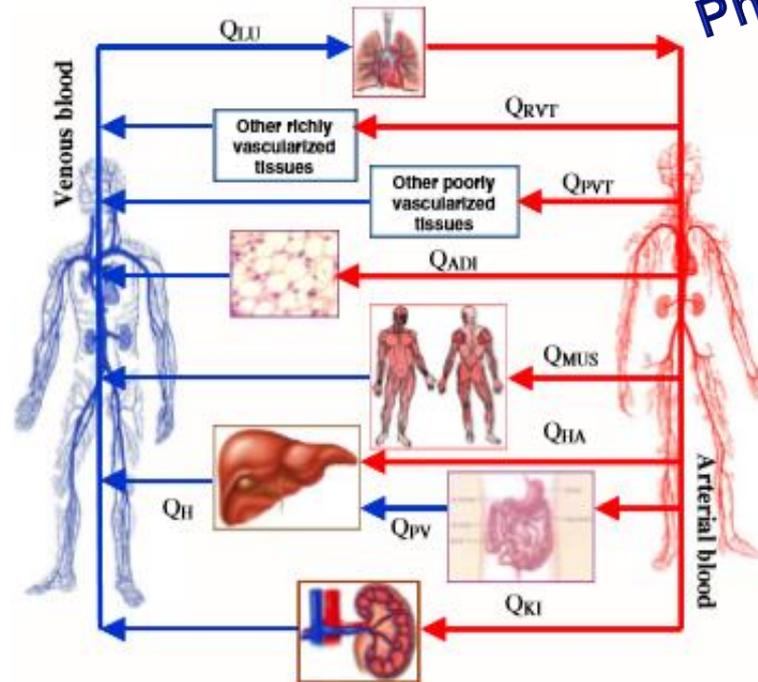
PK/PD modelling

Bottom-up approach – PBPK

Physiologically Based Pharmacokinetics

Physiological frame

- Body/organ weight
- Blood flows
- Tissue composition
- Enzymatic abundance
- GIT



