Model based approaches to target special populations with rational formulation and clinical design strategies

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*Modeling for Oral and Non-Oral Routes*
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Special Populations: Needs and Challenges

- Extensive variety of special populations
  - Patients with renal or hepatic impairment, pregnant women, pediatrics, taking concomitant drugs, different ethnic groups, obese and morbidly obese patients, post-bariatric surgery patients, multiple diseased states, etc.

- Are alternative presentations/formulations required to meet needs of special patients?
  - Unique pharmacokinetic exposure profile required?
  - Presentation/dosage form amenable to patient needs?

- How to predict the behavior of existing or new dosage forms in special populations?
  - Can we identify and quantify risks that could influence patient exposure or variability?

- Do simulations improve understanding of accumulated in vivo data to align medicines for special patients?
Modeling Impact on Drug Product Development and Quality

• Advancements through rapid hypotheses testing (parameter sensitivity) and virtual clinical trials

• Explore feasibility and optimization of drug products
  • Establish targets, interpret data, predict likely outcomes
  • Drug delivery scheme(s), performance boundaries and associate control strategies

• Provide innovative hybrid approaches for unique study designs in exploratory formulation development

• PBPK modeling is used to predict altered intestinal absorption and metabolism
  • Utility for many disease states or population groups including liver cirrhosis, obesity, renal dysfunction, pediatric and geriatric patients, etc.
PBPK Models For Drug Absorption

Mechanistic PK Models: Relationship Between Drug Release, Permeability, Transit Time and Drug Absorption

\[ J_s = \frac{D}{r} \cdot C_s \]

J_s and J_w represent particle dissolution (or drug release) and drug absorption, respectively.

\[ J_w = P_{\text{eff}} \cdot C_s \]

D = Diffusion Coefficient
C_s = solubility
P_{\text{eff}} = effective permeability
r = radius of particle

Intestinal flow rate

Drug absorption is a function of concentration, permeability and time. Therefore factors such as gastric emptying, intestinal flow rate and drug release may impact the amount of drug absorbed.

• Applications
  • Allow prediction of concentration-time profiles of a drug in tissue and plasma prior to in vivo studies.
  • Make possible the extrapolation of kinetic data across unique populations, dose levels, and route of administration.
  • Guide hypothesis-driven experimentation to select drug candidates and formulations.

The main objective is to understand the patient and the formulation so the target plasma concentration vs time curve is achieved (as well as the pharmacodynamic-plasma relationship).
Common Utility of PK Absorption Models for Formulation Design

- Identify formulation needs and opportunities for new populations (pediatric, diseased, geriatric, etc)
- Establish formulation requirements to meet TPP/TMP
- Bridge dosage form modifications throughout clinical development (support relBA, BE, biowaiver applications)
- Early developability and biopharmaceutics risk assessment
- Predict magnitude of pH or food effect for prototype formulations
- Inform target specification limits for dissolution (IVIVC/R) and API particle size/shape/form
- Identify opportunity for enabling technologies (SDD, solubilized, XR, etc.)
- Draft performance targets and design strategy for clinical exploratory formulation studies

Leverage models and clinical/pre-clinical data to inform development, regulatory, and control strategy (FIH through LCM) by identifying biopharmaceutics risks and opportunities
## ADME in Special Populations – Examples

<table>
<thead>
<tr>
<th>Special Population</th>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>Decreased gastric emptying and intestinal motility&lt;br&gt;Higher gastric pH and mucus production.</td>
<td>Increased Vd for lipophilic drugs; Increased AAG; Increased Vd for hydrophilic drugs</td>
<td>Increased metabolism: 3A4, 2C9, 2D6, 2D9&lt;br&gt;Decreased activity: 2C19/1A2, cholinesterase activity</td>
<td>Increased</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Lower surface area and blood flow; Age dependent gastric pH and permeability (higher in cases); Unique intestinal transporter expression</td>
<td>Increased total body water and extracellular fluid; Lower expression of total plasma proteins for infants; Competitive binding of plasma proteins (higher free fatty acid and bilirubin)</td>
<td>Age dependent maturation&lt;br&gt;Increased CYP3A7 (High→ low)&lt;br&gt;Low to high (3A4)</td>
<td>Lower GFR</td>
</tr>
<tr>
<td>Geriatric</td>
<td>Decreased gastric acid secretion (pH higher)</td>
<td>Increased amount of fat (decreased total body water), decreased albumin, increased AAG</td>
<td>Decreased (Phase 1 impacted most)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Obese</td>
<td>Organ size, GI volume parameters, and motility</td>
<td>Increased Vd for lipophilic drugs; Increased AAG-1 (decrease fup for basic drugs)</td>
<td>Increased 2E1; Possible liver damage and reduced CL</td>
<td>High GFR, active tubular secretion</td>
</tr>
</tbody>
</table>
**PBPK Model Development and Evolution**

Extensive parameterization and refinement

- Combination of top-down and bottom-up approaches most often utilized
- Bottom-up predictions of disposition kinetics in the special population can be limited based on available physiological/systems knowledge

Intrinsic System Parameters: Age Dependent Maturation

- **Gastrointestinal tract Volume**
  - Plot showing the volume change over age for males and females.

