Approaches for Obtaining Disposition Parameters for PBPK / PBBM

David Turner

FDA/M-CERSI in-person workshop “Physiologically Based Biopharmaceutics Modeling (PBBM) Best Scientific Practices to Drive Drug Product Quality: Latest Regulatory and Industry Perspectives”

Aug 29-31, 2023

Overview

(Volume of) Distribution for PBPK/PBBM

- Multiorgan PBPK distribution models require tissue Kps, blood flows etc.
- Minimal lumped PBPK distribution models

Clearance for PBPK/PBBM

- IVIVE
- Preclinical species Allometry OR IVIVE with scaling
- Human clearance available (CLiv or CLpo)
- First pass gut and liver metabolism (Bioavailability)

Summary

Vss from Mechanistic Tissue Distribution Models

Predict tissue Kps and thence Vss using tissue composition models

$$V_{ss} = V_p + V_e \times \mathrm{E{:}\,P} + \boxed{Kp,scalar} \sum V_t \times K_p$$

E.g., Rodgers and Rowland Model

Required API Data: BP, fu, logP, Compound Type and pKa(s)

Vss from Clinical Study Available

Kp,scalar *a)* empirical adjustment of model to reproduce "observed" Vss for an API.
b) Individual Kps can be adjusted too or instead

Vss from Pre-Clinical Studies Available Only

a) Animal models have been used to select the "best" mechanistic tissue composition model … and use it for human Kp prediction

b) A *Kp,scalar* can be estimated from animal studies and applied to humans

c) Preclinical studies may also signal specific organs to have elevated Kp

CERTARA

Before Clinical Studies Available: *Kp,scalar* from Species

18 Genentech small molecule compounds (Mao et al 2023 *Biopharm Drug Disp)*

Preclinical IV PK data available (mouse, rat, dog, cynomolgus monkey)

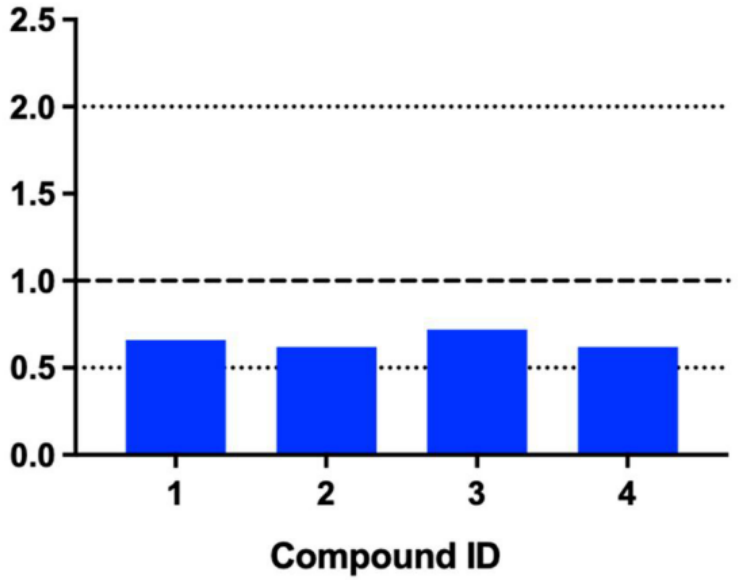
Underprediction of Vss in preclinical species using tissue composition models

– required <u>average</u> species *Kp,scalars* 1.7 – 2.7

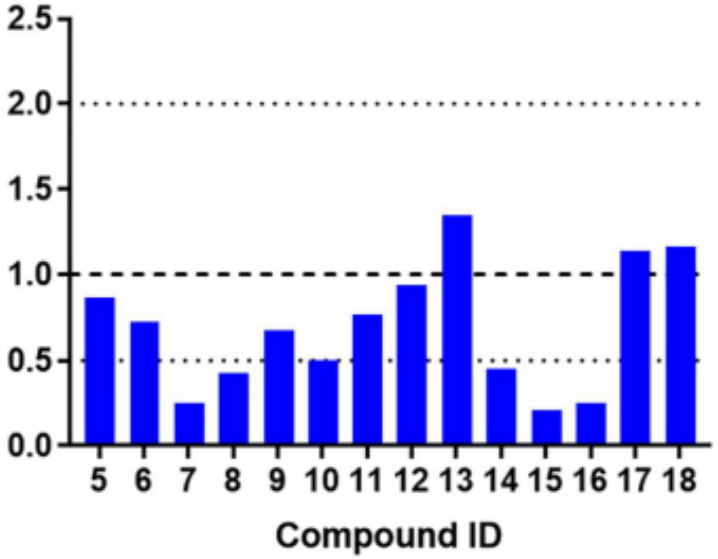
Drug-specific average species *Kp,scalars applied to human Vss prediction*

