EMERGING REGULATORY GUIDANCES AND USE OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC APPROACHES IN DRUG APPROVALS

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3rd SSX Annual Meeting, October 2018
Outline of Presentation

• Overview on use of PBPK M&S in drug development
• Current status of PBPK applications
• Consortium White Paper on use of PBPK in regulatory submissions
• PBPK examples in regulatory submissions
  – Impact of examples related to DDIs
  – Impact of non-DDI examples
  – Pediatric examples
  – MSD examples (Letermovir, Compound A & Ertugliflozin)
• Challenges and gaps for applications of PBPK
Background

- Significant impact of PBPK M&S on regulatory decision making in the past 5 to 6 years
- PBPK modeling impacts all stages of drug development
- Several product labels (>25) in recent years have included information based on PBPK modeling
- Applications of PBPK have focused on DDIs (~70%), special populations (pediatrics, polymorphisms, or race), as well as absorption/formulation issues (i.e. dissolution, particle size)
- Majority (>74%) of the submissions utilizing PBPK approaches were accepted by the EMA & FDA
- Both the EMA and FDA have issued draft guidances on qualification and/or reporting of PBPK M&S
- Cross-Pharma 2017 initiative (co-leads Mohamad Shebley & Punam Sandhu) on White Paper on PBPK model qualification and reporting for regulatory submissions
While in most cases, the primary objective of PBPK modeling was DDI predictions, there are several examples (OLYSIO/sovriAD/simeprevir, EDURANT/rilpivirine, and FARYDAK/Panobinostat) where it has been used successfully for other applications.
Acceptance of PBPK Analyses by FDA or EMA (DDI and non-DDI)

Several Sponsors have ongoing discussions with the PMDA on current submissions.
## Products Containing Dosing Recommendations Informed by PBPK Strategies

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<tbody>
<tr>
<td>Rilpivirine</td>
<td>Ponatinib</td>
<td>Ibrutinib</td>
<td>Blinatumomab</td>
<td>Alectinib</td>
<td>Ribociclib</td>
<td>Acalabrutinib</td>
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<tr>
<td>Rivaroxaban</td>
<td>Simeprevir</td>
<td>Eliglustat</td>
<td>Aripiprazole</td>
<td>Naldemidine</td>
<td>Abemaciclib</td>
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<td>Rivaroxaban</td>
<td>Macitentan</td>
<td>Ruxolitinib</td>
<td>Cobimetinib</td>
<td>Ertugliflozin</td>
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<td>Rivaroxaban</td>
<td>Skyla</td>
<td>Olaparib</td>
<td>Panobinostat</td>
<td>Letermovir</td>
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<td>Rivaroxaban</td>
<td>Naloxegol</td>
<td>Lenvatinib</td>
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<td>Rivaroxaban</td>
<td>Ceritinib</td>
<td>Sonidegib</td>
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<td>Rivaroxaban</td>
<td>Osimertinib</td>
<td>Dolutegravir</td>
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**FDA PBPK Reviews (Total ~ 230; prior to 2010 <20)**

|      | 14 | 16 | 47 | 38 | 40 | 40 | 35 |

**EMA PBPK Reviews (Total ~ 60)**

|      | 5 | 3 | 9 | 10 | 11 | 11 | 13 |

**Sources:**
V Sinha & P Zhao, ASCPT Annual Meeting, San Diego 2016;
PharmaPendium
Use of PBPK for Hepatically / Renally Impaired and Specific Populations

<table>
<thead>
<tr>
<th>Current Gap</th>
<th>Future Proposal</th>
<th>Benefits</th>
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<tbody>
<tr>
<td>~50 to 80% NMEs approved in 2013 / 2014 did not include clear dosing recommendations for severe renal / hepatic impairment</td>
<td>Initial PBPK efforts can focus on dose recommendations for use in hepatically / renally impaired patients</td>
<td>Predicting exposure in sub-populations can prevent unnecessary conduct of lengthy trials</td>
</tr>
<tr>
<td>~15 to 30% NMEs did not include dosing recommendations for mild renal / hepatic impairment</td>
<td>Physicochemical properties, ADME</td>
<td>Early dosing predictions can help recruit patients from specific populations in pivotal/Phase III trials</td>
</tr>
<tr>
<td>Changes in PK and/or dosing recommendations rarely provided for use in pregnant women</td>
<td>Creating models for clearance pathways for each specific population</td>
<td>In some situations M&amp;S might be the only way to predict dosing (e.g. pregnant patients)</td>
</tr>
<tr>
<td>In majority of the cases, no useful information in label for other specific populations</td>
<td>Based on model prediction accuracy, can make recommendations for sub-population (mild, moderate or severe) e.g. Xarelto / Rivaroxaban</td>
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</table>

