SOURCE DATA
Modellers perspectives

Session 2:

Structure, methods and decision criteria for extrapolation (planning) Mapping of the extrapolation with the common framework to clinicians, modelling and stats

Extrapolation workshop; 30/9-2015

Sources of data

In general; all data relevant for describing the interplay between the drug, organism and disease ("systems data")

Useful sources of data include

- Clinical data
  - Adult clinical data on drug in question
  - Paediatric clinical data on drug in question
  - Clinical data on same drug in other conditions
  - Clinical data from other similar drugs in same condition.
- Non clinical data
- In vitro data/ Physiochemical drug data
- Data on biology, physiology, pathophysiology etc

The sources needed will generally depend on the approaches taken

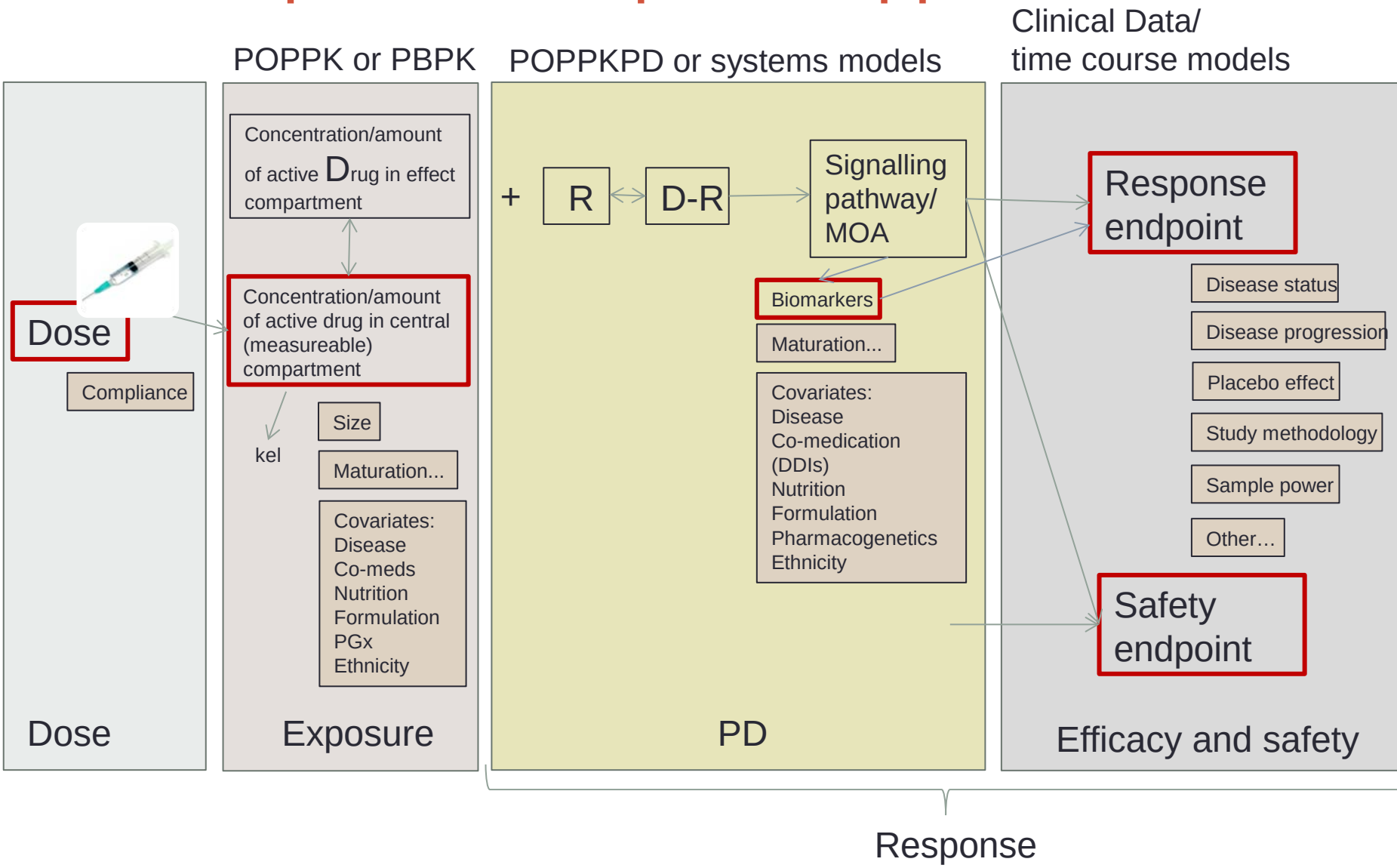
- Need to outline the potential sources per approach?
- Is there a need to set general requirements?

