How to obtain biowaivers for clinical trials using PBPK models, two case studies

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EUFEMED
Workshop 1: Modeling and simulations, including PBPK to improve the clinical development
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Take home messages:

• FDA is open to proposals of using modeling approaches for bioequivalence (BE), or for new drugs, with the proper justification and model verification

• PBPK models can answer a variety of questions from regulatory agencies

• PBPK is a great tool to understand the interconnection between API properties, formulation attributes and human physiology
Outline:

- **Case Study 1**: Crossover trials to show BE after manufacturing changes
- **Case Study 2**: Long-acting injectables (LAI) generic products development
The Key points from U.S. FDA Workshop:

FLIGHT SIMULATOR: LEARNING HOW TO DEVELOP COMPLEX GENERIC DRUG PRODUCTS

• FDA is open to proposals using modeling approaches to establish bioequivalence for the “Test” products, as long as these proposals include information about the modeling approach, scientific justification of the proposed approach and in the end model verification.

• Discuss your proposed BE modeling approach through the pre-ANDA development meeting.
Case Study 1:
Crossover trials to show BE after manufacturing changes
Modeling & Simulations Objectives

- Post-approval, sponsor’s manufacturing process changes resulted in different particle size distributions for new lots
  - Inline milling step added to crystallization process (PE)
- With GastroPlus®, they could apply for a biowaiver by:
  - assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability?
  - predicting the virtual bioequivalence between the “new” and “old” API lots?
Proposed Modeling Tasks

• Part 1: Determine the most appropriate absorption/PBPK model for the API across several doses for the non-engineered lots

• Part 2: Assess the effect of particle size on API exposure for the immediate release (IR) formulation

• Part 3: Evaluate predicted bioequivalence of the tablets manufactured with particle-engineered (PE) API (narrower particle size distribution) versus the tablets manufactured with non particle-engineered (NPE) API (broader particle size distribution)
Part 1: Building the Baseline Model: Key Modeling Parameters

- BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 µg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect
Part 1: Simulation Results for Baseline Models of Non-Engineered Lots

Same baseline absorption model does a good job of predicting the observed plasma concentration-time data across the three different doses of the NPE (“old”) API lots.
Part 2: Parameter Sensitivity Analysis (PSA) Around Mean Particle Radius:

Dose Range: 10 – 1000 mg

PSA was used to establish particle size specifications.

Results indicated that there would be small changes in Fa% until the largest particle sizes of the NPE API lots (> 30 - 40 µm) were reached and the dose exceeded 100 mg.
Part 2: Parameter Sensitivity Analysis (PSA) Around Standard Deviation & Shape Factor: Dose Range: 10 – 1000 mg

PSA was also run to evaluate changes in particle size standard deviation (assuming mean remained constant) and particle shape factor.

Results indicated that there would be insignificant/moderate changes in Fa% across the range of values evaluated.
Part 3: Virtual Bioequivalence Trials: Population Simulator

Incorporate measured variability for physicochemical, formulation and PK parameters into Population Simulator

Capture observed variability from existing clinical PK studies
Part 3: Virtual Bioequivalence Trials: Population Simulator

- Crossover studies simulations for **10 different populations**, each with 25 virtual subjects, were run to predict bioequivalence.

- 100% passing ratios for $C_{\text{max}}$ and AUC were predicted (within the 80-125% limits) between the “new” and “old” API lots (up to 40 µm).

Tistaert, C. AAPS Annual Meeting 2015, Orlando, FL
## Virtual Bioequivalence Study Simulations

<table>
<thead>
<tr>
<th>API Lot</th>
<th>PE/NPE</th>
<th>Dose (mg)</th>
<th>AUC&lt;sub&gt;∞&lt;/sub&gt; (ng.h/mL) (N=250)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL) (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot 5</td>
<td>PE</td>
<td>50</td>
<td>4180</td>
<td>551</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>113.3</strong> (110.7, 116.1)</td>
<td><strong>139.3</strong> (136.0, 142.7)</td>
</tr>
<tr>
<td>Lot 1</td>
<td>NPE</td>
<td>50</td>
<td>3688</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>106.4</strong> (104.3, 108.6)</td>
</tr>
<tr>
<td>Lot 5</td>
<td>PE</td>
<td>100</td>
<td>8242</td>
<td>551</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>103.0</strong> (100.9, 105.1)</td>
<td><strong>106.0</strong> (104.6, 108.6)</td>
</tr>
<tr>
<td>Lot 3</td>
<td>NPE</td>
<td>100</td>
<td>8001</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>102.2</strong> (99.8, 104.6)</td>
<td><strong>100.0</strong> (97.7, 102.4)</td>
</tr>
<tr>
<td>Lot 5</td>
<td>PE</td>
<td>300</td>
<td>24998</td>
<td>3118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>102.2</strong> (99.8, 104.6)</td>
<td><strong>100.0</strong> (97.7, 102.4)</td>
</tr>
<tr>
<td>Lot 4</td>
<td>NPE</td>
<td>100</td>
<td>8395</td>
<td>1123</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>98.2</strong> (96.2, 100.2)</td>
<td><strong>95.1</strong> (93.2, 97.0)</td>
</tr>
<tr>
<td>Lot 5</td>
<td>PE</td>
<td>300</td>
<td>24998</td>
<td>3118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>101.9</strong> (99.8, 104.1)</td>
<td><strong>98.3</strong> (96.3, 100.4)</td>
</tr>
</tbody>
</table>