Consortium White Paper on Use of PBPK in Regulatory Submissions

• Comprised of 35 PBPK modeling scientists

• Represented by 25 companies & Prof. Malcolm Rowland from the simCYP Consortium

• Authors: Mohamad Shebley¹*, Punam Sandhu², Arian Emami Riedmaier¹, Masoud Jamei³, Rangaraj Narayanan⁴, Aarti Patel⁵, Sheila Annie Peters⁶, Venkatesh Pilla Reddy⁷, Ming Zheng⁸, Loeckie de Zwart⁹, Maud Beneton¹⁰, Francois Bouzom¹¹, Jun Chen¹², Yuan Chen¹³, Yumi Cleary¹⁴, Christiane Collins¹⁵, Gemma L. Dickinson¹⁶, Nassim Djebli¹², Heidi J Einolf¹⁷, Iain Gardner³, Felix Huth¹⁷, Faraz Kazmi¹, Feras Khalil¹⁸, Jing Lin¹⁹, Aleksandrs Odinecs²⁰, Chirag Patel²¹, Haojing Rong²², Edgar Schuck²³, Pradeep Sharma⁷, Shu-Pei Wu²⁴, Yang Xu²⁵, Shinji Yamazaki²⁶, Kenta Yoshida¹³, and Malcolm Rowland²⁷


Objective of the PBPK White Paper (2017)

Provide a consortium perspective on aspects of PBPK M&S for regulatory submissions including:

- Consortium perspective on the definition of “qualification vs verification” and “platform vs drug model” in the context of PBPK M&S

- Process for qualifying PBPK platforms (systems parameters vs drug parameters)

- Steps for verification of drug models (sensitivity analysis and parameter identifiability)

- PBPK modeling approaches (bottom-up, top-down and middle-out)

- Examples (low vs medium vs high impact) of use of PBPK in regulatory submissions (DDI and non-DDI examples)

- Development of populations beyond DDIs (eg. pediatric, RI, HI etc.)

- Reporting of M&S data/templates and analyses

- Highlighting challenges and future opportunities
Components of a PBPK Package for Regulatory Submissions

- Virtual Population
- Computational Framework
- System Parameters
- Drug Model Iteration
- Drug Model
- Drug Parameters

Platform Qualification

Model Verification
Qualification of Virtual Populations using PBPK M&S

Healthy Volunteers

- Bottom Up data
- Top Down data
- Physiological data
- Preliminary PBPK model
- Model Verification (refinement if needed)
- Final PBPK model
- Verified healthy volunteer model
- Bottom Up data
- Physiological data
- PK in Special Population
- Final PBPK model

Special Population

- Bottom Up data
- Top Down data
- Physiological data
- Preliminary PBPK model
- Model Verification (refinement if needed)
- Final PBPK model
## PBPK Modeling Approaches and Their Applications

<table>
<thead>
<tr>
<th>Modeling Approach</th>
<th>Data Availability</th>
<th>Examples of modeling scenarios</th>
<th>General Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bottom-Up</strong></td>
<td>Physiochemical properties and blood binding (LogP, pKa, fu_p, B/P)</td>
<td>Projection of human drug distribution</td>
<td>Provide mechanistic understanding</td>
</tr>
<tr>
<td></td>
<td>In vitro permeability and pharmaceutics information</td>
<td>Projection of human PK parameters and FIH dose</td>
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<td></td>
<td>In vitro metabolism and substrate/ perpetrator data</td>
<td>Enzyme DDI projection (victim and perpetrator)</td>
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<td>In vivo ADME information in preclinical species</td>
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<tr>
<td><strong>Top-down</strong></td>
<td>Clinical concentration-time profiles from single or multiple ascending doses with summary of PK parameters</td>
<td>Development of model and identify parameters and their inter-subject variability as well as identifying covariates</td>
<td>Support clinical trial decisions</td>
</tr>
<tr>
<td><strong>Middle-out</strong></td>
<td>Physiochemical properties and in vitro ADME data may be available, but key in vitro quantitative or mechanistic data may be lacking</td>
<td>Refined predictions of DDI (perpetrator or victim)</td>
<td>Provide mechanistic understanding and support clinical trial decisions</td>
</tr>
<tr>
<td></td>
<td>Clinical concentration-time profiles after single and multiple ascending doses with summary of PK parameters</td>
<td>Special populations (pediatrics, organ impairment),</td>
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<tr>
<td></td>
<td>May have clinical DDI data available as a victim and/or perpetrator for key CL pathway(s)</td>
<td>Formulation optimization or selection; in silico bioequivalence</td>
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<td></td>
<td>In vivo human ADME or mass-balance data</td>
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High vs. Medium vs. Low Regulatory Impact PBPK Analysis

