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Statistics and Pharmacometrics Interest Group (SxP)

ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS

Importance of Pharmacometric Programming

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What is Pharmacometrics

Pharmacometrics is a branch of science concerned with **mathematical models** of **biology**, **pharmacology**, **disease**, and **physiology** used to **describe and quantify interactions between xenobiotics and patients**, including **beneficial effects and adverse effects** resultant from such interfaces*

Maclean JR, et al. *Ther Clin Risk Manag*. 2011

Exposure is more proximal to outcome than dose

* Barrett JS, et al., *Journal of Clinical Pharmacology*, 2008.

Types of Pharmacometric Models*

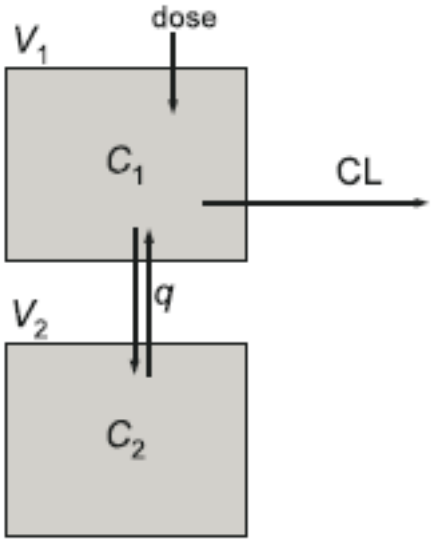
Type	Describes	Empirical	Mechanistic
Pharmacokinetic (PK)	Concentration-time profile of drug	Compartmental	Physiologically Based (PBPK)
Pharmacodynamic (PD) PK-PD Dose-Response Exposure-Response	Pharmacological response • PD biomarkers • Efficacy endpoints • Safety endpoints	• Direct • Indirect • Effect-Compartment • Time-to-Event • Markov • Model-Based Meta Analysis	Quantitative Systems Pharmacology (QSP)
Disease progression	Time-course of disease and response to intervention	• Symptom relief • Disease modifying	QSP

- *Pharmacometric models have pharmacological and statistical components*
- *Empirical Models: All parameters need to be estimated*
- *Mechanistic Models: Common system parameters values need not be estimated*

Examples of PK Models

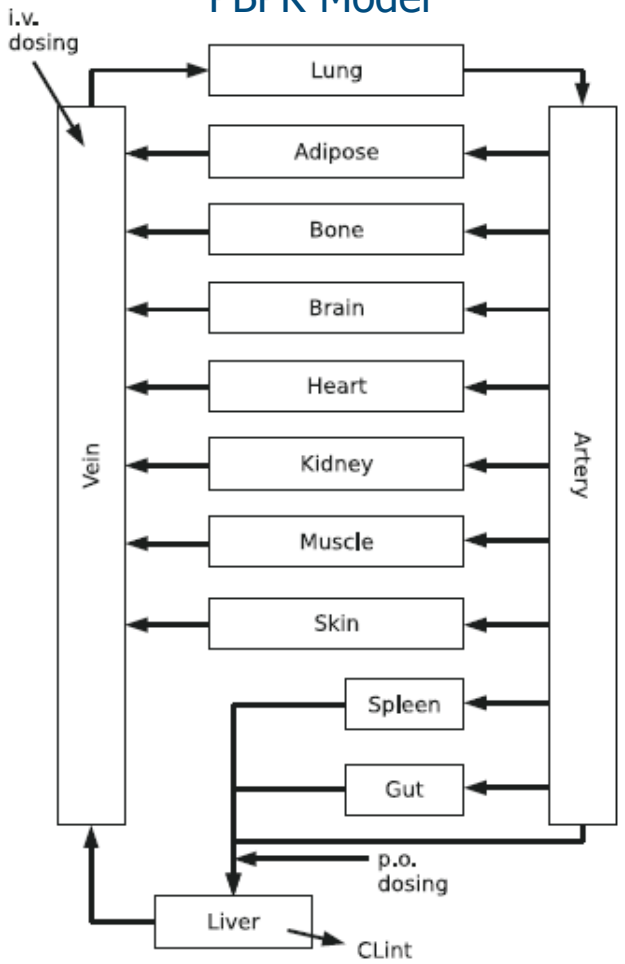
Empirical

2-Compartment Model (Intra-Venous Dose)



