Saying “I do” to the QSAR/PBPK marriage in GastroPlus™ to predict chemical exposure for safety evaluation

John DiBella, M.S.
Simulations Plus, Inc.
Simulations Plus (NASDAQ: SLP): end-to-end M&S solutions provider

Discovery → Preclinical → Clinical

- ADMET Predictor™
- GastroPlus™
- MedChem Studio™
- MedChem Designer™
- DDDPlus™
- MembranePlus™
- COMING SOON: PKPlus™
- KIWI™

Consulting Services and Collaborations
Saying “I do” to the QSAR/PBPK marriage...

2,4-D

Goal: **reliably** and **efficiently** utilize PBPK modeling to reduce animal/human testing
Outline

• The GastroPlus PBPK modeling platform:
  – What makes it unique?
  – How does it address your challenges?
• Demonstration: PBPK modeling of 2,4-dichlorophenoxyacetic acid in 60 seconds
• Future directions
Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)
- #1-ranked commercial QSAR models
- #1-ranked commercial model for absorption rate calculations
- Paracellular absorption process
- Mechanistic precipitation model
- Nonlinear gut metabolism and transport
- Human and animal physiology models
  - Dog, rat, mouse, cyno & rhesus monkeys, minipig, rabbit

PBPK Modeling
- #1-ranked Kp calculation method
- Adjustments of plasma lipid binding
- Human and animal physiology models
  - Same as above
- Unlimited metabolite tracking
- Transporter-based IVIVE – automated scaling of tissue PStc
- Customization of model without equation writing

Human and animal physiology models
Unlimited metabolite tracking
Transporter-based IVIVE – automated scaling of tissue PStc
Customization of model without equation writing

Physiologically based Pharmacokinetics (PBPK)
But wait! It’s more than oral absorption...

Pulmonary (PCAT™)

Oral Cavity (OCCAT™)

Dermal (TCAT™)

Ocular (OCAT™)
# How does GastroPlus address your challenges?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do I have the time &amp; expertise to write code and manage updates?</td>
<td>No equation writing AND customization options available</td>
</tr>
<tr>
<td>How do I define all of the parameters required for a PBPK model?</td>
<td>#1-rated QSAR models integrated for complete <em>in silico</em> solutions</td>
</tr>
<tr>
<td>What about other species or different populations?</td>
<td>Complete database of animal and human (American &amp; Asian – pediatrics and adults) physiology models included</td>
</tr>
<tr>
<td>What if my chemical is exposed through several dosing routes?</td>
<td>Mechanistic models for oral, pulmonary, dermal, and ocular delivery</td>
</tr>
<tr>
<td>How am I going to predict both local and systemic concentrations?</td>
<td>Track all variables and easily capture output in Excel</td>
</tr>
<tr>
<td>Where do I start with all of the chemicals I have?</td>
<td>Batch mode, automated sensitivity analysis and optimization available</td>
</tr>
<tr>
<td>How possible is it to predict metabolite exposure?</td>
<td>Unlimited metabolite tracking options</td>
</tr>
<tr>
<td>I am guessing the commercial tools must be expensive?</td>
<td>Flexible licensing options and expert consulting support</td>
</tr>
<tr>
<td>Will my commercial provider be around for the long haul?</td>
<td>Publically traded for &gt;18 years &amp; counting</td>
</tr>
</tbody>
</table>

And...
Regulatory scientists trained on GastroPlus PBPK modeling
Demonstration:

2,4-dichlorophenoxyacetic acid*  
(* not in any of our training sets)

- **Modeling approach:**
  - Import chemical structure
  - Create PBPK model
    - Study: 5 males varying in weight between 70-90 kg
    - Create a default 22-year-old American Male PBPK model (82.5 kg)
    - Calculate tissue Kps and Vss
  - Define passive kidney filtration clearance (Fup * GFR)
  - Predict liver microsomal CLint
  - Simulate oral exposure (single dose; 5 mg/kg)
- **Set up time:** < 60 seconds
2,4-dichlorophenoxyacetic acid: PBPK model inputs from chemical structure and default physiological parameters

![Chemical structure of 2,4-dichlorophenoxyacetic acid]

| Predicted value
<table>
<thead>
<tr>
<th>from ADMET Predictor v7.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeability (cm/s *10^-6)</td>
</tr>
<tr>
<td>Aqueous solubility (mg/mL)</td>
</tr>
<tr>
<td>pKa</td>
</tr>
<tr>
<td>logP</td>
</tr>
<tr>
<td>Plasma protein binding (%)</td>
</tr>
<tr>
<td>Blood:plasma ratio</td>
</tr>
<tr>
<td>Passive filtration clearance [Tup * GFR] (L/hr)</td>
</tr>
<tr>
<td>Intrinsic clearance (L/hr)</td>
</tr>
</tbody>
</table>

Compound window: Physicochemical properties & dosing regimen

Gut Physiology window: Gut physiological parameters

Pharmacokinetics window: PBPK model parameters
Future directions

- Expand QSAR predictions to other metabolic pathways

- Predict “species-specific” metabolism kinetics
- Investigate other clearance mechanisms
  - e.g., biliary secretion & renal clearance
- Transporters – the next frontier...