**High**

Impact on drug labels and/or waiving a clinical study
- Prediction of CYP or UGT-mediated DDIs
- DDIs in pharmacogenetic subpopulations (e.g. CYP2D6 poor/intermediate/high metabolizers)
- Exposure under gastric pH-modifying agents

**Medium**

An area of evolving knowledge:
- Prediction of enzyme-based DDIs early for planning of the clinical program/studies
- Prediction of transporter-based DDIs
- Dose adjustments in the pediatric population

**Low**

Lack of clinical data to verify assumptions & parameters:
- Prediction of human PK prior to FIH study
- Lack of clinical data in special populations (e.g. pregnant women)
Regulatory Agency Specific Requests for PBPK Modeling from Sponsors

1. Build a model to consider nonlinear PK or explain potential mechanisms of nonlinear PK.

2. Build a full PBPK model to consider P-gp contribution to the biliary excretion of the drug.

3. Simulate DDI or drug exposure at steady-state or using different dosing regimens. Provide sensitivity analysis of inhibition parameters (e.g. Ki).

4. Simulate drug concentrations in tissues to explore the reason for certain AEs observed in the clinic. Simulate drug plasma concentrations in disease populations.

5. Simulate impact of genetic polymorphisms on the PK of parent and/or metabolite.
Impact of DDI PBPK Examples in Submissions

- **Accepted by FDA & EMA**
  - Lesinurad (CYP2C9 substrate): cautionary language in label for use in poor metabolizers
  - Sonidegib (CYP3A substrate): DDI study at lower dose & DDI study with moderate inhibitor not required
  - Eliglustat (CYP2D6 & CYP3A substrate): simulations provided guidance on use with moderate/strong CYP2D6/CYP3A inhibitors and CYP2D6 phenotypes
  - Naloxegol (CYP3A & P-gp substrate): adjust dose when administered with CYP3A and P-gp inhibitors

- **Accepted by FDA but not EMA**
  - Olaparib (CYP3A substrate, MBI and inducer): EMA did not accept CYP induction results
  - Crizotinib (CYP3A substrate & MBI); EMA noted that IVIVE for induction is not well established
  - Osimertinib (CYP3A substrate); adjust dose when co-administered with CYP3A inducers

- **Accepted by EMA but not FDA**
  - Compound X (UGT substrate): EMA accepted dosing recommendations based on modeled inducers being of similar potency to those studied clinically, whereas FDA remarked on lack of data

Impact of Non-DDI PBPK Examples in Submissions

- Lesinurad
  - Addressed Dissolution Aspects
- Canagliflozin
  - Addressed Particle Size Specifications on Oral F
- Ribociclib
  - Impact of PPIs on Absorption
- Pediatrics (see next slide)
- Compound Y
  - Impact of Race/Genotype (2C19 Polymorphism)
- Blinatumomab
  - PD of Drug-Mediated DDIs
Pediatric PBPK Examples in Submissions

- **Eribulin**: Assessed starting dose in children
- **Quetiapine**: Bridged formulations (including XR) from adults to children
- **Deflazacort**: Effect of CYP3A4 perpetrators in children
- **Compd. Z**: Used immediate release model to predict exposure following modified release; optimizing study design (CNS, Oncology and CV)
MSD EXAMPLES

Example 1: Letermovir
Example 2: Compound A
Example 3: Ertugliflozin
Example 4: Special Populations
Example 1: Letermovir

