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

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

Pang and Rowland, JPK Biopharm 1977

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

- 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 Factors**

(MPGGL, HPGL)

Liver weight

Liver

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

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

<table>
<thead>
<tr>
<th>System</th>
<th>AFE</th>
<th>Ref</th>
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<td>2.3</td>
<td>Obach DMD 27, 1350, 1999</td>
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<td>6.2</td>
<td>Ito, Pharm Res, 22, 103, 2005</td>
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<td>Stringer, Xeno, 38, 1313, 2008</td>
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<td>Ring, J Pharm Sci, 100, 490, 2011</td>
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<td>Hallifax, Pharm Res, 27, 2150, 2010</td>
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<td>Jones, Clin Pk, 50, 311, 2011</td>
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<td>Heps</td>
<td>2.4</td>
<td>De Buck DMD, 35, 1766, 2007</td>
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<td></td>
<td>5.2</td>
<td>Stringer, Xeno, 38, 1313, 2008</td>
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<tr>
<td></td>
<td>5</td>
<td>Hallifax 2011</td>
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<td></td>
<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>
</tr>
<tr>
<td></td>
<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)
"Q\textsubscript{gut}', a minimal model

\[ F_g = \frac{'Q\textsubscript{gut}' \cdot \text{fu\textsubscript{gut}} \cdot CL\textsubscript{int-gut}}{'Q\textsubscript{gut}'} \]

\[ 'Q\textsubscript{gut}' = \frac{CL\textsubscript{perm} \cdot Q\textsubscript{villi}}{CL\textsubscript{perm} + Q\textsubscript{villi}} \]

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**Yang et al., CDM, 2007**

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**Gertz et al., DMD, 2010**
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
Demographic Features of Healthy and Disease Populations

Randomly Generated

Frequency

Defined by real data

Age

HV

Disease
Age Distribution in Target Population

Addicts

- MALE
- FEMALE

CVD

Frequency

Age Category

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The Complexity of Covariate Effects as Applied to CL

- Plasma Proteins & Haematocrit
- Ethnicity
- Disease
- Age (Distribution in Population)
- Serum Creatinine
- MPPGL
- HPGL
- Renal Function
- Body Surface Area
- Height
- Weight
- Liver Volume
- Cardiac Output
- 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)

Liver Weight = Liver Volume $\times$ Liver Density

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

$0.00718 \times \text{Ht}^{0.725} \times \text{Wt}^{0.425} f(\text{age})^x$
Converting $CL_{u\text{int}}$ to $CL_H$

$CL_{u\text{int}} = CL_{u\text{int}} \times MPPGL \times \text{Liver Weight}$

$CL_H = \frac{Q_H \times fu_B \times CL_{u\text{int}}}{Q_H + fu_B \times CL_{u\text{int}}}$

$fu_B = \frac{fu}{C_B/C_p}$

$Q_H = \% CO$

$CO = f(age, BSA)$

$C_B/C_p = (E:P) \times HC + (1 - HC)$

$HC = f(age) + f(sex)$

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

$f(age) + x$
Revised *in vivo* ontogeny functions for CYP1A2 and 3A4

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

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**CYP1A2 ontogeny**

- Theophylline i.v.
- Relative expression vs. Age (y)

**CYP3A4 ontogeny**

- Midazolam i.v.
- Relative expression vs. Age (y)

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

Johnson et al 2006

y = 87.674x - 14.497
R^2 = 0.9988

921 subjects

BSA (m^2)

GFR (ml/min)

Johnson et al 2006

923 subjects

923 subjects

De Cock et al 2014

Rubin et al 1949

Hayton 2000

1760 subjects

63 subjects

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Maturation of Biliary Clearance Appears to be Rapid

Azithromycin

Ceftriaxone

Digoxin

Buprenorphine

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

**Equation:**

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

**Equation:**

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

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

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

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

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

In absence of changes in dynamics of binding:

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

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

![Graph showing in-house testing results.]

\[ y = 0.0012x^2 - 0.4357x + 196.38 \]
\[ R^2 = 0.0475 \]

![Graph showing height variation with age.]

\[ y = 478573x - 1.346 \]

![Graph showing liver weight variation with age.]

\[ y = 6566.4x^{0.752} \]
\[ R^3 = 1 \]

![Graph showing kidney weight variation with age.]