Inform transitions

Relevant levels of transition in paediatric developments:

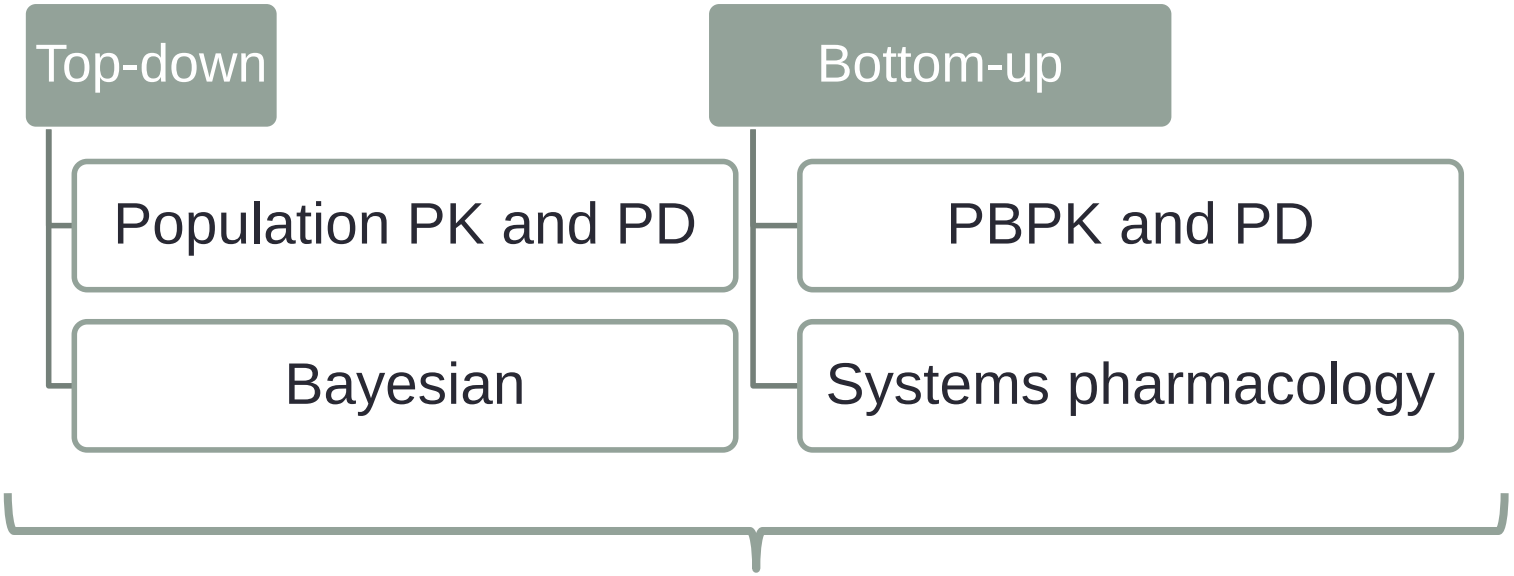
- Inform clinical study design or replace a study
- Source to target population
  - adult to children
  - between children of different age groups
  - *animal to human*
  - *physiochemical and in vitro to in vivo*
- Dose to Exposure
- Exposure to Response
  - exposure to PD endpoint/biomarker
  - PD endpoint/biomarker to clinical efficacy and safety endpoints

Dose Exposure Response approaches



Different data sources and confidence in the data.