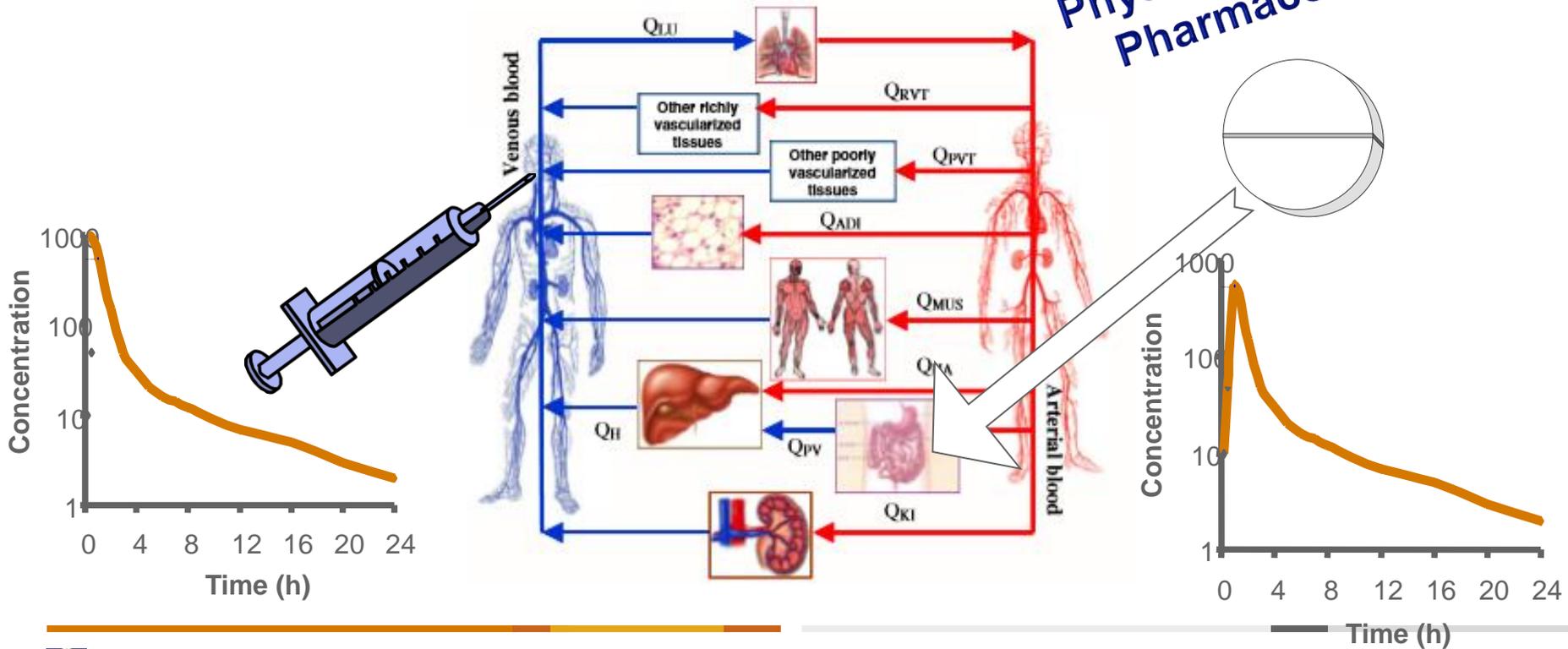
Drug parameters

- Phys-chem properties
- Protein binding
- Blood to plasma ratio
- permeability
- Enzymatic clearance
- Transport clearance

PK/PD modelling

Bottom-up approach – PBPK

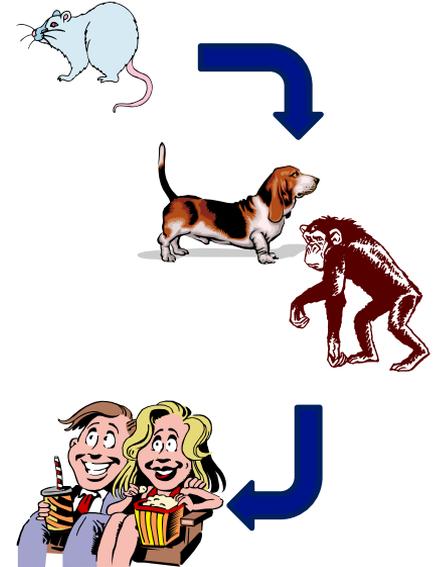
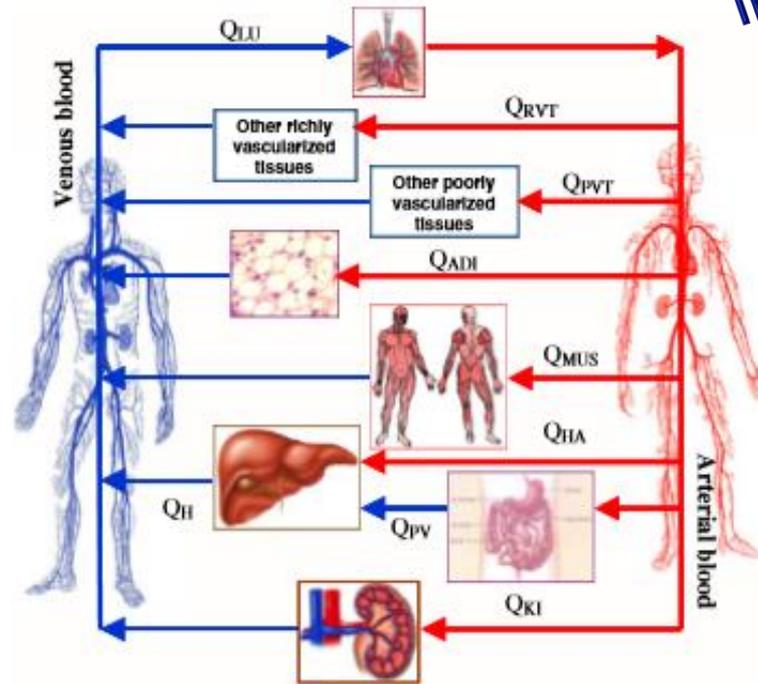
Physiologically based
Pharmacokinetics