- **Blood Flow Through Organ**
  - Plots for Small Intestine and Large Intestine, showing blood flow (in liters per minute) over age (years) for males and females.
Pediatric Populations

• “one-size-fits-all” cannot be assumed
  • Many physiological processes do not develop linearly with body size and show dramatic differences

• Children represent ~40% of the world’s population, with only ~10% of marketed drugs on approved for pediatrics

• Children under the age of two are the most heterogeneous
  • Maturation of organ development, drug metabolizing enzymes and transporters, protein binding, etc

• Few pediatric drug trials include neonates (<5%)
  • 10-fold difference in weight (0.5–5 kg) between preterm and full-term infants

• 44 products failed pediatric drug development trials submitted to the FDA between 2007 and 2014. (Momper JD., Mulugeta Y., Burckart GJ., Clinical Pharmacology and Therapeutics, 2015)
  • “Innovative study methodologies and an increased use of clinical trial simulation and PK/PD modeling in pediatric trials should allow for a decrease in the failure rate in the next decade.”
Pediatric development is at the forefront of applying PBPK models
- Constraints on clinical study design and conduct
- Need to leverage prior accumulated knowledge from adults and mechanistic understanding of children
- Receive direct requests from HAs regarding PBPK models (even if omitted from applications)
A physiologically based PK (PBPK) model was developed to further characterize PK and exposure, including maturation effects on clearance, and used to support dose proposals in combination with popPK models.

**Conclusion**

The PBPK model provides some support to the similarity in the exposure of the two formulations.
## Special Populations – Example Pediatric PBPK Models

### Published examples of regulatory submissions (Pediatric PBPK)

<table>
<thead>
<tr>
<th>Workflow</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug 4</th>
<th>BMS-1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>BMS-2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verify adult PBPK model with clinical data sets</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Justify scaling of age-dependent ADME in pediatric PBPK model</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Application

| Plan first pediatric study                                              | +      | +      | -      | +      | -                 | +                 |
| Optimize study design(s)                                                | +      | +      | -      | +      | +                 | +                 |
| Verify model for age groups                                             | +      | -      | +      | -      | +                 | +                 |
| Recommend starting dose for age groups (target exposure)                | +      | +      | -      | +      | -                 | +                 |

Additional applications:  
- *Fed physiology (food effect - dose with food), pediatric dosage form BE mechanistic understanding, dissolution specifications.*  
- *Formulation technology selection and design* 

Considerations for Pediatric PBPK Absorption Models

1) Distribution

1. Protein binding
   - Highly protein bound in adults, literature suggest less binding in infants
   - Lower expression of total plasma proteins for infants
     - [Alpha1 acid glycoprotein] ~1/2 adult value at birth (binds basic drugs), [albumin] also lower for infants
     - Competitive binding of plasma proteins (free fatty acid and bilirubin at higher levels for infants)

2. Volume of distribution (% total body water and fat)
Considerations for Pediatric PBPK Absorption Models

2) *Metabolism*

- Phase I activity is reduced in neonates, increases progressively during the first 6 mo of life, *exceeds adult rates by the first few years for some drugs*, slows during adolescence, and usually attains adult rates by late puberty
  - CYP3A4 activity ~30-50% by 1-3mo and adult levels by ~6mo-1yr
  - Utilize known in vitro kinetics and in vivo enzyme expression

3) *Absorption*

- Majority of physiological attributes close to adult for infants ~>1yrs
  - Variability from diet and physiological response (STT, GE, gastric pH, etc.) can be significant

Adult and Pediatric Food Effect Simulations

*In vitro data (dissolution input)*

- Fasted: SGF → FaSSIF
- Fed: SGF → FeSSIF
  
  *(fed ACAT, pH=4.9, STT=1hr, disso profile, Q_{liver inc})*

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**Pediatric powder dosage form (fed): lower Cmax, little to no AUC change**

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**Symbols = fasted observed, >2 and <12 yrs**
**Lines = G+ simulated fasted (solid) and fed (dashed)**

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**Pediatric fed state exposure is very similar to adult food effect:**

- Cmax: ~20%
- AUC(0-t): ~0%
GastroPlus Population Simulation – Pediatric Food Effect