Mechanistic

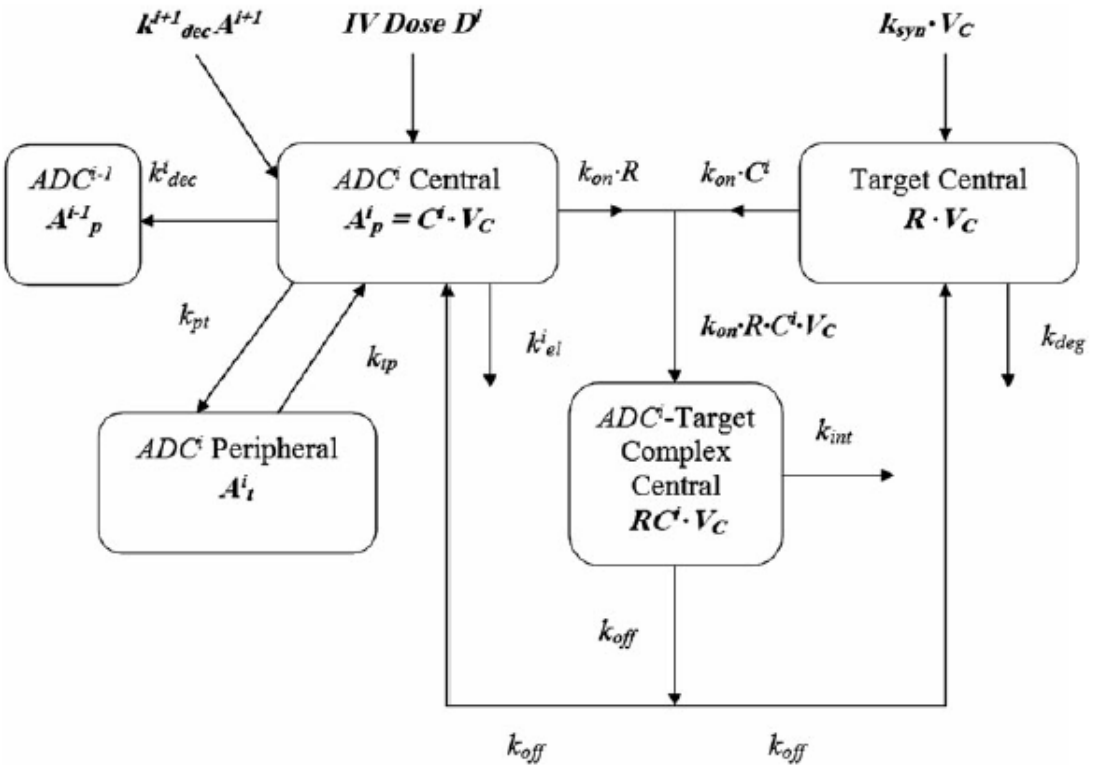
PBPK Model



Pilari S, and Huisinga W. *J Pharmacokinet Pharmacodyn*. 2010

Example of Semi-Mechanistic PK Model