PK/PD modelling

Bottom-up approach – PBPK

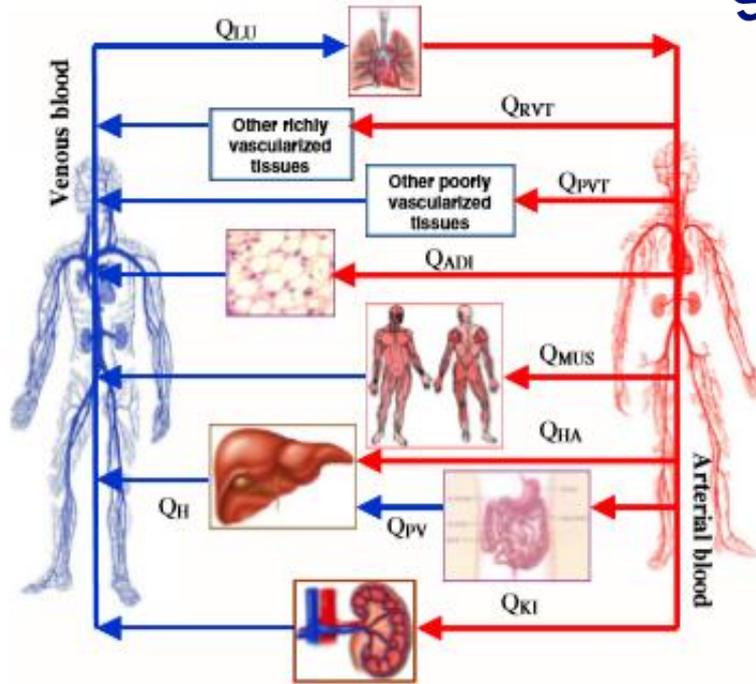
Interspecies scaling
FIH



PK/PD modelling

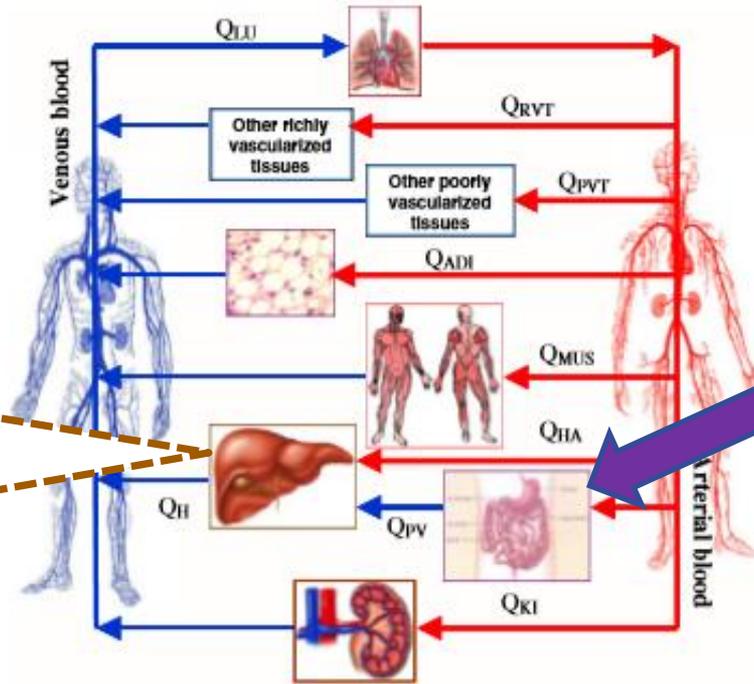
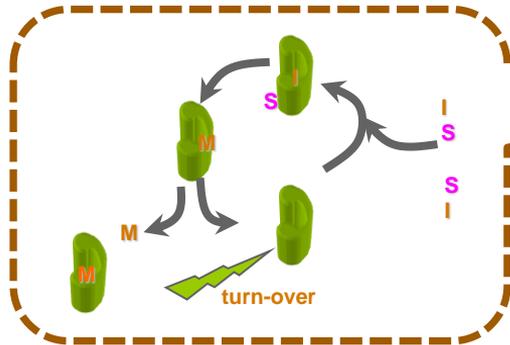
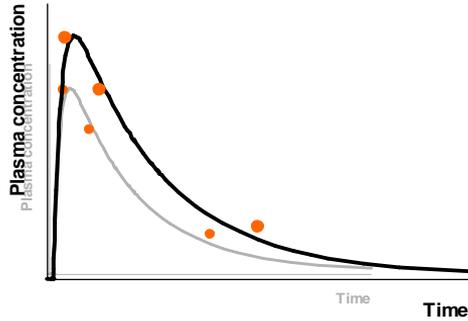
Bottom-up approach – PBPK

