Introduction to PBPK

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Outline

• Introduction
  – What is PBPK?
  – PBPK models of absorption, distribution and metabolism and elimination

• Application of PBPK in pharmaceutical research and development
  – Past uses
  – Recent developments

• Experience at Roche
  – Extrapolation of human pharmacokinetics
  – Some benefits of the PBPK approach from discovery to the clinic

• Considerations for PBPK modeling in pediatric populations
What is physiologically based pharmacokinetic (PBPK) modeling?

\[ C(t) = \sum_{i} C_i e^{-k_i t} \]

Absorption

Model parameters include:

**Physiology**
- Intestinal fluid volume
- Intestinal transit times
- Intestinal pH
- Luminal surface area
- Metabolizing enzyme expression

**Drug specific**
- Solubility
- Particle size
- Charge
- Lipophilicity
- Formulation

Distribution

Model parameters include:

**Physiology**
- Blood flow
- Tissue perfusion
- Tissue volume
- Tissue composition

**Drug specific**
- Lipophilicity
- Charge
- Tissue partitioning
- Plasma protein binding
- Membrane permeability


Venous

<table>
<thead>
<tr>
<th>Arterial</th>
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</thead>
<tbody>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Plasma</td>
</tr>
<tr>
<td>Extracellular</td>
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<tr>
<td>Intracellular</td>
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</tbody>
</table>
Model parameters include:

**Physiology**
- Blood flow
- Enzyme amounts

**Drug specific**
- Drug lipophilicity
- Drug charge
- Plasma protein binding
- Membrane permeability
- Enzyme kinetics

Some key benefits of PBPK

- Framework for integration of \textit{in-vitro} data
- \textit{a priori} prediction of PK is feasible
- Kinetics in tissue (effect) compartments can be estimated
- Extrapolation across species, routes of administration and doses
- Modeling of sub-populations (e.g. obese patients, elderly)
- Modeling of variability and uncertainty

\textbf{BUT}

- Although the benefits are numerous the growth in use has been at best steady

PBPK: Time for wider use?

- Limitations in computing power – but this is not a factor for some years
- PBPK too complicated?
- Shortage of experts?

- Tools are now very user friendly
- Training and support available
PBPK for extrapolation of human PK

**Empirical Methods**

Log PK = a • BW^y

- simple
- frequently inaccurate
- predict average parameters
- predict only parent compound
- data intensive (in vivo PK)

**PBPK**

- +/- more sophisticated
- Need training for use
- consider variability and uncertainty
- predict full profiles
- easily inked to PD models
- potential to predict metabolites
A strategy for human PBPK predictions

Molecular descriptors; in vitro and in silico ADME data

PBPK animal

Simulation

Model refinements

Confirmation

PBPK Man

Simulation

In vivo preclinical data

Any mismatch suggests violation of model assumptions. Additional processes to be considered.

# PBPK model refinements

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Clearance</th>
<th>Distribution</th>
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</thead>
<tbody>
<tr>
<td>Aqueous solubility</td>
<td>Liver microsomes</td>
<td>Predicted tissue partitioning</td>
</tr>
<tr>
<td>PAMPA or in silico permeability</td>
<td>Predicted binding</td>
<td>Perfusion limited</td>
</tr>
<tr>
<td>Biorelevant solubility</td>
<td>Hepatocytes</td>
<td>Measured tissue partitioning (rat)</td>
</tr>
<tr>
<td>Caco2 permeability</td>
<td>Active transport processes</td>
<td>Permeability limited tissue model</td>
</tr>
<tr>
<td>Intestinal metabolism</td>
<td>Measured in vitro binding</td>
<td>with active transport</td>
</tr>
<tr>
<td>Efflux / Influx transport</td>
<td>Renal clearance</td>
<td></td>
</tr>
<tr>
<td>GI fluid degradation</td>
<td>Biliary excretion</td>
<td></td>
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<tr>
<td>Formulation effects</td>
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</tbody>
</table>

**Preliminary**

**Refined**
PBPK accuracy superior to empirical methods

**PREDICTION ACCURACY ~ 90%, n=19**

**Observed AUC (hr*ug/L)**

**Predicted AUC (hr*ug/L)**

**PREDICTION ACCURACY ~ 40%, n=19**

**Observed AUC (hr*ug/L)**

**Empirical (Dedrick)**

**PBPK**
PBPK additional benefits in understanding

Based on pre-clinical data, what is the mechanism of elimination?

- Hepatic metabolism
  - Does in vitro data predict hepatic clearance in pre-clinical species?
    - Yes
      - Use in vitro data for prediction in man
    - No
      - Consider extra-hepatic metabolism; non-linearities; variability; binding issues
  - Does GFR x fup method predict hepatic clearance in pre-clinical species?
    - Yes
      - Use GFR x fup method for prediction in man
    - No
      - Use lin method (if CL_R in ≤3 species available) or allometry (if CL_R in >3 species available)

- Renal excretion
  - If this pathway is significant, do not perform prediction in man

- Biliary excretion
PBPK throughout research and development

- Lead Optimization
- Clinical Lead Selection
- EIH Enabling
- Phase 1
- Phase 2/3

Candidate selection based on expected human PK/PD profile

PBPK model refinement
Assist clinical data interpretation
Assist formulation development
DDI simulations

Simulation of in vivo PK (PD) profiles based on in vitro and physicochemical inputs

Rational Prediction of PK (PD) in man

DDI simulations
Formulation development & IVIVC
Considerations for a PBPK model in pediatrics

• Existing PBPK in adults can be leveraged
• PBPK allows the known physiological differences between adults and children to be accounted for
  – E.g. changes in body fat, plasma proteins, organ size development,
• Known maturation in clearance processes can be incorporated
  – E.g. specific cytochrome P450s and renal clearance maturation
• Allows variability to be included (e.g. in clearance as shown by Johnson)
• Several examples of application are encouraging as to the benefits of this approach

Acknowledgements

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