Tool box for pharmacological M&S



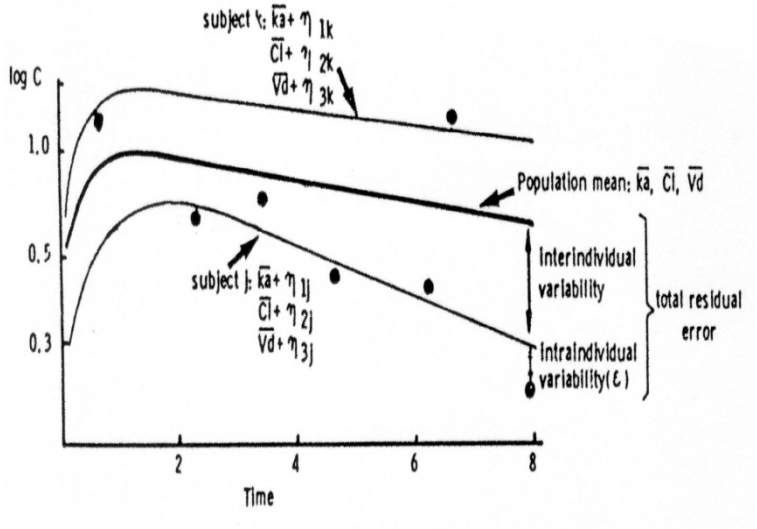
Combine methods to use all existing knowledge

Clinical trial simulations to optimize trial design

Population PKPD- Data sources

Primary data source:
Clinical data:
Pharmacokinetics
Pharmacodynamics
Covariate data

Supporting data:
Physiological data: on clearance, Vd and F to support PK model
Systems data/ in vitro data to support PKPD model
Factors linked to variability
Assumptions
Uncertainty



Possible determinants of Inter-subject variability:

- Age, Body Weight or Surface Area, gender, race
- *Genetic:* CYP2D6, CYP2C19
- Renal (Creatinine Clearance) or Hepatic impairment, Disease State
- *Concomitant Drugs*
- *Other Factors:* Diet, Circadian Variation, Formulations