- **Letermovir Background:**
  
  - Human cytomegalovirus (CMV) terminase inhibitor for prophylaxis of CMV infection in allogenic hematopoietic stem-cell transplant (HSCT) recipients
    - Administered orally or as 1 hr intravenous infusion at a dose of 480 mg once-a-day
  
  - Primarily excreted as unchanged drug in feces
  
  - Time-dependent inhibitor and inducer of CYP3A
  
  - Reversible inhibitor of CYP2C8
  
  - Inhibitor of OATP1B1 and OATP1B3
  
  - DDI effects on CYP3A and OATP1B evaluated in clinic with midazolam and atorvastatin, respectively
  
  - PBPK approach used to assess potential of letermovir to perpetrate DDIs when co-administered with CYP2C8 probe substrates rosiglitazone and repaglinide
    - Simulations helped inform US prescribing information/product label

Letermovir: Qualification of PBPK Perpetrator Model & Prediction of CYP2C8 Inhibition

Drug Interaction Mechanisms of Letermovir as a Perpetrator (relevant in vitro Interaction Parameters)

- CYP3A Inhibition: $k_{\text{inact}} = 2.838$ $h^{-1}$, $K_I = 35$ $\mu M$
- CYP3A Induction: $E_{\text{max}} = 5.32$, $EC_{50} = 0.77$ $\mu M$
- Hepatic CYP3A $k_{\text{deg}}$: 0.03-0.008 $h^{-1}$
- OATP1B1 Inhibition: $K_I = 1.45$ $\mu M$
- CYP2C8 Inhibition: $K_I = 0.22$ $\mu M$

Qualification of the PBPK Model of Letermovir as a Perpetrator in Healthy Volunteers

- Simulation of Letermovir Plasma Concentration-Time Profiles in Healthy Subjects
- Qualification of Letermovir DDI Mechanisms with CYP3A and OATP1B Substrates
- Qualification of CYP3A Interaction Mechanism with Midazolam DDI Study
- Qualification of OATP1B1 Interaction Mechanism with Atorvastatin DDI Study
- Sensitivity Analysis of CYP2C8 $K_I$

Set of Parameters that Best Reproduce Clinical Observations

- CYP3A
  - $k_{\text{inact}} = 2.838$ $h^{-1}$
  - $K_I = 35$ $\mu M$
  - $k_{\text{deg}} = 0.0193$ $h^{-1}$
- OATP1B1
  - $K_I = 0.29$ $\mu M$
- CYP2C8
  - $K_I = 0.147$-$0.22$ $\mu M$

Prediction of DDIs of Letermovir as a Perpetrator at Therapeutic Doses

- Midazolam as a substrate (CYP3A)
- Repaglinide as a substrate (CYP2C8, CYP3A, OATP1B1)
- Rosiglitazone as a substrate (CYP2C8)

Simulation of Letermovir Plasma Concentration-Time Profiles in HSCT Patients

Letermovir PBPK Model Assumptions

a) Parameters qualified from DDI studies in healthy volunteers can be applied to HSCT patients
   - The reduced exposure following oral administration of 480 mg of letermovir to HSCT recipients is due to reduced absorption as exposure was similar following IV dosing

b) OATP1B1 and 1B3 are responsible for active uptake of the drug into the liver and active hepatic uptake is saturable

c) Active hepatic uptake was assigned to OATP1B1, representing the composite OATP1B-mediated uptake transporter from both OATP1B1 and OATP1B3

d) OATP1B1 Ki value obtained through sensitivity analysis is close to the in vivo OATP1B1 Ki

e) Intrinsic clearance via glucuronidation was assigned to UGT1A1, representing the composite UGT-mediated glucuronidation from both UGT1A1 and UGT1A3

f) Recovery of intact parent in feces is primarily due to excretion of intact drug based on estimated bioavailability of ~90%.
PBPK Model Successfully Captured Letermovir PK

- Greater than dose proportional PK (Cmax and AUC) after IV and PO Dosing
- AUC is the target for clinical efficacy
Letermovir: PBPK Model-Informed Magnitude of CYP2C8 DDI Potential

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Predicted Fold Change in AUC Relative to Observed</th>
<th>Predicted Fold Change in Cmax Relative to Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>3.64 (3.41, 3.89)</td>
<td>2.34 (2.21, 2.48)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>1.55 (1.49, 1.60)</td>
<td>1.40 (1.36, 1.45)</td>
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</tbody>
</table>