Evans and Relling, Science 286, 487 (1999)
Backup Slides
The Big Picture – drug inputs

Structure → in silico

in vitro experiments

Physical properties - Peff, Sw, pKa, logP, Fup, Rbp

in vitro constants: $V_{max}(s)$, $K_m(s)$, $K_i(s)$, EC50, etc...

Structure → in silico

Formulation: dose, dosage form

IV/Oral PK data

in vitro metabolism

PKPlus™- Vd, CL, K12, K21, K13, K31

PBPKPlus™ - CLint

GastroPlus™

Scale to in vivo processes

Therapeutic/Adverse Effect Data

Dissolution and absorption
Plasma/tissue concentration profiles
Nonlinear kinetics (and DDI)
PBPK/PD modeling
Select government collaborations

• FDA Center for Food Safety and Nutrition (CFSAN)
  • Extended Research Collaboration Agreement (RCA) with CFSAN to provide Quantitative Structure-Activity Relationship (QSAR) model-building capabilities to predict toxicities for large number of substances that can be in foods as additives or contaminants
  • First peer-reviewed articles from FDA scientists published in 2014

• NIH: National Toxicology Program (NTP)
  • Completed second year of 3-year collaboration with NTP to utilize GastroPlus PBPK and ADMET Predictor™ QSAR modeling to prioritize testing of chemicals for the Tox21 program
  • Presented work at past two Society of Toxicology (SOT) meetings – first publications expected in 2016
What about our QSAR models?

Independent comparison of aqueous solubility predictors
(Dearden JC. Exper. Opin. Drug Discovery 2006 1:31)

<table>
<thead>
<tr>
<th>Software</th>
<th>% Compounds predicted within</th>
<th>q^2</th>
<th>s</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>SimulationsPlus</td>
<td>64.8</td>
<td>0.82</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>ACD/AutoAlert</td>
<td>61.5</td>
<td>0.73</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Pharma Algorithms ADME Bases</td>
<td>59.0</td>
<td>0.67</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>ChemSilico</td>
<td>59.8</td>
<td>0.67</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>ACD Labs</td>
<td>59.0</td>
<td>0.73</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>ACD Labs</td>
<td>51.6</td>
<td>0.67</td>
<td>0.73</td>
<td></td>
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<tr>
<td>PredictionBase</td>
<td>48.7</td>
<td>0.66</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>ESSL</td>
<td>44.9</td>
<td>0.60</td>
<td>0.84</td>
<td></td>
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<tr>
<td>VEGA-WEAN</td>
<td>40.5</td>
<td>0.41</td>
<td>0.82</td>
<td></td>
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<tr>
<td>ACDow 2</td>
<td>44.3</td>
<td>0.53</td>
<td>0.86</td>
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<tr>
<td>Qik Prop</td>
<td>47.6</td>
<td>0.57</td>
<td>0.91</td>
<td></td>
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<tr>
<td>SPARC</td>
<td>42.9</td>
<td>0.72</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Cerius ADME</td>
<td>37.7</td>
<td>0.69</td>
<td>0.92</td>
<td></td>
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<tr>
<td>WSKOWIN</td>
<td>41.0</td>
<td>0.69</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>ADMEWORKS Predictor</td>
<td>31.4</td>
<td>0.62</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>ACD/PK</td>
<td>38.5</td>
<td>0.69</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>CHEMICAP</td>
<td>23.2</td>
<td>0.75</td>
<td>1.02</td>
<td></td>
</tr>
</tbody>
</table>

*Based on 115 compounds; SPARC could not calculate solubility of 3 compounds.
*Based on 166 compounds, using key method with calculated melting point, which was not available for 6 compounds; kindly calculated by Fred. G. Schüttler.