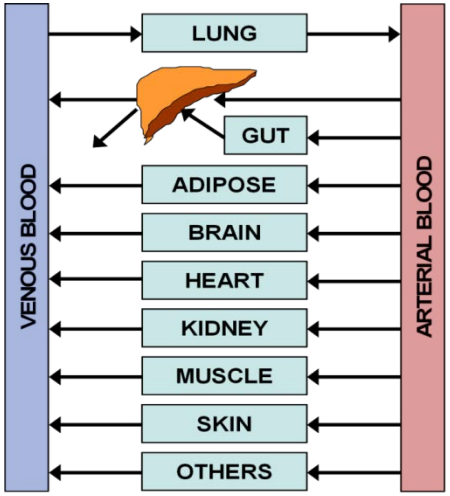
PBPK/System modelling

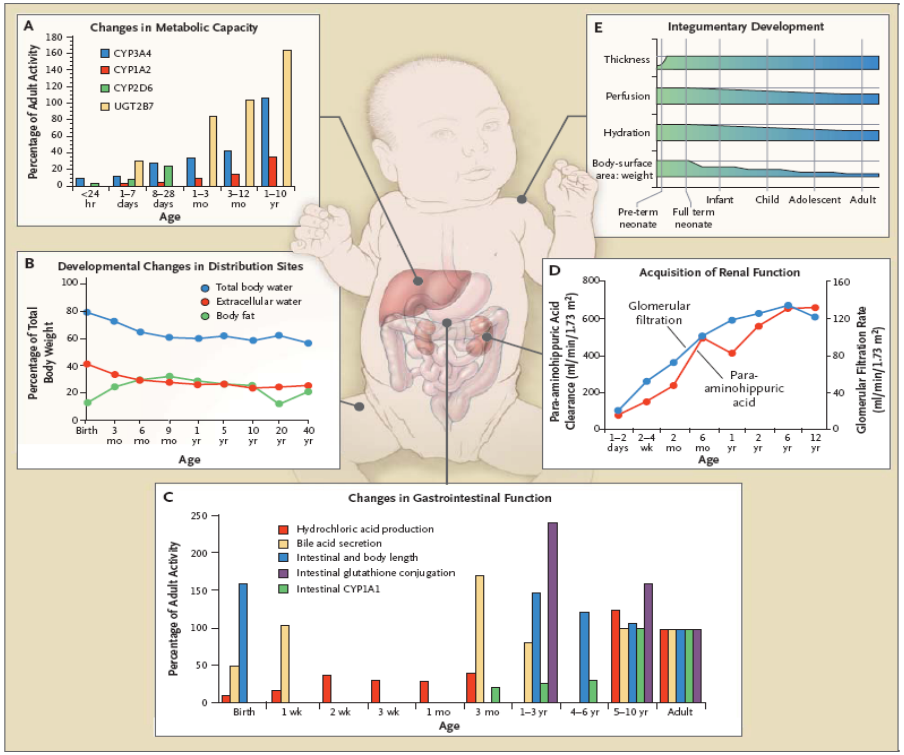
System model

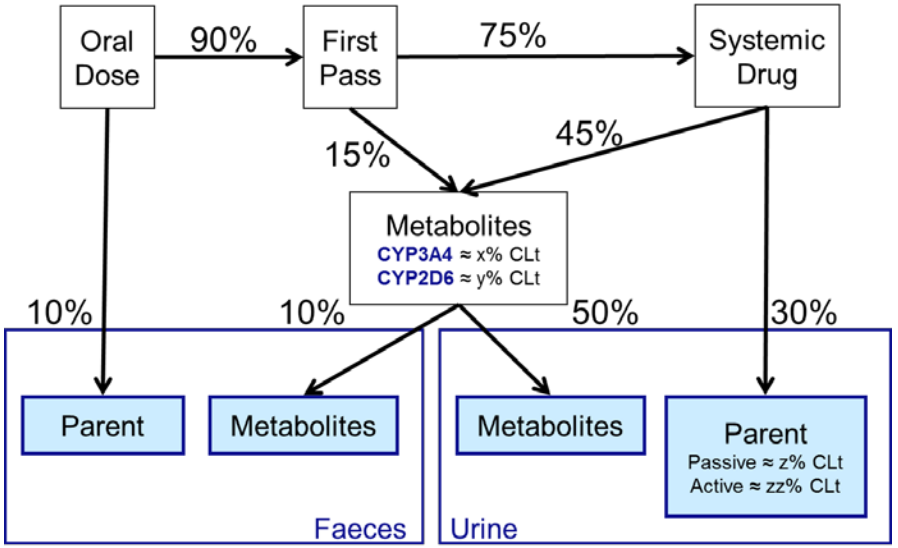
Anatomy
Biology
Physiology
Pathophysiology
Patient/disease extrinsic factors

Drug specific parameters

ADME, PK, PD and MOA
Metabolism
Active transport/Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding







Systems models - data sources

Physiological data

- Variety of sources
- Historical
- Data often lacking
- Populations in software reflect variability in physiology/ enzymology.