**Notes:**
- API: active pharmaceutical ingredient; AUC<sub>∞</sub>: area under the plasma concentration-time curve from time 0 to infinite time; CI: confidence interval; C<sub>max</sub>: maximum observed plasma concentration; GM: geometric mean; GMR: geometric mean ratio; NPE: non-particle-engineered; PE: particle-engineered

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Tistaert, C. AAPS Annual Meeting 2015, Orlando, FL
Summary

• A mechanistic, physiologically-based absorption/PK model was constructed in GastroPlus and validated across three dose levels (50, 100, and 300 mg) using in vivo data collected from tablets manufactured with non-particle engineered API.

• Parameter sensitivity analysis showed that mean particle size would be the main property that determines whether formulations are likely to be bioequivalent, regardless of dose.

• Virtual bioequivalence trial simulations showed, that for a sufficiently powered study the population-derived $C_{\text{max}}$ and AUC values would be bioequivalent between the tablets manufactured with non-particle engineered (NPE) vs. new particle engineered (PE) API, up to 40 $\mu$m particle size, regardless of the dose.

• Regulatory agencies approved the sponsor’s biowaiver application
Case Study 2:
Long-acting injectables
generic product development
Goal of the project

- Long-acting injectable (LAI) formulations include biodegradable injectable microspheres and in-situ gelling implants. Compendial in vitro release methods for these complex formulations are not well developed, and demonstration of BE for these products can be challenging.


The FDA consider these LAI as “complex products”
In 2015, Simulations Plus and a major pharmaceutical company received a grant from the FDA to improve the pre-existing model for in vitro in vivo correlation (IVIVC) within GastroPlus®.
In \textit{vitro}-\textit{In vivo} correlation: Mechanistic absorption model

- **Working definition:**
  “A predictive mathematical treatment describing the relationship between an \textit{in vitro} property of a dosage form (e.g., the rate or extent of drug release) and a relevant \textit{in vivo} response (e.g., plasma concentration-time data)”


- **Method:**
  - **Inputs:**
    - Physiological parameters
    - Drug properties (solubility, Peff, logP, pKa, etc.)
    - PK data
    - In vitro dissolution profile
  - **Outputs:**
    - A model that combines all available \textit{in silico}, \textit{in vitro} and \textit{in vivo} information and provides:
      - \textit{in vivo} dissolution, absorption and bioavailability vs. time profiles
      - Description of site dependent absorption
      - Description of tissue contributions to first pass extraction

Deconvolution

\textit{in vivo} dissolution vs. time along the gut

Weibull Function
**In vitro-In vivo correlation (IVIVC):**

Mechanistic absorption model

- **Method:**

Find the correlation between the deconvoluted *in vivo* release and *in vitro* dissolution profiles.

Predict the plasma concentration-time profile using the IVIVC and *in vitro* dissolution curve.
The *in vivo* release profiles for LAIs are often complex and cannot be described well with a single or double-Weibull function (typically sufficient for deconvolution of *in vivo* release profiles for standard oral formulations). This issue was addressed by adding triple-Weibull function.

Simulated Cp-time profiles after SC injection of one LAI formulation in rat. The *in vivo* release profile was fitted as double-Weibull (top) and triple-Weibull (bottom) function with 3 objective function weighting schemes.
Weibull Controlled Release Profile

Comments:
In Vitro Amt [mg] =

\[
\text{%DoseReleased} = \max \left( 1 - f_1 \exp \left( \frac{-(t - T)^{b_1}}{A_1} \right) - f_2 \exp \left( \frac{-(t - T)^{b_2}}{A_2} \right) - f_3 \exp \left( \frac{-(t - T)^{b_3}}{A_3} \right) \right)
\]

Weibull Parameters

\( I \) (time lag) (hrs): 1
Max (total released) (%): 100

Select Weibull Function:
- Double Weibull

Phase 1
- Fraction: 1
- Time scale (hrs): 1

Phase 2
- Fraction: 0
- Time scale (hrs): 1

Phase 3
- Fraction: 0
- Time scale (hrs): 1

Find Initial Estimates  Fit Weibull Function  Cancel  OK
Flexibility of the Weibull Function?