Data are presented as Geometric Mean Ratio (90% Confidence Interval)

- Prospective PBPK DDI predictions were helpful in adding language in the US Prescribing Information/label indicating that increase in plasma concentrations of repaglinide and rosiglitazone are anticipated due to inhibition of CYP2C8 by Letermovir.
Letremovir: Mixed Acceptance of PBPK Modeling Effort by Agencies

FDA
• Agency accepted LET PBPK model
• Main goal of predicting a CYP2C8-based interaction was successful
• Agency concurred with LET being a moderate CYP2C8 inhibitor

FDA: PBPK Model Application
• Agency further proposed simulations to inform on special population and perpetrator impact
  • Request for simulating DDIs with midazolam, digoxin and cyclosporine at 480 mg IV
  • Effect of hepatic impairment at therapeutic dose levels
  • Simulation of DDI effect of two moderate CYP3A inhibitors
## Letermovir: Mixed Acceptance of PBPK Modeling Effort by Agencies

### EMA
- Agency did not accept the PBPK model due to low confidence in modeling OATP1B-mediated clearance of LET
- Requested further qualification of OATP1B pathway of LET and additional qualification of OATP1B inhibition by LET
- Therefore, use of repaglinide was not recommended with letermovir (added to the SmPC/label).
- However, CYP2C8 DDI study was not required

### PMDA
- Agency requested justification for PBPK DDI simulations in lieu of a dedicated clinical DDI study
Example 2: Compound A Drug Interaction Potential with Moderate CYP3A Inhibitors in Adults

- **Metabolism and Elimination:**
  - Oxidative metabolism via CYP3A
  - P-gp substrate, but does not play a significant role in elimination and absorption
  - Renal elimination ~15% of the total clearance

- **Overall PBPK Strategy:**
  - Develop an adult PBPK model early on in development (Phase I)
  - Use adult model for prediction of DDIs with moderate CYP3A inhibitors
  - Develop a pediatric model to propose starting doses for different age groups

- **Background:**
  - Co-administration of Compound A with a strong CYP3A inhibitor such as ketoconazole increased the AUC by ~3-fold and $C_{\text{max}}$ by ~1.3-fold.
  - Clinical studies have been conducted with a strong CYP3A inhibitor and moderate to strong inducers
  - Dedicated trial with a moderate CYP3A inhibitor is not planned

- **Modeling Strategy:**
  - Develop PBPK model with all available data; qualified with DDI studies (ketoconazole, rifampin etc.)
  - Simulated DDIs with diltiazem and verapamil to inform dose recommendations for moderate CYP3A inhibitors.
Compound A: Simulation of DDIs with Moderate CYP3A Inhibitors

- DDI simulations were conducted with Compound A PBPK model for diltiazem and verapamil at clinically relevant dosing regimens.
- The simulation results combined with the ~3-fold increase in AUC and ~1.3-fold increase in Cmax observed with ketoconazole and the low clearance of Compound A, suggested that moderate CYP3A inhibitors are likely to result in a 2-fold increase in AUC and Cmax.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Simulated GMR (90% Confidence Interval)</th>
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</thead>
<tbody>
<tr>
<td>Diltiazem 120 mg CR TID, with 100 mg Compd. A on Day 2</td>
<td>AUC (0-inf): 1.88 (1.81, 1.96), Cmax: 1.08 (1.08, 1.09)</td>
</tr>
<tr>
<td>Verapamil 80 mg CR TID, with 100 mg Compd. A on Day 2</td>
<td>AUC (0-inf): 1.39 (1.33, 1.45), Cmax: 1.05 (1.04, 1.05)</td>
</tr>
</tbody>
</table>

CR: Conventional Release
QD: once-a-day, TID: three times-a-day
Compound A Pediatric Modeling

Background:

- Doses to be administered to pediatric cohorts based on age, with the intent to obtain pediatric PK to confirm dose selection in each age group
  - Adolescents 12 to 18 years
  - Children 6 to 11 years
  - Children 2 to 5 years
  - Children 6 months to 2 years
  - Infants 1 to 6 months
  - Neonates < 4 weeks

Modeling Strategy:

- PBPK was used to propose initial starting doses for each cohort
  - Adult SimCYP model available, qualified with ketoconazole data
  - Rifampin data available to provide additional qualification
  - Phase I adult model updated with PopPK oral CL and Vdss

- For each age group, predicted the dose required to achieve PK targets
Example 3 Ertugliflozin: Use of PBPK to Simulate UGT Inhibition

- Pharmacokinetics of ertugliflozin are comparable in healthy subjects and patients with type 2 diabetes
- Metabolized largely by UGT1A9 & UGT2B7 to two pharmacologically inactive metabolites, minimal metabolism by CYPs
- Balanced elimination between urine and feces; largely excreted as parent compound
- Substrate of P-glycoprotein and Breast Cancer Resistance Protein

Drug Interaction Potential:
- Parent and glucuronide metabolites are not CYP or UGT inhibitors
- Not an inhibitor of transporters
- Not a CYP inducer
- Co-administration with rifampin (a CYP and UGT inducer) resulted in approx. 39% and 15% decrease in AUC and Cmax, respectively (changes not clinically relevant)
- Overall, dose adjustments not required (recommended doses are 5 mg and 15 mg once-a-day)

US Prescribing Information:
Physiologically-based PK (PBPK) modeling suggests that coadministration of mefenemic acid (UGT1A9 inhibitor) may increase the exposure and C_{max} of ertugliflozin by 1.51- and 1.19-fold, respectively. These changes in exposure are not considered clinically relevant.
Example 4: Cmax and AUC Ratios of Various Compounds Following Oral or Intravenous Administration to Non-Japanese and Japanese Healthy Subjects at the Clinical Dose

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Non-Japanese Subjects</th>
<th>Japanese Subjects</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ Ratio$^a$</td>
<td>AUC Ratio$^a$</td>
</tr>
<tr>
<td>A</td>
<td>10 mg</td>
<td>0.846</td>
<td>0.933</td>
</tr>
<tr>
<td>B</td>
<td>2 mg</td>
<td>1.37</td>
<td>1.26</td>
</tr>
<tr>
<td>C</td>
<td>160 mg</td>
<td>1.05</td>
<td>1.14</td>
</tr>
<tr>
<td>D</td>
<td>400 mg</td>
<td>1.01</td>
<td>0.957</td>
</tr>
<tr>
<td>E</td>
<td>100 mg</td>
<td>0.699</td>
<td>1.10</td>
</tr>
<tr>
<td>F</td>
<td>100 mg</td>
<td>1.02</td>
<td>0.805</td>
</tr>
<tr>
<td>G</td>
<td>8 mg/kg</td>
<td>Not Applicable$^b$</td>
<td>1.07</td>
</tr>
<tr>
<td>H</td>
<td>20 mg</td>
<td>0.698</td>
<td>1.02</td>
</tr>
<tr>
<td>I</td>
<td>150 mg</td>
<td>0.703</td>
<td>1.43</td>
</tr>
</tbody>
</table>

$^a$ Ratios of predicted values to observed values (predicted/observed).

$^b$ Cmax ratio for Compound G is not applicable as the compound is administered intravenously.

Conclusion: The PBPK models were able to successfully predict PK in the Japanese population.