Drug dependent parameters

- Variety of sources
- Non standardised in vitro assays
- No incorporation of variability
- Complex pathways

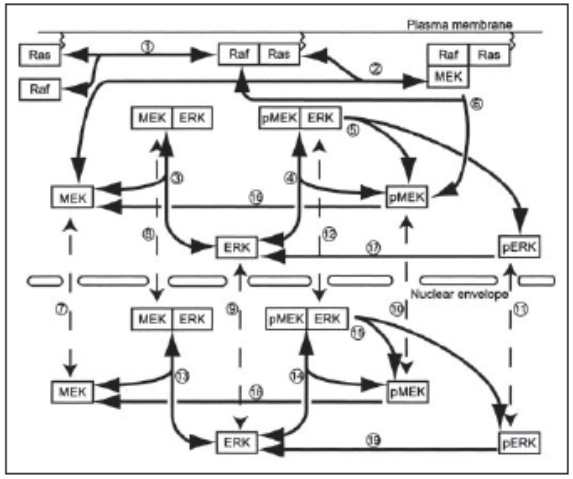


FIGURE 6. Minimum essential model of the Ras/ERK MAPK cascade. The cascade starts from Ras, which is arbitrarily set to reproduce the EGF-induced activation. The *arrows* represent the reactions specified in the supplemental material. *p*, phospho-.

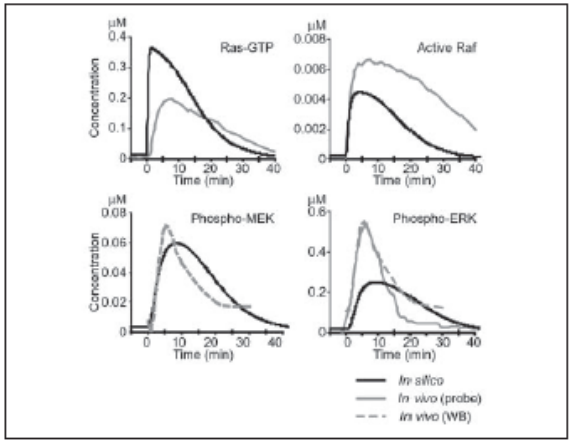
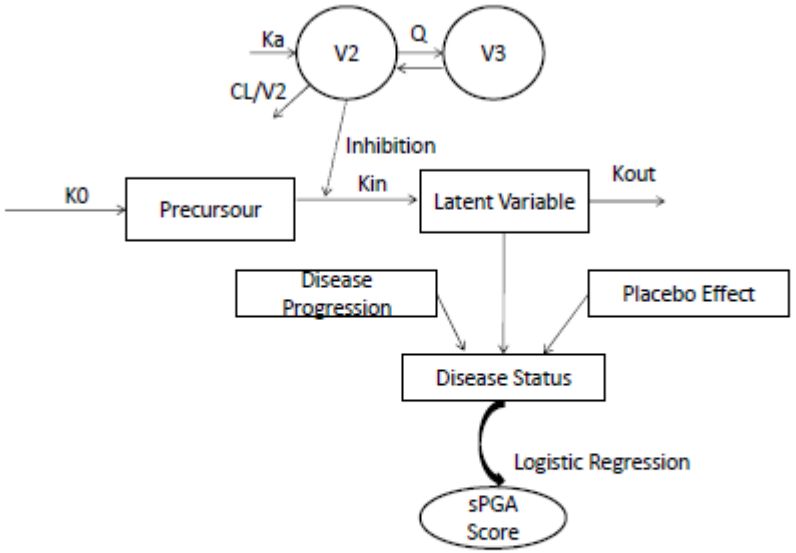


FIGURE 7. Kinetics of the components of the Ras/ERK MAPK cascade. The activation of Ras, Raf, and ERK was monitored *in vivo* by FRET imaging (probe) and/or Western blotting (WB). The kinetics of MEK and ERK activation were from Fig. 2.