Predicted by Trained with MAE RMSE R^2
ACD/Percepta v. 12 15932 lit pK_a 0.77 1.05 0.84
ADMET Predictor v. 6.1 14147 lit pK_a 0.73 0.95 0.86
ADMET Predictor v. 7.0 14149 lit pK_a + 19467 Bayer pK_a 0.51 0.67 0.93

Independent comparison of pK_a predictors
(Fraczkiewicz et al., J. Chem. Inf. 2015)

Independent comparison of logP predictors
(Tetko & Poda, 2007)
Recent validation: QSAR/PBPK marriage

Building QSAR models for clearance using 15-30 in vivo rat CL measurements:
>75% of compounds predicted within 2-fold

Lawless et al. (2015) ISSX Annual Meeting
Using QSAR & PBPK to predict human F%:
70% of compounds predicted within 2-fold
Allometric Scaling vs. PBPK: *in vitro-in vivo* extrapolation (IVIVE)

**Summary of IV profile prediction accuracy**

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>PROFILE</th>
<th>Vss</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AFE</td>
<td>% within 2-fold error (3-fold error)</td>
</tr>
<tr>
<td>GastroPlus</td>
<td>-11.7 (1)</td>
<td>1.4</td>
<td>90 (100)</td>
</tr>
<tr>
<td>PKSim</td>
<td>-6.4 (2)</td>
<td>1.7</td>
<td>70 (90)</td>
</tr>
<tr>
<td>Current Pfizer Approach</td>
<td>-3.8 (3)</td>
<td>1.6</td>
<td>75 (85)</td>
</tr>
<tr>
<td>SimCYP – hlm</td>
<td>5.6 (4)*</td>
<td>1.5</td>
<td>80 (95)</td>
</tr>
<tr>
<td>SimCYP – rhCYP</td>
<td>7.8 (5)*</td>
<td>1.5</td>
<td>80 (95)</td>
</tr>
<tr>
<td>ChloePK</td>
<td>8.5 (6)*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Summary of Oral profile prediction accuracy**

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>PROFILE</th>
<th>AUC</th>
<th>% within 2-fold error (3-fold error)</th>
<th>AFE</th>
<th>% within 2-fold error (3-fold error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AFE</td>
<td>% within 2-fold error (3-fold error)</td>
<td>AFE</td>
<td>% within 2-fold error (3-fold error)</td>
</tr>
<tr>
<td>GastroPlus</td>
<td>-9.8 (1)</td>
<td>2.7</td>
<td>50 (72)</td>
<td>2.0</td>
<td>67 (72)</td>
</tr>
<tr>
<td>Current Pfizer Approach</td>
<td>-5.3 (2)</td>
<td>3.9</td>
<td>33 (56)</td>
<td>2.5</td>
<td>44 (61)</td>
</tr>
<tr>
<td>SimCYP - rhCYP</td>
<td>-3.7 (3)</td>
<td>3.0</td>
<td>56 (67)</td>
<td>2.2</td>
<td>61 (72)</td>
</tr>
<tr>
<td>SimCYP - hlm</td>
<td>5.7 (4)*</td>
<td>3.6</td>
<td>41 (53)</td>
<td>2.7</td>
<td>53 (59)</td>
</tr>
<tr>
<td>PKSim</td>
<td>6.1 (5)*</td>
<td>4.7</td>
<td>22 (39)</td>
<td>5.0</td>
<td>17 (33)</td>
</tr>
<tr>
<td>ChloePK</td>
<td>7.0 (6)*</td>
<td>2.8</td>
<td>39 (50)</td>
<td>2.4</td>
<td>50 (61)</td>
</tr>
</tbody>
</table>

Cole et al., 2008 – Asian ISSX Meeting
AstraZeneca: Comparison of absorption predictions (Mol. Pharmaceutics, 2016)

performed similarly in capturing dependencies on dose and particle size. In conclusion, it was shown that all three software packages are useful to guide formulation development. However, as a consequence of the high fraction of inaccurate predictions (prediction error >2-fold) and the clear trend toward decreased accuracy with decreased predicted $r_{abs}$ observed with Simcyp, the results indicate that GI-Sim and GastroPlus perform better than Simcyp in predicting the intestinal absorption of the incompletely absorbed drugs when a higher degree of accuracy is needed. In addition, this study suggests that modeling and simulation research groups should perform systematic model evaluations using their own input data to maximize confidence in model performance and output.
Peer-reviewed publications

• There are several hundred peer-reviewed journal articles citing the use of GastroPlus – most are from our clients:

GastroPlus Publication List
• In 2013, scientists from 17 companies in North America and Europe formed the GastroPlus User Group

• To date, >850 members on the LinkedIn group page – membership is free!

Mission Statement

Discuss best practices, Q&A and FAQs
Present and advance M&S science via social media, webinars and face-to-face meetings
Establish pre-competitive areas of research and collaboration across industry and academia
Understand and influence regulatory expectations for M&S submissions