Target-Mediated Drug Disposition (TMDD) Model for an Antibody-Drug Conjugate

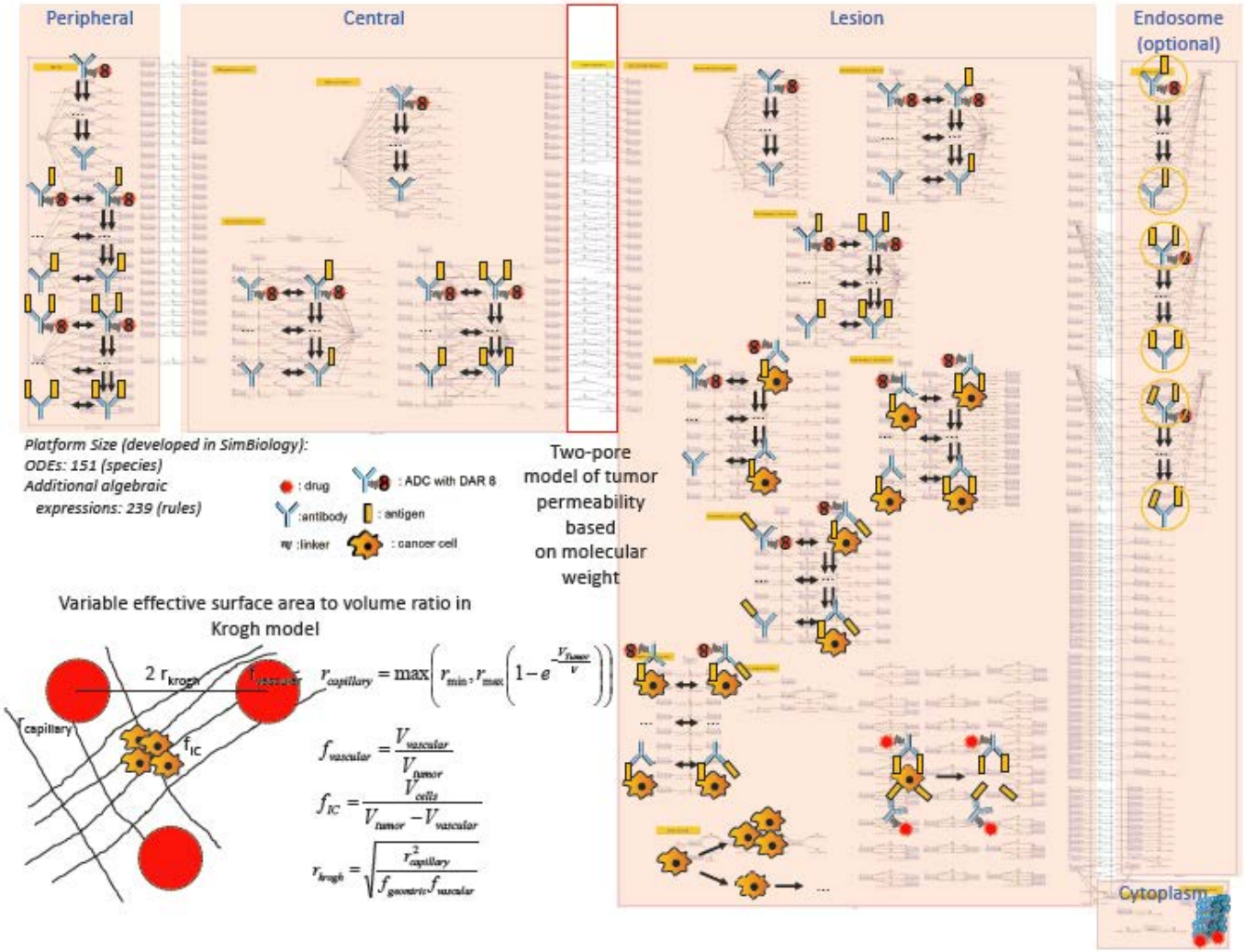


Interaction between drug and receptor requires simultaneous modeling of PK and PD