- Pediatric simulation of food effect
  (48 subjects, age 2-12, >80% male, suspension)

Treatment A – Fasted
Treatment B - Fed

Simulations identify minimal potential for food effect in pediatric population consistent with observed behavior in adult subjects
# Modified Release Tablet (Adult and Pediatric)

<table>
<thead>
<tr>
<th>Formulation Attribute</th>
<th>Biopharmaceutics assessment (In silico, in vitro, in vivo)</th>
<th>Outcome/Significance</th>
</tr>
</thead>
</table>
| Release rate IVIVC/R   | - In vivo matrix tablet release has positive deviation from in vitro  
                        | - In vitro release from hydrophilic matrix has shear sensitivity | Prototype compositions with more diffusion controlled release for clinical assessment  
Adaptive clinical trial to verify release target for new dosage form/mechanism  
Can new release kinetics achieve same exposure profile? |
| Dosage form (tablet/multi-particulates) | - Multi-particulate technology has release lag time and more disperse GI transit time  
                        | - Multi-particulate must release faster for equivalent exposure | |
| Dose levels            | - Demonstrated XR release rate and manufacture is drug load specific (+ dose size limitations) | Set critical design element for prototype formulations  
Use PBPK and allometry to ID target for development  
GastroPlus aligned for exposure predictions |
Pediatric PBPK Model Development

- Compound specific parameters
- Anatomical/physiological/biochemical parameters
- Clinical Trial PK data (including human site of absorption data)

Basic Adult PBPK model (ADME/Solution PK)

Adult PBPK model refinement and evaluation (phase 1 and phase 2 studies)

- Age specific anatomical and physiological parameters (Simcyp/GastroPlus Pediatric Population)
- Age specific clearance - CYP3A4 & Esterase (slow, CES1, or no ontogeny); no scale on biliary CL

Pediatric PBPK Model

Pediatric PBPK Model evaluation and refinement
Design of Pediatric MR Dosage Form via Adult IVIVC/R

Release rate:

Slow

Medium

Fast

Deconvolute MR tablet formulations
Simulated *in vivo* release – IVIVC/R

- All in vivo profiles track in vitro data for early time points (<~2-3hrs) and exhibit positive deviation for ~2-10hrs.
- Impact of hydrodynamics and in vivo motility.
- Diffusion and erosion for matrix tablet in vivo... minimal erosion in vitro
Design of Pediatric MR Dosage Form via Adult IVIVC/R

Alter hydrophilic matrix tablet dimensions
- Requires new composition
- Model formulation space to design exploratory clinical studies and identify IVIVC/R

<table>
<thead>
<tr>
<th>Treatment Release rate</th>
<th>Observed/Simulated</th>
<th>$C_{\text{max}}$ rel%</th>
<th>$\text{AUC}_{(0-t)}$ rel%</th>
<th>$\text{AUC}_{(0-\infty)}$ rel%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original MR tablet</td>
<td>Observed (target 100%)</td>
<td>87%</td>
<td>103%</td>
<td>102%</td>
</tr>
<tr>
<td>Fast</td>
<td>Observed</td>
<td>133%</td>
<td>125%</td>
<td>118%</td>
</tr>
<tr>
<td></td>
<td>Simulated</td>
<td>138%</td>
<td>124%</td>
<td>118%</td>
</tr>
<tr>
<td>Medium</td>
<td>Observed</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td></td>
<td>Simulated</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Slow</td>
<td>Observed</td>
<td>76%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Simulated</td>
<td>80%</td>
<td>82%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Achieved IVIVC level A Correlation from Mechanistic PBPK model
Target Criteria for Pediatric Dose Selection

• Entire population
  • 10th percentile < PK parameter < 90th percentile

• Average within population
  • 80-125% of the adult exposure
  • PK parameters $C_{ssavg}$, $C_{tau}$, $C_{max}$
    • Represent markers for efficacy and safety
Target is to select a dose whose exposure is above the 10% since $C_{tau}$ is the driver for efficacy
PBPK and Allometry Recommended Approaches

- Age 2-<6 year old (12 -21 kg), X mg
- Age 6-<12 year old (21-45 kg), 2X mg
- Age 12 -<18 year old (42-73 kg), 4X mg

Simulations determine best formulation and dose strength to support clinical testing across all target pediatric ages/weights
Simulated Impact of Gastric Bypass on Weak Base (BCS Class 2)

• Methods
  – Software: GastroPlus
  – IR tablet, fasted administration
  – Simulations were performed at:
    • Gastric volumes of 100%, 75%, 50% and 25%.
    • Gastric emptying $T_{50} = 0.25$ and $0.001$ hr
    • Gastric pH = 1.3 to 6.0
    • Dose volume of 10-250ml

