Future development of PBPK science – opportunities and barriers

Iain Gardner PhD
Head of Translational DMPK Science
Certara-Simcyp
Future directions of PBPK Science

• Building confidence for expanded applications in predicting fate of drugs in special populations

• Coupling with detailed quantitative systems pharmacology models to assess impact of PK on pharmacological response

• Integrating with more detailed physical pharmacy models to assist with *in silico* formulation design and workflows
  - IVIVE-guided virtual bioequivalence

• Individualizing dosage regimens via patient avatars as part of personalized medicine initiative

• More robust analytical handling of observed data for reverse-translation
  - Bayesian fitting of models to data in combined PBPK-POP-PK framework

Pravin R. JadHAV, PhD, MPH1, Jack Cook, PhD2, Vikram SinHA, PhD3, Ping Zhao, PhD4, Amin Rostami-Hodjegan, PharmD, PhD5, Vaishali SahasrabudHE, PhD2, Norman Stockbridge, MD, PhD3, and J. Robert Powell, PharmD6

Figure 1. Conceptual distribution of data availability vs dose recommendation need for specific populations.

Abduljalil et al., ACoP, 2017
Dynamically Coupled PBPK-QSP/TS models

- Technology challenges to combine PBPK and systems biology approaches largely overcome
  - applications already being published

Kierzek et al, CPT:PSP, 2019
A Virtual Workbench for Formulation Design: IVIVE guided VBE

API: e.g. Posaconazole

Surfactant
Excipients
Buffers etc

Target Populations, Healthy vs Patients, between and within subject variability

In vitro experiments

Optimisation/
Virtual BE

Systemic Concentration (mg/L)

Time (h)
Virtual twin and just-in-time dispensing

One-size-fits-all dosing
Stratified dosing
Precision dosing

Stratification
- Patients are grouped by: Disease, Subtypes, Demographics, Clinical features, Biomarkers

Personalisation
- Patient individual: Preferences, Clinical features, Medication history, Environment, Behaviours & habits, Biomarker

Precision medicine/dosing

‘The virtual-twin’ in action
Individualised dose prediction. DDI screening with AI directed alternatives

PBPK + Liquid Biopsy
Barriers

• Further verification and qualification of models needed
  o Sometimes lack of quality data in public domain

• Scientific and technological advances still needed
  o Pharmaceutical workbench
  o Virtual twin
  o Transporter abundance and scaling and DDI prediction
    - Progress being made with PET data and *in vitro* modelling approaches

• Recognition of open science approach to PBPK platform development
  o Models/data should be published in peer reviewed journals
    - For complex models line by line code review is not practical

• Effort needed to collate and curate and analyze quality data for PBPK models is still under appreciated