Special populations
pediatrics



PK/PD modelling

Bottom-up approach – PBPK

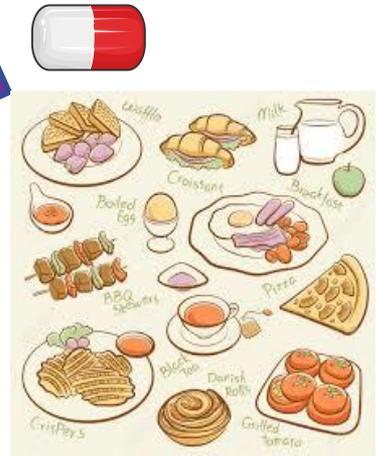
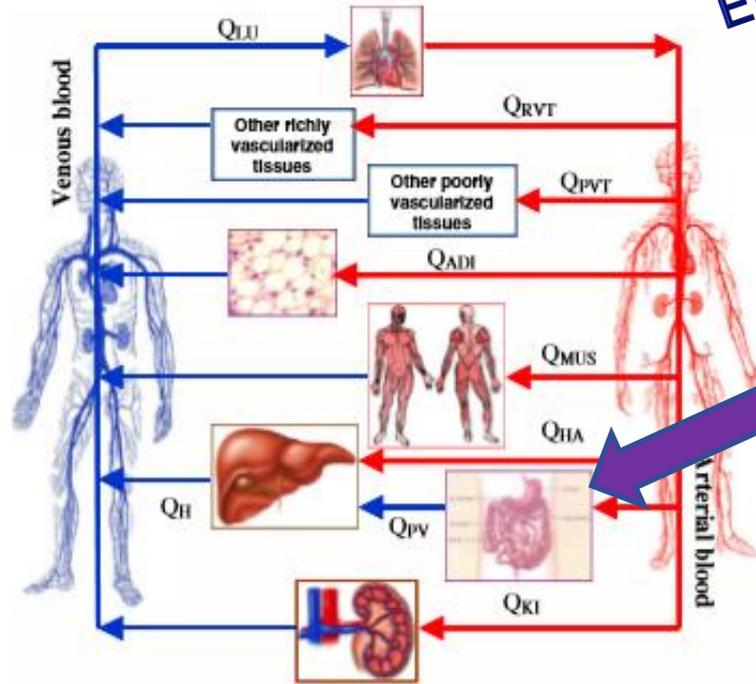