• Increased gastric pH in newly partitioned pouch (low acid secretion)
• Bypass of upper SI limits mixing of drugs with bile acids
Reduced stomach transit time and volume partially accounts for poor exposure in bypass subject

<table>
<thead>
<tr>
<th>Test</th>
<th>Cmax, ng/mL</th>
<th>AUC_{0-24}, ng-h/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE T_{50} = 0.25 hr</td>
<td>66.10</td>
<td>241.83</td>
</tr>
<tr>
<td>GE T_{50} = 0.001 hr</td>
<td>27.96</td>
<td>133.57</td>
</tr>
</tbody>
</table>

250 ml dose volume
Low acid secretion and higher intestinal pH further reduce exposure (Suggests likelihood of the very poor observed exposure)

<table>
<thead>
<tr>
<th>Test</th>
<th>Cmax, ng/mL</th>
<th>AUC(0-24), ng-h/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE T₅₀ = 0.25 hr</td>
<td>66.10</td>
<td>241.83</td>
</tr>
<tr>
<td>GE T₅₀ = 0.001 hr, pH 6.0</td>
<td>10.60</td>
<td>98.97</td>
</tr>
</tbody>
</table>

Enabled dosage form (e.g. solution or amorphous) viable options to avoid dependence on in vivo physiology for rapid dissolution.
Evaluation of an In Silico PBPK Post-Bariatric Surgery Model through Simulating Oral Drug Bioavailability of Atorvastatin and Cyclosporine

AS Dewitt1, D Pode1, K Rowland-Yee2, M Jamel1, A Åberg1, H Christensen1, D M Ahn2 and A Roestam-Hodgson1,2

An increasing prevalence of morbid obesity has led to dramatic increases in the number of bariatric surgeries performed. Altered gastrointestinal physiology following surgery can be associated with modified oral drug bioavailability ($F_{in}$). In the absence of clinical data, an indication of changes to $F_{in}$ via systems pharmacology models would be of value in adjusting dose levels after surgery. A previously developed virtual "post-bariatric surgery" population was assessed through mimicking clinical investigations.

Selected Agents with Potential for Decreased Absorption in Patients Who Have Undergone Bariatric Surgery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Site(s) of Absorption</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Hydrolyzed to active form, enalaprilat, in stomach; absorbed in small intestine</td>
<td>May exhibit decreased activity; consider other angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Ketonazole</td>
<td>Likely absorbed in stomach because acidic medium required for absorption</td>
<td>Absorption likely to be negligible; consider alternative agents</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Likely stomach and proximal small intestine due to rapid and complete absorption</td>
<td>Monitor for and advise patients of decreased efficacy</td>
</tr>
<tr>
<td>Metformin</td>
<td>Slowly and incompletely absorbed in duodenum</td>
<td>Increased monitoring of blood glucose; drug requirements can decrease as weight loss occurs</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>Absorbed rapidly and completely, indicating stomach and duodenum</td>
<td>Monitor blood pressure; medication requirements may decrease as weight loss occurs</td>
</tr>
<tr>
<td>Niacin</td>
<td>Primarily absorbed in duodenum</td>
<td>Administer with low-fat snack to maximize absorption</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Stomach</td>
<td>Monitor for decreased efficacy; switching to orally disintegrating tablet will not increase absorption (still absorbed in stomach)</td>
</tr>
<tr>
<td>Quetiapine fumarate</td>
<td>Exact location unknown, but likely stomach and duodenum due to rapid absorption</td>
<td>Monitor for decreased efficacy</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Unknown; decreased absorption documented in patients with steatorrhea and malabsorption</td>
<td>Consider other agents; monitor blood pressure in the postoperative period; need for antihypertensives may decrease as weight loss occurs</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Absorption site unknown, but must be hydrolyzed to the active form in stomach</td>
<td>Consider other agents; monitor serum lipids</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Absorbed rapidly and completely; absorption affected by food</td>
<td>Absorption time may increase, resulting in delay to effect; take on an empty stomach</td>
</tr>
</tbody>
</table>

Takeaway: Quantitative Modeling for Special Populations

• Access to special populations will remain a challenge (considerations for ethics and limited subject availability)
• Modeling and simulation of clinical behavior will grow steadily in applications for special populations
• Detailed understanding of physiologic variables in the population of interest is required, but not always available, which can limit utility of modeling in special populations
• Characterization of unique physiological traits of special populations must become a persistent focus
  – Expanded knowledge facilitates modeling to support efficient trial design, treatment needs (dose level, release rate and duration) and interpretation of clinical data.
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