Pred/Obs Human Vss or V/F

Human Vss from <u>IV data</u>



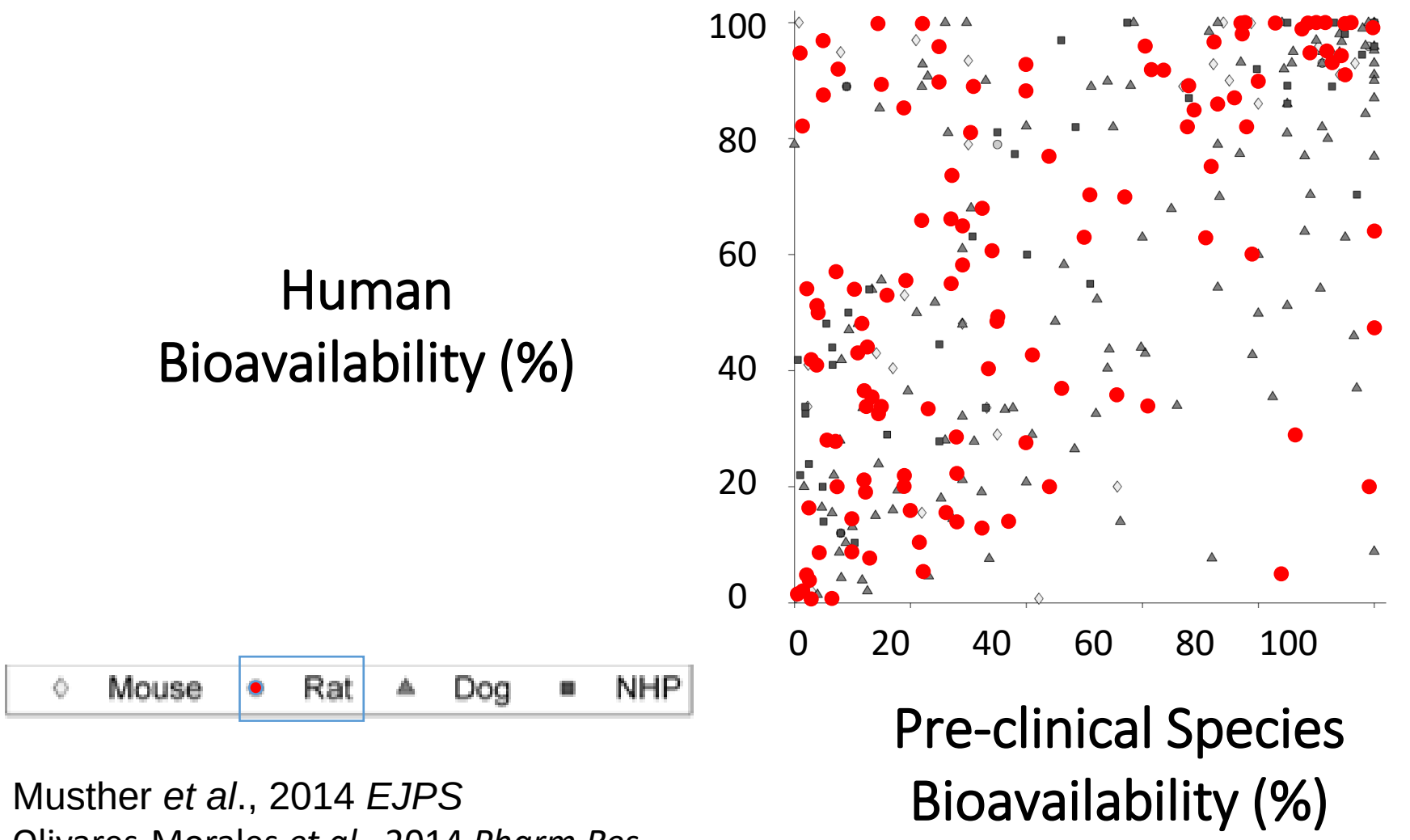
Human V/F Prediction (<u>Oral data</u>)



$F_{species}$ vs F_{human}?