DDI



Bottom-up approach – PBPK

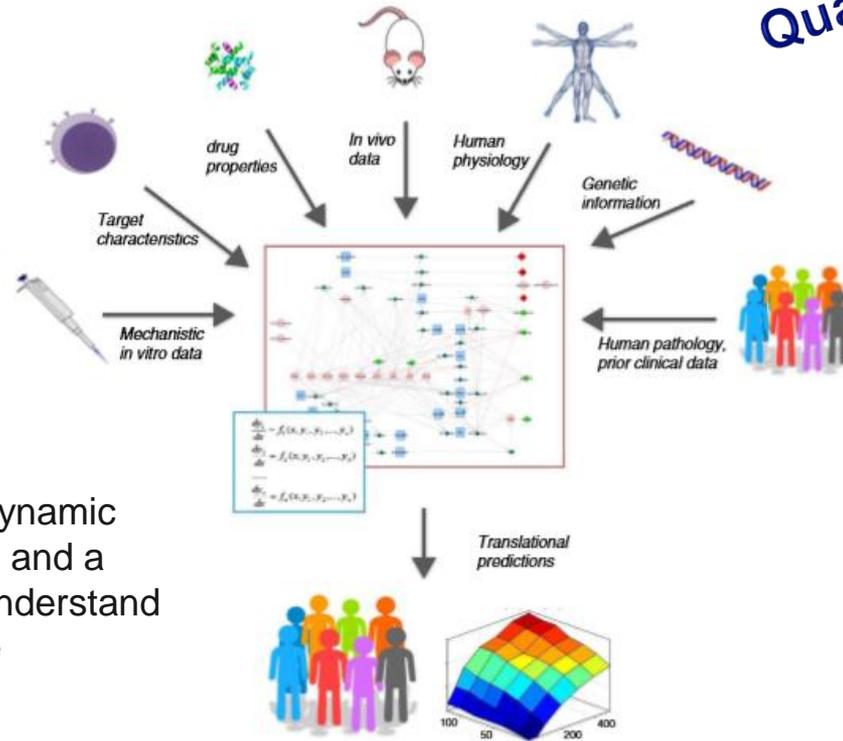
Enabling formulations
Food effect



PK/PD modelling

Integrative approach – PBPK and beyond

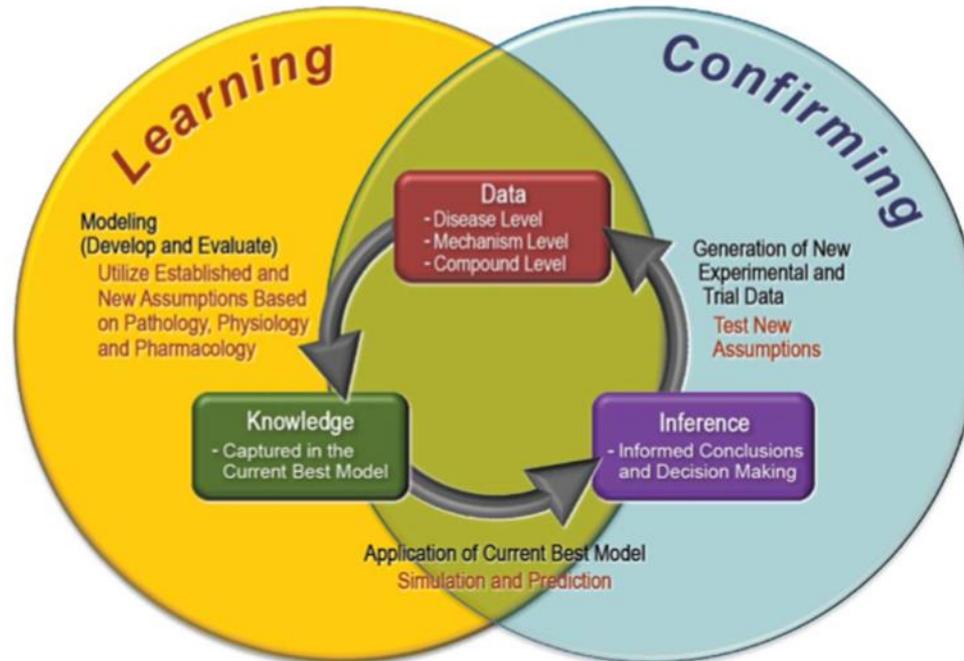
Quantitative System
Pharmacology



Quantitative analysis of the dynamic interactions between drug(s) and a biological system that aims to understand the system as a whole

Principles of modelling

Any model should evolved with time and knowledge



Principles of modelling

| Take home messages

- A model has to fit for purpose
- A model can be from descriptive to fully mechanistic
- Model building/use: learn and confirm

Everything should be made as simple as possible but no simpler – A. Einstein

All models are wrong, but some are useful – Georges E. P. Box

Thanks!