In Vitro In Vivo Extrapolation and its Applications in Predicting PK Population Variability

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Outline

• Clearance concept

• In Vitro In Vivo Extrapolation (IVIVE)

• Linking PBPK and IVIVE, accounting for variability

• Transporters

• Industry/Regulators views

• Future prospects
Well-stirred liver model

FACTORS AFFECTING DRUG METABOLISM


Commentary: A physiological approach to hepatic clearance
Wilkinson and Shand, CPT, 1975

\[ \text{CL} = Q \left[ f_{B,\text{Out}} \frac{\text{CL}_{\text{int}}}{f_{B,\text{Out}} \text{CL}_{\text{int}} + Q} \right] \]

Pang and Rowland, JPK Biopharm 1977

\( f_{B,\text{Out}} = \frac{\text{Unbound drug in venous blood}}{\text{Whole emergent blood concentration}} \)

- Unbound concentration of drug in blood cells equates to the unbound concentration in plasma.
- Emergent venous blood is in equilibrium with that in the liver.

Rowland, Benet and Graham, JPK Biopharm 1973
Yang et al., DMD, 2007
In Vitro - In Vivo Extrapolation (IVIVE)

Mechanistic Models

Scaling factors

\( \text{in vitro} \quad \text{CL}_{\text{int}} \)

\( \text{in vivo} \quad \text{CL}_{\text{int}} \)

**Scaling Factor**

\( \text{CL}_{\text{int}} \text{ per g Liver} \)

Liver weight

\( \text{CL}_{\text{int}} \text{ per Liver} \)

\( \text{CL}_{\text{int}} \text{ per Liver} \)
### Accuracy of IVIVE approaches for human CL or CLint

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<td>Ito, Pharm Res, 22, 103, 2005</td>
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<td>Jones, Clin Pk, 50, 311, 2011</td>
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<td>De Buck DMD, 35, 1766, 2007</td>
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<td>Stringer, Xeno, 38, 1313, 2008</td>
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<td>5</td>
<td>Hallifax 2011</td>
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<td>7.6</td>
<td>Naritomi DMD 31, 580, 2003</td>
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<td>Recombinant CYP</td>
<td>1.53 PT</td>
<td>Stringer DMD, 37, 1025, 2009</td>
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<tr>
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<td>2.15 WS</td>
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Generally many literature studies shows under-prediction from *in vitro* systems. Can be corrected using an empirical scaling factor. Need to understand for your *in vitro* system if this is necessary.
IVIVE predictions – Improvements over years

- Non-specific binding (Obach, DMD, 1999, Riley et al., DMD, 2005)
- Recombinant CYPs and ISEF values (Galetin et al., DMD, 2004; Proctor et al. Xenobiotica, 2004)
- In vitro modelling to account for hepatic uptake (Soars et al., DMD, 2007)
- Adding BSA and HAS-FAS to HLM (Rowland et al., DMD, 2008)
- Accounting for the difference in drug ionization in extracellular and intracellular tissue water (Berezhkovskiy, J Pharm Sci, 2011)
- Integrating uptake, metabolism, biliary excretion, and sinusoidal efflux (Umehara and Camenisch, Pharm Res, 2012)
- Incorporating ionisation and protein binding (Poulin et al., J Pharm Sci, 2012)
Gut wall metabolism

‘Q_{gut}', a minimal model

$$F_g = \frac{\'Q_{gut}' }{\'Q_{gut}' + f_{vu_{gut}} \cdot CL_{u_{int-gut}}}$$

$$\'Q_{gut}' = \frac{CL_{perm} \cdot Q_{villi}}{CL_{perm} + Q_{villi}}$$

Yang et al., CDM, 2007

Observed $F_g$ vs. Predicted $F_g$

Gertz et al., DMD, 2010

Observed $F_g$ vs. Predicted $F_g$
Special populations

**Systems Data**
- Age
- Weight
- Tissue Volumes
- Tissue Composition
- Cardiac Output
- Tissue Blood Flows
  - [Plasma Protein]

**Drug Data**
- MW
- LogP
- pKa
- Protein binding
- BP ratio
- In vitro Metabolism
- Permeability
- Solubility

**Trial Design**
- Dose
- Administration route
- Frequency
- Co-administered drugs
- Populations

**Mechanistic IVIVE linked PBPK models**

**Prediction of drug PK (PD) in population of interest**

Jamei et al., DMPK, 2009, Rostami-Hodjegan, CPT, 2012

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Demographic Features of Healthy and Disease Populations

Randomly Generated

Frequency

Defined by real data

HV

Disease

Age
Age Distribution in Target Population

Addicts

MALE
FEMALE

CVD

Frequency

Age Category

CERTARA

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The Complexity of Covariate Effects as Applied to CL

Plasma Proteins & Haematocrit

Ethnicity

Disease

Age
(Distribution in Population)