Gibiansky L, and Gibiansky E. *J Pharmacokinet Pharmacodyn*. 2014

Example of QSP Model

QSP Model for Antibody Drug Conjugates

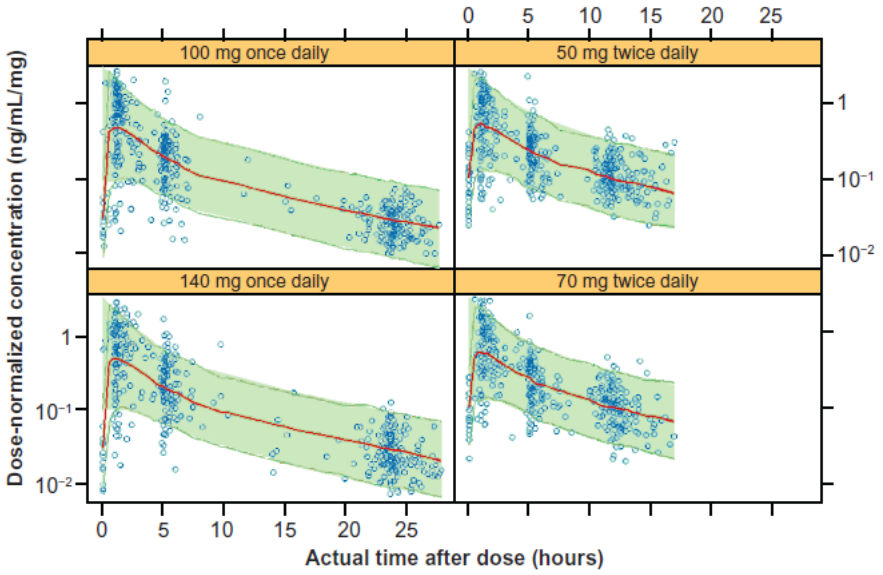


Cheng Y, et al. *AAPS J*. 2017

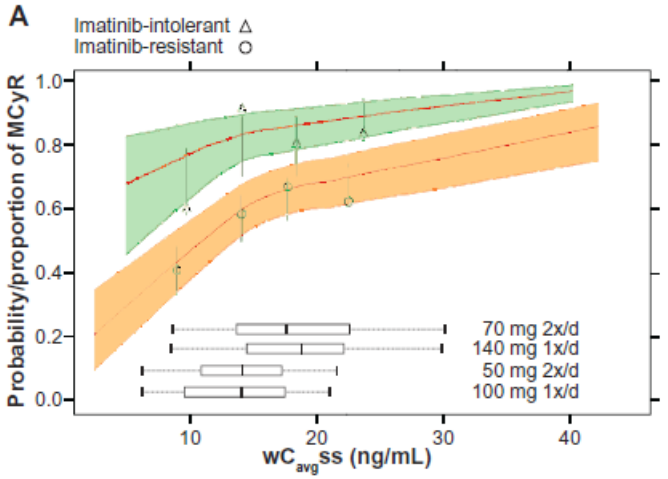
Example of Empirical Population PK and Exposure-Response Models

