Predicting Drug Clearance in Humans using Non-clinical Data

Part 3: Comparative Assessment of Prediction Methods of Human Clearance

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Introduction

• PK ultimately to estimate dose and dosing frequency requirements for FTIH (safe starting dose) and PoC (therapeutic dose), which impacts:
  – Relative ranking of candidates and selection of backup/follow-up compounds
  – Formulation type and strength development
  – Cost of goods estimate
  – Dose range for safety assessment studies
  – LLQ and HLQ for drug assay
  – Estimate of drug-drug interaction (DDI) potential

• This work evaluated several methods of predicting human PK based on in vitro and non-clinical species data for a dataset of compounds with diverse physicochemical properties that are representative of newer compounds, which exhibit greater potency and tissue specificity.

Evaluation of 29 methods for 19 IV compounds (19 allometric and 10 IVIVE) to predict human CL

<table>
<thead>
<tr>
<th>ID</th>
<th>Description</th>
<th>ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Simple allometry (SA)</td>
<td>15</td>
<td>Single Species (Rat) allometry (SSS_rat)</td>
</tr>
<tr>
<td>2</td>
<td>Multieponential allometry (MA)</td>
<td>16</td>
<td>Single Species (Dog) allometry (SSS_dog)</td>
</tr>
<tr>
<td>3</td>
<td>SA with pb correction (SSA_up)</td>
<td>17</td>
<td>Rat-dog-human proportionality (TS_rat-dog)</td>
</tr>
<tr>
<td>4</td>
<td>M__up</td>
<td>19</td>
<td>Rat &amp; dog CL + compound characteristics (Q SAR_{rat-dog})</td>
</tr>
<tr>
<td>5</td>
<td>Rule of Exponent (ROE)</td>
<td>20</td>
<td>CLint-microsomes with Physiologically Based Scaling Factor (PBSF_mic)</td>
</tr>
<tr>
<td>6</td>
<td>ROE__up</td>
<td>21</td>
<td>PBSF_mic_up</td>
</tr>
<tr>
<td>9</td>
<td>fu Intercept Correction Method (FCIM)</td>
<td>22</td>
<td>PBSF_mic_up/huinc-meas</td>
</tr>
<tr>
<td>10</td>
<td>Rat-human correction for LBF (SS__up)</td>
<td>23</td>
<td>PBSF_mic_up/huinc-calc</td>
</tr>
<tr>
<td>10</td>
<td>Dog SS__up</td>
<td>24</td>
<td>CLint-hepatocytes with PBSF (PBSF_hep)</td>
</tr>
<tr>
<td>11</td>
<td>Rat SS__up__up</td>
<td>25</td>
<td>PBSF_hep_up</td>
</tr>
<tr>
<td>11</td>
<td>Dog SS__up__up</td>
<td>27</td>
<td>PBSF_hep_up/huinc-calc</td>
</tr>
<tr>
<td>13</td>
<td>Dog-human proportionality (SS__up)</td>
<td>28</td>
<td>CLint-microsomes with Rat Scaling Factor (RSF_rat)</td>
</tr>
<tr>
<td>14</td>
<td>Rat-human proportionality (SS__up)</td>
<td>27</td>
<td>PBSF_hep_up/huinc-calc</td>
</tr>
</tbody>
</table>

*Methods that included <9 compounds (N=8) or <40% within 2-fold/<80% within 10-fold (N=4) excluded from table.*
Fold error of predicted CL (IV)

- fold error between predicted and observed values
- average fold error
- 2-fold error range

X-axis: numbers in parentheses represent proportion of drugs predicted within 2-fold

Predicting Human Clearance (IV)

Top-performing Methods for Predicting Human Clearance (IV)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>TS&lt;sub&gt;rat-dog&lt;/sub&gt;</th>
<th>FCIM&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ROE</th>
<th>QSAR&lt;sub&gt;rat-dog&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 2-fold</td>
<td>67%</td>
<td>72%</td>
<td>72%</td>
<td>60%</td>
</tr>
<tr>
<td>Within 3-fold</td>
<td>94%</td>
<td>83%</td>
<td>83%</td>
<td>87%</td>
</tr>
<tr>
<td>Within 10-fold</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>AFE</td>
<td>0.83</td>
<td>0.77</td>
<td>1.05</td>
<td>0.74</td>
</tr>
<tr>
<td>AAFE</td>
<td>1.69</td>
<td>1.63</td>
<td>1.71</td>
<td>1.71</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.30</td>
<td>0.28</td>
<td>0.33</td>
<td>0.29</td>
</tr>
<tr>
<td>CCC</td>
<td>0.79</td>
<td>0.80</td>
<td>0.76</td>
<td>0.87</td>
</tr>
</tbody>
</table>

1. fu correction particularly helpful when b exponent >1

AFE: average fold error
AAFE: absolute average fold error (accuracy)
RMSE: root mean square error (precision)
CCC: concordance correlation coefficient (GOF between predicted and observed)

• Single Species Methods 11 (rat or dog SS<sub>LBP-fup</sub>) and 13/14 (SS<sub>dog</sub> & SS<sub>rat</sub>) performed fairly well too, with ≥72% of predicted within 3-fold and none >10 fold of observed
  • SS<sub>dog</sub> predicted 72% within 2-fold of observed
• For 2 best IVIVE methods, 78-83% of predicted within 3-fold (<8% >10-fold)
  • Human microsomes with pb correction for plasma and incubation media
  • Human hepatocytes (without pb correction)