CERTARA

Clearance: Preclinical Species vs Human Bioavailability



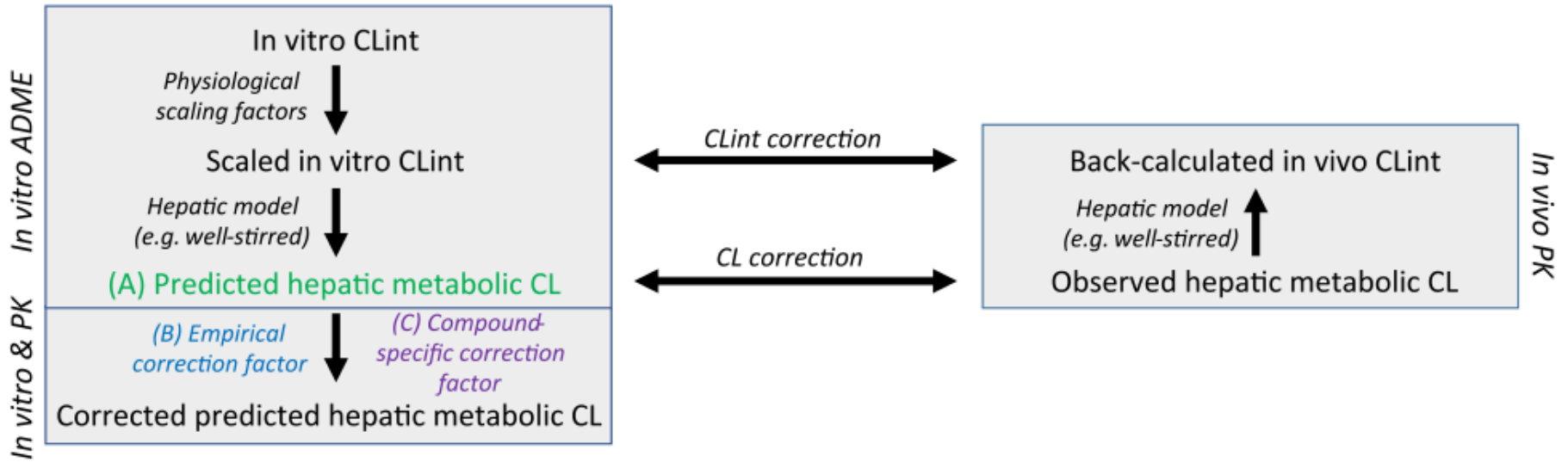
Musther *et al.*, 2014 *EJPS*
Olivares-Morales *et al.*, 2014 *Pharm Res*
Cao *et al.* 2006 *Pharm Res*

CERTARA

Clearance

Current Approaches for Predicting Human PK for Small Molecule Development Candidates: Findings from the IQ Human PK Prediction Working Group Survey

Petersson et al
2022 AAPS J



Defining in vitro – in vivo correlation (IVIVC) and extrapolation (IVIVE) for the prediction of in vivo clearance

IVIVE
1) Predict human hepatic metabolic CL directly from human in vitro data (A)
2) As (1) but incorporating an empirical correction factor (CL or CLint) based on IVIVE correction for clinical PK data from other compounds (B)

IVIVC
Define compound-specific correction factor based on preclinical IVIVE correction factors (CL or CLint). Incorporate this compound-specific correction factor when scaling from human in vitro CLint data (C)

Fig. 1 Defining IVIVC and IVIVE for predicting hepatic metabolic CL

CERTARA

Only human CLiv or CLpo only available? First pass effects?

CLiv Back-calculation of hepatic intrinsic clearance using Well Stirred Model

% CYP3A4 known?

Enables assignment of CYP3A4 CLint

→ ability to predict both gut and liver (1st pass) metabolism

CLpo Analogous back-calculation approach to CLiv

Assume Fg =1

fa needs to be known/assumed/predicted

CERTARA

Summary

Approach taken to handle disposition depends on data available and therefore stage of development

Vss can be reasonably well translated from preclinical studies or mechanistic methods informed by them (e.g., via Kp,scalar)

Clearance can sometimes be scaled from preclinical studies, but you don't know when it can't be (slide 5)

- IVIVE can be informed by scalars/additional clearance from animal studies

- First pass gut and liver metabolism
  - F_{human} does not correlate with $F_{species}$
  - Even where fa does correlate (rat vs human)

CERTARA