E-R: Efficacy

Dasatinib Plasma Concentration-Time Profile

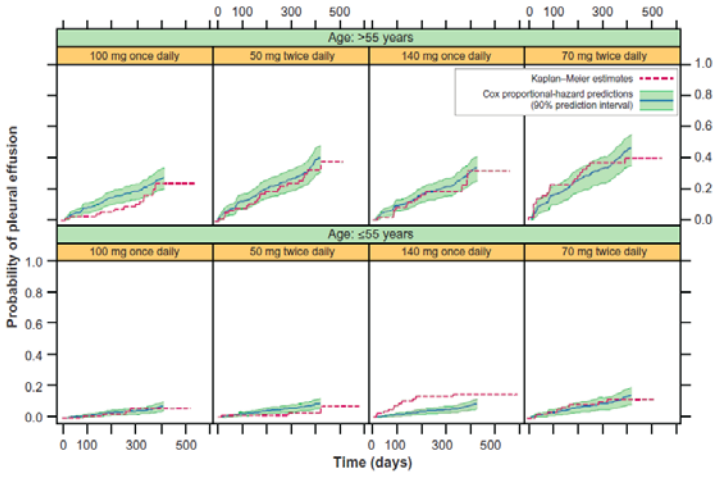


Pr(MCyR) vs Exposure



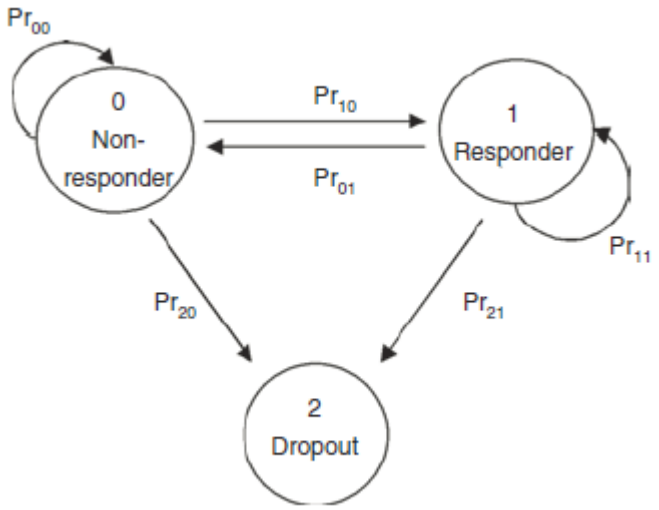
E-R: Safety

Cumulative Pr(Pleural Effusion), by Dose and Age

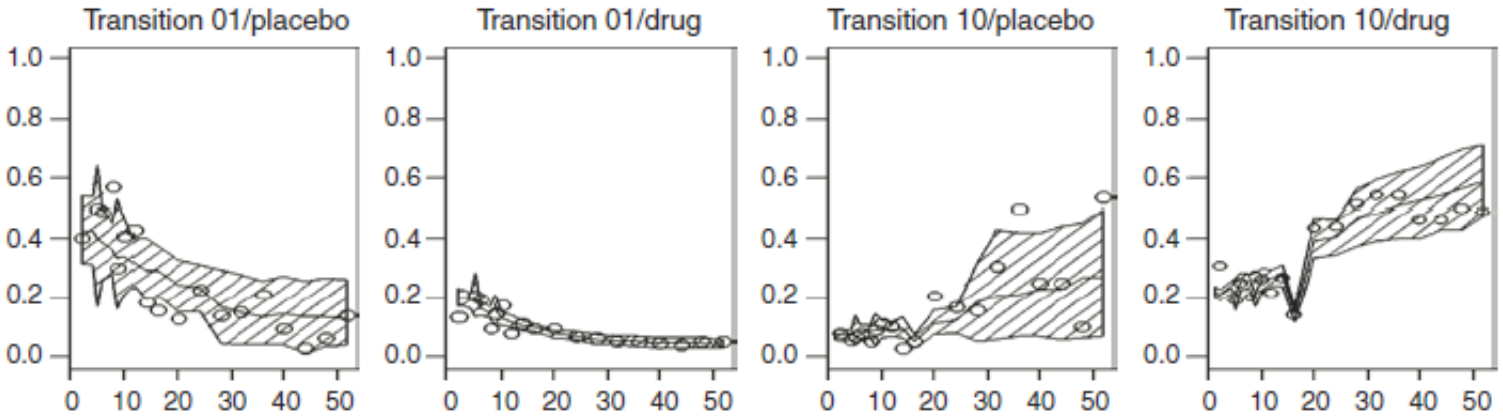


Wang X et al. *Clin Pharmacol Adv Appl.* 2013

Example of Markov Model



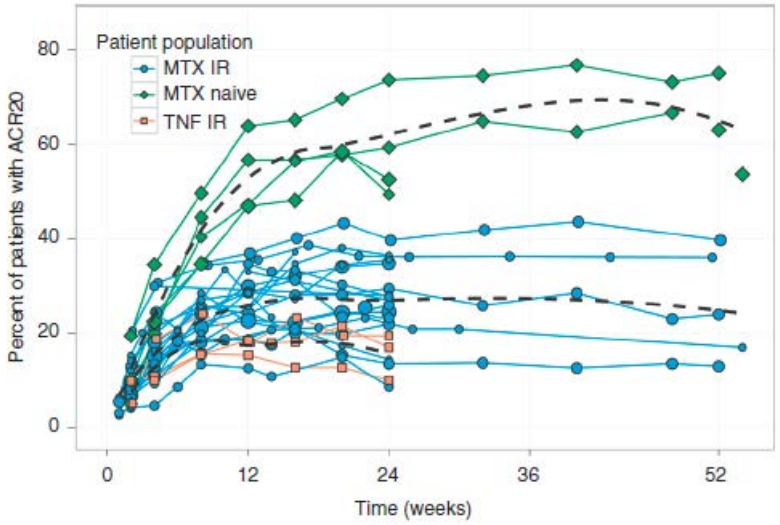
Effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis.