CL (IV) Considerations/Learnings

• Several methods were able to predict CL (IV) within 3-fold of observed >75% of the time, but some had outliers (>10-fold)
• Top-performing methods predicted human CL (IV) within 2-fold for ≥67% of compound, 3-fold for ≥83% of compounds, and 10-fold for 100% of compounds
• Although top-performing methods included data from more than one nonclinical species, some single species methods performed well too
• Generally, use of in vivo data was better able to predict than in vitro data
• Allometry:
  • Simple Allometry (SA) tended to over-predict CL (IV)
  • Single species allometry (SSS<sub>rat</sub> and SSS<sub>dog</sub>) predictions of CL (IV) were similar to or sometimes better than predictions based on SA or MA
  • Protein binding correction did not improve predictions for SA, Multiexponential Allometry (MA), or Rule of Exponents (ROE)
  • human CL (IV) better predicted for moderate-high CL (IV) compounds with SA exponent b between 0.5 & 1
CL (IV) Considerations/Learnings

- **IVIVE**
  - Several cases where predicted CL (IV) with >10-fold error
  - Correction for protein binding changed prediction from over- to under-prediction potentially because the fup/fuc ratio was generally < 1
    - fup/fuc = 0.37 ± 0.43 rat, 0.35 ± 0.30 dog, 0.33 ± 0.37 monkey, and 0.26 ± 0.35 human
  - human CL (IV) & non-clinical species CL (IV) less well predicted for compounds with low fup and low CLint
    - Correction for both plasma and microsomal binding performed best
      - Potentially because a correction for only plasma binding resulted in predicted CL values close to zero (inconsistent with in vivo) for low fup and low CLint compounds
  - Hepatocyte data demonstrated a slight advantage compared to microsome data in term of prediction accuracy. This was demonstrated for all species.

CL (IV) Comparison to Previous Efforts by Others

- **Allometry**
  - The relative good performance of 1- and 2-species methods vs use of >2 species is a consistent finding in PhRMA 2011, Tang 2007 and Hosea 2009.
  - Across datasets, those that contained several drugs with moderate-high CL(IV) in human and/or SA b exponent between 0.5 and 1 had higher degree of prediction accuracy.
  - The accuracy of prediction of either total or unbound PK parameters by allometric methods was comparable within the PhRMA 2011 and Hosea 2009 datasets
  - pb correction improved SA prediction of human CL(IV) for Sinha 2008 compared to PhRMA dataset, possibly because Sinha compounds had lower fup and higher proportion of compounds had SA b exponent >1

• IVIVE
  – Correction for both plasma and microsomal pb performed best in PhRMA, Obach 1997, and Hosea 2009 (PO) datasets
  – For Hosea 2009 (PO), IVIVE using human liver microsomes was as accurate as single-species scaling for compounds primarily cleared by liver metabolism. This observation is less obvious for the PhRMA dataset.

Predicting Human AUC (PO)

• AUC(PO)=Dose/CL/F
  – Requires prediction of both CL and F; thereby compounding error
• Evaluation of 51 prediction methods (combining 22 CL and 5 F prediction methods) for 106 orally administered compounds
• Evaluation of 15 allometric methods to directly scale CLpo for same 106 orally administered compounds
• F methods:
  – Average across species
  – Single species value
  – Allometry
Top-performing Methods for Predicting Human AUC (PO)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>SS_{dog} + F_{avg}</th>
<th>ROE + F_{avg}</th>
<th>QSAR_{rat-dog} + F_{avg}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 2-fold</td>
<td>46%</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>Within 3-fold</td>
<td>58%</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>Within 10-fold</td>
<td>89%</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>AFE</td>
<td>1.08</td>
<td>0.95</td>
<td>0.79</td>
</tr>
<tr>
<td>AAFE</td>
<td>2.95</td>
<td>3.50</td>
<td>3.15</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.64</td>
<td>0.71</td>
<td>0.64</td>
</tr>
<tr>
<td>CCC</td>
<td>0.83</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>

AFE: average fold error
AAFE: absolute average fold error (accuracy)
RMSE: root mean square error (precision)
CCC: concordance correlation coefficient (GOF between predicted and observed)

• Similar top methods as CL (IV)
• No method predicted AUC (PO) within 3-fold ≥60% of time
• 35/66 methods have >20% of predicted values outside 10-fold
  *This highlights the difficulty in predicting F
AUC (PO) Considerations/Learnings

- Many methods were able to predict CL (IV) within 3-fold of observed >75% of the time, but the best method for estimating AUC (PO) was only able to predict within 3-fold 59% of the time
- Monkey not better than other species (generally underpredicted AUC (PO))
  - Dog best predictor
- Low solubility additional factor leading to poor prediction (in addition to low in vivo CL and SA exponent b <0.5 or >1)
- F is the most difficult parameter to predict – need better methods!

Overall Schematic of Human CL (IV or PO) Prediction Accuracy
Findings of Other Studies

• Accurate prediction of human CL for low E, extensively metabolized drugs is challenging
  – IVIVC: better predictor for compounds with measurable turnover (Beaumont)
  – Allometry for unbound CL is only appropriate for compounds where hepatic CL is <50% of hepatic blood flow (Beaumont)
  – Rate of metabolite appearance in human liver microsomes is a more sensitive method of assessing in vitro CLint; this requires understanding of metabolic pathway (Beaumont)
• ROE may not correct well for b exponent <0.55 and >1.3; the use of a fixed exponent developed in two species can provide more accurate predictions across the range of b exponent values (Tang, 2007).


Issues/Path Forward

• Limitations/Issues
  – Data collected across PhRMA companies may have increased variability in the data due to differing laboratory & assay conditions and procedures
    • Beaumont 2011 showed result differences between two labs that evaluated the same set of compounds
  – Limited number of IV compounds
  – Lack of complete physicochemical properties, such as polar surface area and molar refractivity, did not allow for assessment of predictive performance vs these properties
• Path Forward
  – Better understanding of importance of transporters in human PK prediction
  – Better prediction of F needed