Body Surface Area

Liver Volume

Cardiac Output

Height

Weight

Cardiac Index

Liver Weight

Intrinsic Clearance

Cardiac Output

Liver Weight

Intrinsic Clearance

Body Surface Area

Liver Volume

Cardiac Output

Height

Weight

Cardiac Index

Liver Weight

Intrinsic Clearance

Body Surface Area

Liver Volume

Cardiac Output

Height

Weight

Cardiac Index

Liver Weight

Intrinsic Clearance

Cardiac Index

Liver Weight

Intrinsic Clearance

Cardiac Index

Liver Weight

Intrinsic Clearance

Cardiac Index

Liver Weight

Intrinsic Clearance
Converting $\text{CL}_{\text{int}}$ to $\text{CL}_H$

$\text{MPPGL} = 10$

$\text{CL}_{\text{int}} = \text{CL}_{\text{int}} \cdot \text{MPPGL} \cdot \text{Liver Weight}$

(whole liver)

$\text{Liver Weight} = \text{Liver Volume} \times \text{Liver Density}$

$\text{Liver Volume} = 0.722 \cdot \text{BSA}^{1.176} \text{ (L/m}^2\text{)}$

$0.00718 \times \text{Ht} \times 0.725 \times \text{Wt} \times 0.425$

$\text{f(age)} + x$

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Converting $\text{CL}_{u\text{int}}$ to $\text{CL}_H$

\[
\text{CL}_{u\text{int}} = \text{CL}_{u\text{int}} \times \text{MPPGL} \times \text{Liver Weight}
\]

\[
\text{CL}_H = \frac{Q_H \times \text{fu}_B \times \text{CL}_{u\text{int}}}{Q_H + \text{fu}_B \times \text{CL}_{u\text{int}}}
\]

\[
\text{fu}_B = \frac{\text{fu}}{C_B/C_P}
\]

\[
Q_H = \% \text{CO}
\]

\[
\text{CO} = f(\text{age, BSA})
\]

\[
C_B/C_P = (E:P) \times \text{HC} + (1 - \text{HC})
\]

\[
\text{HC} = f(\text{age}) + f(\text{sex})
\]

\[
0.00718 \times \text{Ht}^{0.725} \times \text{Wt}^{0.425}
\]

\[
f(\text{age}) + \text{x}
\]
Revised *in vivo* ontogeny functions for CYP1A2 and 3A4

(Leong *et al*., CPT 2012; 91: 926-931)
UGT Ontogeny

Leiden Collaboration – Top down vs bottom up ontogeny for UGT2B7
- Morphine
- Zidovudine

Strassburg et al 2002
Burchell et al 1989
Onishi et al 1997
Leakey et al 1987
Coughtrie et al 1988
Miyagi and Collier 2007
Zaya et al 2006
Pacifici et al 1990
Pacifici et al 1982
Choonara et al 1989
UGT2B7 ontogeny ‘Top down’ vs ‘Bottom up’

- Take home message is that pattern of ontogeny appears to be reasonable except for early neonates
- But under-prediction of CL across age band with morphine.
Maturation of Biliary Clearance Appears to be Rapid

Azithromycin

Ceftriaxone

Digoxin

Buprenorphine

Johnson et al Drug Metab Dispos. 2016
Variation in Protein Binding (fu)

\[ \text{Alb} = 1.1287 \ln(\text{Age}) + 33.746 \]

\[ \text{AAG}_{g/L} = \frac{0.887 \times \text{Age}_D^{0.38}}{8.89^{0.38} + \text{Age}_D^{0.33}} \]

\[ \text{fu} = \frac{1}{1 + \frac{[P]}{K_D}} \]

\[ K_D = \text{Dissociation Constant} \]

\[ [P] = \text{Serum Protein Concentration} \]

In absence of changes in dynamics of binding:

\[ \text{fu} = \frac{1}{1 + \left[ \frac{[P]}{[P]_{pop^*}} \times \frac{1 - \text{fu}_{pop^*}}{\text{fu}_{pop^*}} \right]} \]

*pop is the population under investigation i.e. paediatric
Developing and testing a Geriatric population

**In house testing**

- Obs
- Pred

**Height (males 66 to 96 y)**

\[ y = 0.0012x^2 - 0.4357x + 196.38 \]

\[ R^2 = 0.0475 \]

**Liver weight (Male)**

\[ y = 478573x^{-1.346} \]

**Kidney weight (Female)**

\[ y = 6566.4x^{-0.752} \]

\[ R^2 = 1 \]

**Parkinson et al 2004**

**CYPs**

Fig. 4. Effects of age on CYP activity in human liver microsomes. No statistically significant differences were determined by linear regression analysis with the exceptions of CYP2A6, \( P = 0.08 \); CYP2D6, \( P = 0.005 \); and CYP2E1, \( P = 0.006 \).
Scaling from in vitro: drug data vs systems data

Liver

**In vitro data**

\[ \frac{J_{\text{max}}}{K_m} \text{ or } C_{\text{Lu}_{\text{int}, T}} \]

\[ \text{HHEP} \rightarrow \text{HPLG} \rightarrow \text{CL}_{\text{Lu}_{\text{int}, T}} \text{ per g Liver} \]

\[ \text{Liver Weight} \]