Parkinson et al. 2014

Clinical
Simulated
Power (Simulation)

Fig. 4. Effects of age on CYP activity in human liver microsomes. No statistically significant differences were determined by linear regression analysis with the exception of CYP3A2, \( P = 0.012 \), CYP2D6, \( P = 0.041 \), and CYP2E1, \( P = 0.006 \).
Scaling from in vitro: drug data vs systems data

**Liver**

*In vitro data*

\[ J_{\text{max}}/K_m \text{ or } CLu_{\text{int, T}} \]

\[ \text{HHEP} \]

\[ \text{CLu}_{\text{int, T}} \text{ per g Liver} \]

\[ \text{CLu}_{\text{int, T}} \text{ per Liver} \]

**SF 1:**

REF/RAF\textsubscript{HHEP}

**SF 2:**

HPGL

**SF 3:**

Liver Weight

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**Intestine**

*In vitro data*

\[ J_{\text{max}}/K_m \text{ or } CLu_{\text{int, T}} \]

\[ \text{Caco-2, MDCK-II, LLC-PK1 etc.} \]

\[ \text{CLu}_{\text{int, T}} \text{ per Liver} \]

**SF 1:**

REF/RAF\textsubscript{Jejunum I}

**Scaling via the Permeability and Surface area product**

**Replacement / Additional Organ**

\[ J_{\text{max}}/K_m \text{ or } CLu_{\text{int, T}} \]

\[ \text{CLu}_{\text{T}} \text{ per whole organ} \]

User needs to scale to whole organ!

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**Brain**

*In vitro data*

\[ J_{\text{max}}/K_m \text{ or } CLu_{\text{int, T}} \]

\[ \text{H-BMv} \]

\[ \text{CLu}_{\text{int, T}} \text{ per g Brain} \]

\[ \text{CLu}_{\text{int, T}} \text{ per Brain @ BBB} \]

**SF 1:**

REF/RAF\textsubscript{H-BMv}

**SF 2:**

H-BMvPGB

**SF 3:**

Brain Weight

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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 $[S]_{EC}$
  - Active Uptake: $\frac{CL_{int} \cdot K_m \cdot [S]_{EC(t)}}{K_m + [S]_{EC(t)}}$
  - $CL_{PD} \cdot [S]_{EC(t)}$
- **Intracellular Volume**
  - $[S]_{IC}$
  - $fu_{cell}$
  - $CL_{PD} \cdot [S]_{IC(t)}$

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

### 5 Compartment Model - Transwell

Heikkinen et al., 2010 Mol Pharmaceutics

Korzekwa et al., 2012 DMD
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
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<tr>
<td>Olysio (Simeprevir)</td>
<td>Hepatitis C</td>
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<tr>
<td>Xarelto (Rivaroxaban)</td>
<td>Thrombosis &amp; Embolism</td>
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<tr>
<td>Edurant (Rilpivirine)</td>
<td>HIV infection</td>
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<tr>
<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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<tr>
<td>Zykadia (Ceritinib)</td>
<td>Lung Cancer</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>
</tr>
<tr>
<td>Revatio (Sildenafil)</td>
<td>Pulmonary Hypertension</td>
</tr>
<tr>
<td>Bosulif (Bosutinib)</td>
<td>Myelogenous Leukemia</td>
</tr>
<tr>
<td>Lynparza (Olaparib)</td>
<td>Advanced Ovarian Cancer</td>
</tr>
<tr>
<td>Movantik (Naloxegol)</td>
<td>Opioid Induced Constipation</td>
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<tr>
<td>Tagrisso (Osimertinib)</td>
<td>Metastatic NSCLC</td>
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<td>Iclusig (Ponatinib)</td>
<td>Chronic Myeloid Leukemia</td>
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<td>Cerdelga (Eliglustat)</td>
<td>Gaucher Disease</td>
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<td>Jevtana (Cabazitaxel)</td>
<td>Prostate Cancer</td>
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<td>Cotellic (Cobimetinib)</td>
<td>Metastatic Melanoma</td>
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<td>Lenvima (Lenvatinib)</td>
<td>Thyroid cancer</td>
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<tr>
<td>Aristada (Aripiprazole)</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