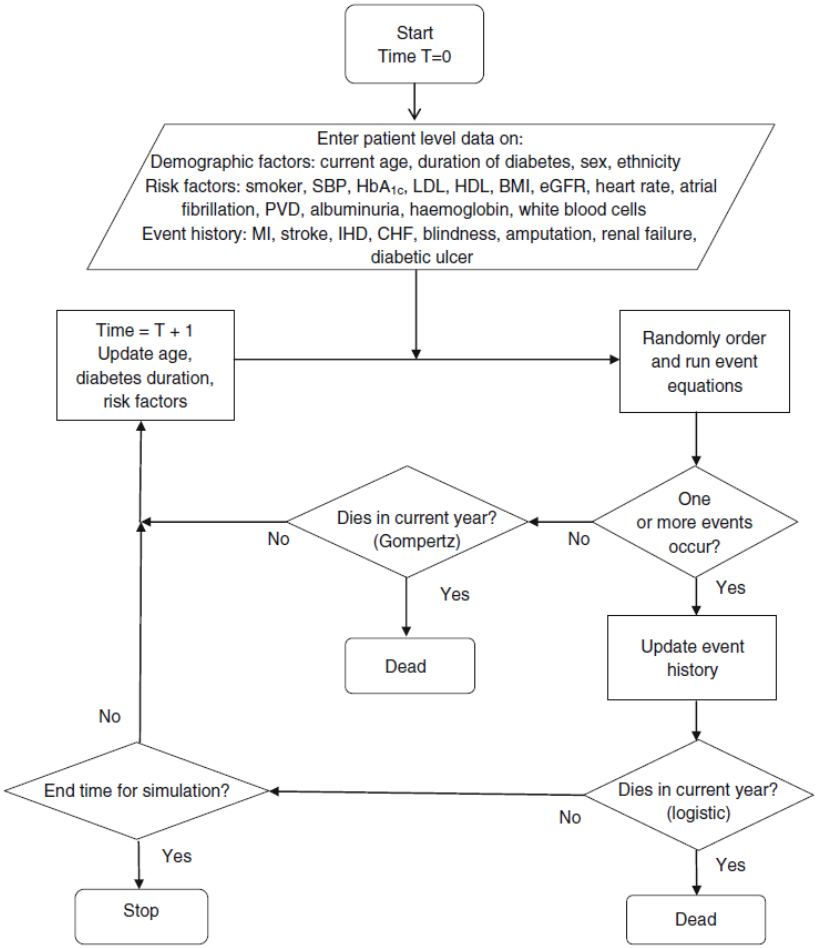
Property	In silico	In vitro	In vivo
Drug and dose form properties			
Log D	√	√	√
Acid or base	√	√	
pKa	√	√	
Solubility	√	√	√
Drug distribution parameters			
Plasma protein binding	√	√	
Blood/Plasma partitioning	√	√	
Microsome binding	√	√	
Permeability	√	√	√
Tissue Kp's	√	√	√
Pharmacokinetic parameters			
Volume of distribution	√	√	√
Plasma clearance	√	√	√
Clearance (renal)		√	√
Clearance (metabolic)		√	√
Clearance (active)		√	√
Oral bioavailability	√	√	√
Gut extraction	√	√	√
First pass hepatic extraction	√	√	√
Pharmacodyamics- Multiple pathways			
Vmax	√	√	√
Km	√	√	√
Time dependancy	√	√	√

Extended time course models



Abbreviations: CL = clearance; K0 = precursor rate in; Ka = absorption rate constant, Kin = latent-variable rate in; Kout = latent variable dissipation rate constant; V2 = central volume; V3 = peripheral volume; Q = inter-compartmental clearance.

Figure 8.23. **Schematic representation of the sPGA time course model.**



Limited longer term clinical data:

- 1358 patients at 12 weeks
- 270 patients at 60 weeks

Extensive clinical data

- 5102 patients
- 89,760 patient years of data

Conclusions

- The source of data depends on the transition being made and the approach being used.
- All data should be considered that describes the interplay between the drug, the subject and the disease.
- Requirement for transparency about the source of the data.
- Systems modelling is important for a thorough mechanistic understanding but uncertainty around many parameters.