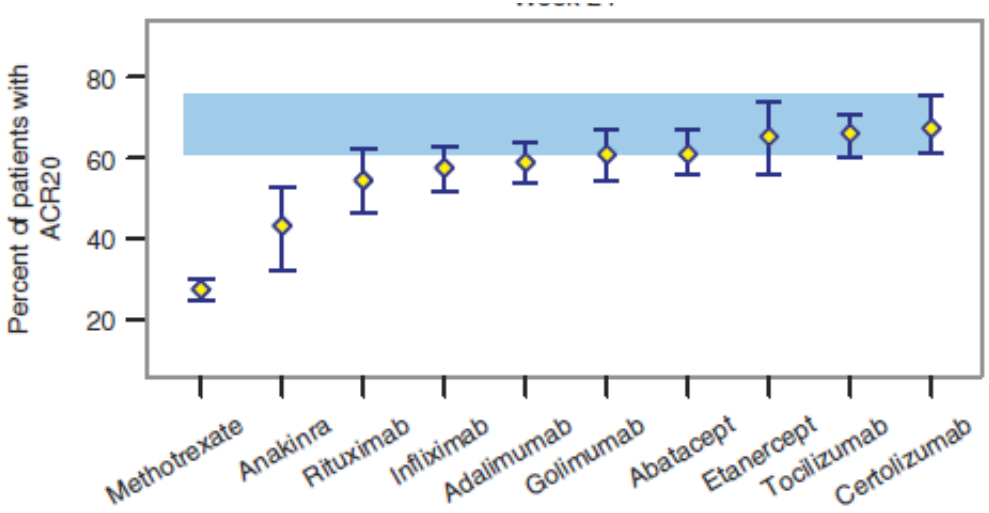
Lacroix BD, et al. *Clin Pharmacol Ther*. 2009