<table>
<thead>
<tr>
<th>Area of PBPK application</th>
<th>Specific Purpose</th>
<th>PK Characterization</th>
<th>Knowledge Gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDTs involving enzymes</td>
<td>Drug as victim</td>
<td>For enzymes expressed in multiple sites (liver, intestine, kidney), difficult to assess in vivo contribution of each site to metabolism. The requirement of in vivo DDI studies for each enzyme is difficult to justify.</td>
<td>Abundance data for non-CYP mechanismsSufficient clinical datasets for qualification of non-CYP3A mechanisms</td>
</tr>
<tr>
<td></td>
<td>Drug as perpetrator</td>
<td>Appropriate range for sensitivity analysis for in vitro data ( (K_i, k_{\text{inact}}, EC_{50} \text{ and } E_{\text{max}}) ) is key to ensuring a realistic assessment of DDI.</td>
<td>Sufficient clinical datasets for qualification of non-CYP3A mechanisms IVIVE for non-CYP mechanisms</td>
</tr>
<tr>
<td>DDTs involving transporters</td>
<td>Drug as victim</td>
<td>As above, additionally difficult to determine the relative contribution of transporter(s) vs enzyme(s) to elimination of the drug</td>
<td>IVIVE and scaling factors</td>
</tr>
<tr>
<td></td>
<td>Drug as perpetrator</td>
<td>As above for ‘Drug as perpetrator’</td>
<td>Sufficient clinical datasets for qualification</td>
</tr>
<tr>
<td>Extrapolation from healthy to other populations</td>
<td>Pediatrics, Elderly, Obese, Pregnancy, Ethnic bridging/pharmacogenetics, Organ impairment</td>
<td>Mechanistic understanding of PK in base population may be challenged by lack of IV data. When multiple enzymes/transporters are involved, difficult to determine the relative contribution of each pathway to elimination of the drug.</td>
<td>Additional pathways or compensatory mechanisms not observed in base population. Difficult to verify in vivo relevance of enzyme and transporter abundance, ISEFs and pharmacogenetic data for different enzymes.</td>
</tr>
<tr>
<td>Absorption/formulation related</td>
<td>Food-drug interactions</td>
<td>Assessment of ( Fa ) and contributing mechanisms difficult in the absence of IV data, when ( Fg ) and ( Fh ) cannot be estimated.</td>
<td>IVIVE and IVIVC for BCS II and IV drugs</td>
</tr>
</tbody>
</table>
Summary

• PBPK approaches provide a mechanistic opportunity to explain differences in exposure in populations

• Help describe/understand characteristics of clinical data to facilitate extrapolation to different populations

• Diverse applications of the use of PBPK models in drug discovery and development

• Use of PBPK modeling for Letermovir helped predict changes in exposure related to inhibition of CYP2C8 substrates and informed the labeling language

• PBPK modeling also helped address potential DDIs when Ertugliflozin is co-administered with UGT inhibitors and informed the labeling language

• PBPK approaches can also help shorten drug development times to address the “drug lag” which has been identified as a concern for drug development (Ichimaru, Toyoshima and Uyama, Clin. Pharmacol. Ther., 2010, 88(4), 454-457).
Acknowledgements

- Nancy Agrawal
- Tjerk Bueters
- Tammie Cabalu
- Dapeng Chen
- Carolyn Cho
- Chris Gibson
- Georgy Hartmann
- Sreeraj Macha
- Karsten Menzel
- Stacey Polsky-Fisher
- Conrad Raab
- Rosa Sanchez
- Vikram Sinha
- Ying-Hong Wang
- Larissa Wenning
- Kelly Yee
- PPDM Members
- simCYP PBPK Consortium Members
- Ernie Callegari (Pfizer)
- Pfizer & Co. Inc. (Ertugliflozin collaboration)
- SSX ORGANIZING COMMITTEE
Acknowledgements: Consortium White Paper on Use of PBPK in Regulatory Submissions

• Comprised of 35 PBPK modeling scientists

• Represented by 25 companies & Prof. Malcolm Rowland from the simCYP Consortium

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THANK YOU
Abbreviations

- ADME: Absorption, Distribution, Metabolism, Excretion
- AE: Adverse Event
- BCS: Biopharmaceutics Classification System
- CNS: Central Nervous System
- CV: Cardiovascular
- CYP: Cytochrome P450
- DDI: Drug-Drug Interaction
- EMA: European Medicines Agency
- FDA: Food & Drug Administration
- FIH: First-in-Human
- HI: Hepatically Impaired
- HSCT: Hematopoietic Stem Cell Transplantation
- HV: Healthy Volunteers
- LET: Letermovir
- ISEF: Inter System Extrapolation Factors
- IV: Intravenous
- IVIVC: In Vitro-In Vivo Correlation
- IVIVE: In Vitro-In Vivo Extrapolation
- MBI: Mechanism Based Inhibitor
- MD: Multiple Dosing
- M&S: Modeling & Simulation
- NME: New Molecular Entity
- OATP: Organic Anion Transporting Polypeptide
- PBPK: Physiologically Based Pharmacokinetic
- P-gp: P-glycoprotein
- PK: Pharmacokinetics
- PMDA: Pharmaceuticals & Medical Device Agency
- P.O. Per Os administration
- PPI: Proton Pump Inhibitor
- RI: Renally Impaired
- SD: Single Dose
- SmPC: Summary of Product Characteristics