**SF 1:** REF/RAF_{HHEP}

**SF 2:** HPGL

**SF 3:** Liver Weight

Kidney

**In vitro data**

\[ \frac{J_{\text{max}}}{K_m} \text{ or } C_{\text{Lu}_{\text{int}, T}} \]

\[ \text{PTC} \rightarrow \text{CL}_{\text{Lu}_{\text{int}, T}} \text{ per g Kidney} \]

\[ \text{Kidney Weight} \]

**SF 1:** REF/RAF_{PTC}

**SF 2:** PTCPKG

**SF 3:** Kidney Weight

Brain

**In vitro data**

\[ \frac{J_{\text{max}}}{K_m} \text{ or } C_{\text{Lu}_{\text{int}, T}} \]

\[ \text{H-BMv} \rightarrow \text{CL}_{\text{Lu}_{\text{int}, T}} \text{ per g Brain} \]

\[ \text{Brain Weight} \]

**SF 1:** REF/RAF_{H-BMv}

**SF 2:** H-BMVpGB

**SF 3:** Brain Weight

Intestine

**In vitro data**

\[ \frac{J_{\text{max}}}{K_m} \text{ or } C_{\text{Lu}_{\text{int}, T}} \]

\[ \text{Caco-2, MDCK- II, LLC-PK\textsubscript{1} etc.} \rightarrow \text{CL}_{\text{Lu}_{\text{int}, T}} \text{ per Liver} @ \text{BBB} \]

**SF 1:** REF/RAF_{Caco-2, MDCK- II, LLC-PK\textsubscript{1} etc.}

**SF 2:** Liver Weight

**SF 3:** Liver Weight

Replacement / Additional Organ

\[ \frac{J_{\text{max}}}{K_m} \text{ or } C_{\text{Lu}_{\text{int}, T}} \]

**CL_{\text{Lu}_{\text{int}, T}}**

**SF 1:** REF/RAF_{Replacement / Additional Organ}

**SF 2:** Jejunum I

**SF 3:** Jejunum I

User needs to scale to whole organ!

SF: Scaling Factor
Translating *in vitro* effective concentrations to concentrations at the site of action

- Mechanistic, multi-compartmental tissue models (brain, kidney, liver, lung and intestine) are available
- Enable more reliable estimates of intracellular tissue concentrations
Modelling *in vitro* assays – a must to do!

### 2 Compartment Model

**Incubation Medium Volume**

- **Free** $[S]_{EC}$

**Intracellular Volume**

- $[S]_{IC}$
- $f_{u_{cell}}$

**Active Uptake**

\[
\frac{CL_{int} \cdot K_m \cdot [S]_{EC(t)}}{K_m + [S]_{EC(t)}}
\]

- $CL_{PD} \cdot [S]_{EC(t)}$

- $CL_{PD} \cdot [S]_{IC(t)}$

Baker et al., Xenobiotica, 2007; Soars et al., Mol Phar, 2009; Poirier et al., Mol Pharm, 2009; Menochet et al., J Pharm Exp Ther, 2012

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### 5 Compartment Model - Transwell

Heikkinen et al., 2010 Mol Pharmaceutics

Korzekwa et al., 2012 DMD

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<td>Xarelto (Rivaroxaban)</td>
<td>Thrombosis &amp; Embolism</td>
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<tr>
<td>Edurant (Rilpivirine)</td>
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<td>Imbruvia (Ibrutinib)</td>
<td>Lymphoma and Leukemia</td>
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<td>Opsumit (Macitentan)</td>
<td>Pulmonary Hypertension</td>
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<td>Zykadia (Ceritinib)</td>
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<td>Odozmzo (Sonidegib)</td>
<td>Basal Cell Carcinoma</td>
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<tr>
<td>Farydak (Panobinostat)</td>
<td>Multiple myeloma</td>
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<td>Revatio (Sildenafil)</td>
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<td>Lynparza (Olaparib)</td>
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<td>Opioid Induced Constipation</td>
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<td>Lenvima (Lenvatinib)</td>
<td>Thyroid cancer</td>
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<td>Aristada (Aripiprazolel)</td>
<td>Schizophrenia</td>
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Quantitative IVIVE of Tissue Toxicity Supported by European Commission 7th FP Predict-IV Grant

Figure 1: Components of the four integrative modeling steps followed in Predict-IV.

Hamon et al., Toxicology in Vitro, 2015
Summary

- In a systems pharmacology paradigm, the bottom-up approach to modeling and simulation of the ADME processes of a chemical, is a valuable tool in integrating available prior information and improving decision making.

- Improvement in the in vitro systems which can act as surrogates for in vivo reactions relevant to ADME

- Advances in the understanding of the extrapolation factors

- Advances in the development of mechanistic models of the human body

- Facilitate predicting PK characteristics in a wide range of healthy or disease populations accounting for age, sex, ethnicity, genetic, etc variability

- Moving towards PBPK coupling with systems biology models to predict toxicity endpoints/biomarkers and their associated variability from in vitro data