Example of Model-Based Meta-Analysis: Rheumatoid Arthritis

ACR20 vs Time, Patient Type



Pr(ACR20) at Week-24, by Drug



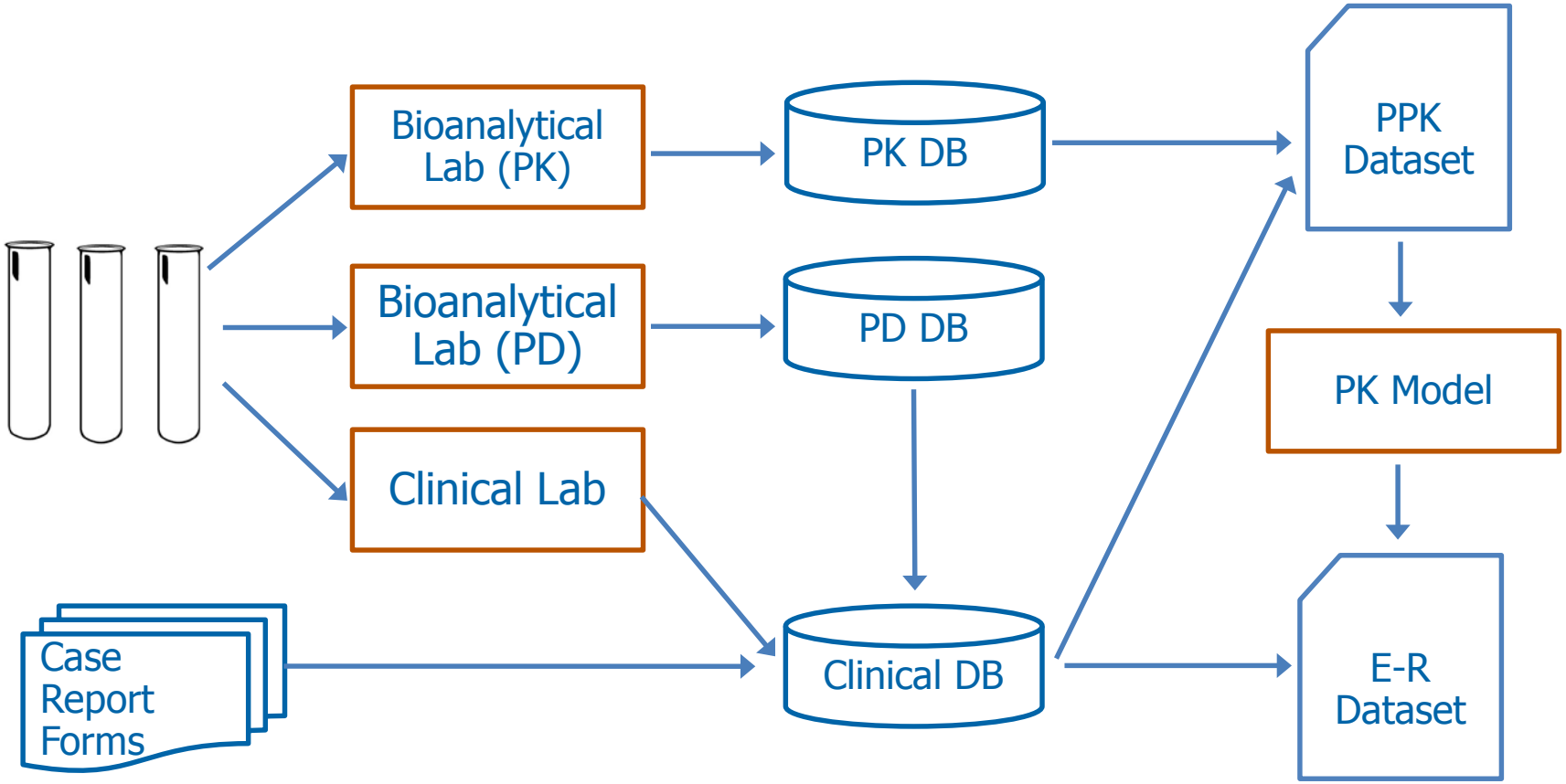
Demin I, et al. *Clin Pharmacol Ther.* 2012

Common Software

- **NONMEM***
- BUGS
- GastroPlus
- MATLAB (SimBiology Toolbox)
- MONOLIX
- Phoenix NLME
- R
- SAS
- SimCYP
- STAN

*NONlinear Mixed-Effects Model

Typical Data Flow



- *PK and clinical data are generally stored in different databases*
- *Estimated exposures are generally used in E-R analyses*

Challenges in PK Dataset Preparation

- There may be more than one dependent variable
  - Parent-metabolite PK models
  - Simultaneous PK-PD models (eg TMDD)
- Full dosing history is typically not available for drugs not administered in the clinic (generally orally or subcutaneously administered drugs)
  - Requires imputation of dose time and amount
  - Correct time of sample relative to dose is essential
- Time-varying covariates may not be available at all PK observation time-points (eg anti-drug antibodies)
  - Requires imputation or modeling of time-varying covariates
- Covariate values may have to be derived
  - Estimated GFR: derived from demographic, physical measurements, and clinical lab data
  - Concomitant medications grouped into classes

Challenges in E-R Dataset Preparation

- Exposure measures have to first be determined by a PK model (from sparse PK data samples)
  - Potentially several summary measures of exposure
  - May require entire conc-time curve
- Data requirements can vary widely, depending up the E-R model, even for models describing the same indication/purpose
  - Binary/ordered categorical
  - Single/Repeated measures
  - Multiple dependent variables
  - Mixed responses (categorical and continuous)

Summary

- Pharmacometrics encompasses a wide variety of models
- Data for which may come from multiple sources
  - Clinical and PK databases
  - Nonclinical and invitro experimental data
  - Literature data
- Analysis datasets
  - may have several dependent variables
  - often require imputation of missing or unavailable data

The pharmacometric model is only as good as the quality of data

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8. Demin I, Hamrén B, Luttringer O, Pillai G, Jung T. Longitudinal Model-Based Meta-Analysis in Rheumatoid Arthritis: An Application Toward Model-Based Drug Development. Clin Pharmacol Ther. 2012;92(3):352-359