GastroPlus offers single-, double-, and triple-Weibull function for optimization of *in vivo* release profile, which cover a wide variety of release profile shapes.
Optimization Target Criteria

When fitting the *in vivo* release profile against the entire observed Cp-time profile, the error on Cmax is often higher than allowed by the IVIVC criteria due number of other concentration points outweighing the contribution of the single Cmax value.

This issue will be addressed by adding option to include additional weight on Cmax during deconvolution in IVIVCPlus™ module.

Simulated Cp-time profiles for 3 naltrexone LAI microsphere formulations.

Top row shows deconvolution results with target observed Cp-time profile,

Bottom row shows deconvolution results with additional weight added to Cmax value.
Insufficient *in vitro* Sampling

Insufficient *in vitro* sampling may cause difficulties matching the shape of the predicted Cp-time profile even with an otherwise valid IVIVC (correct prediction of Cmax and AUC). This issue will be addressed by adding an option to use interpolated *in vitro* profile in IVIVCPlus module.

IVIVC for huperzine A LAI microspheres. Plots on the left are showing IVIVC created from 2 LAI formulations using only the measured *in vitro* points (top) and interpolated *in vitro* points at the early timepoints (bottom). Plots on the right are showing corresponding predicted and observed Cp-time profiles for third LAI formulation.
Variability in IVIVC Across Formulations

The \textit{in vivo} release profiles were successfully deconvoluted using a triple-Weibull function for all formulations; however, the differences in the deconvoluted \textit{in vivo} release profiles are not accurately captured by the differences in the measured \textit{in vitro} release profiles.

Literature search was performed to identify possible mechanisms responsible for differences between \textit{in vitro} and \textit{in vivo} release for LAI formulations.

Top: Simulated Cp-time profiles for 4 orntide LAI microsphere formulations after successful deconvolution of \textit{in vivo} release profiles.

Bottom: Deconvoluted \textit{in vivo} release profiles (left) and IVIVC plot (right) for 4 orntide LAI microsphere formulations.
The Tissue Response to PLGA Microsphere Administration

- The tissue response to PLGA microsphere administration can be divided into three phases:
  1. Acute phase of the inflammatory response
  2. Onset of the chronic phase of inflammation
  3. Fibroblasts infiltration and collagen deposition

The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres
Quantitative Evaluation and Modeling of the Depot Infiltration: Immune Cell Layer

Darville et al, Toxicologic Pathology, 2016, Vol. 44(2) 189-210

Depot

Infiltrated cells
Intramuscular: Immune Cell Layer
Outcomes

- Implementing *in vitro* drug release from PLGA microspheres in DDDPlus.

- Additional functionalities added to the IVIVC module in GastroPlus
  - *Triple Weibull* function for deconvolution
  - The capability of perfuming IVIVC using *interpolated data*
  - Adding *Shifting and Scaling* function to the list of correlation functions
  - Adding users the capability of choosing different optimization function as part of deconvolution
  - Adding the option for *Setting the intercept to zero* to Deconvolute then Correlate.
  - Adding Intramuscular and Subcutaneous route of administration to the IVIVC module in GastroPlus.

- Immune Cell Layer (ICL) Model
Summary

• The mechanistic absorption model-based IVIVC was improved to be able to successfully deconvolute the *in vivo* dissolution profile for LAI based on clinical PK data.

• Correlation process was improved to better linked in *vitro* and *in vivo* release profiles

• Other mechanism seem to be important *in vivo*: inflammation and immune cell infiltration

• Regulatory agencies have access to these models and will use them for BE guidance development and reviews
Publications/Presentations

- Jul 16, 2017-CRS
  Simulation of in vitro Dissolution and Degradation of Orntide-loaded PLGA Microspheres
  Mullin J, van Osdol W, Lukacova V, Woltosz WS, Bolger MB

- Nov 2016-AAPS
  Development of an In Vitro Mechanistic Model that Describes Drug Release from Risperidone Long Acting Injectable Microspheres
  James Mullin; Viera Lukacova; Walter Woltosz; Michael B. Bolger

- Nov 14, 2017-AAPS
  Development of In Vitro-In Vivo Correlation for Long Acting Injectable Microsphere Formulations
  Shahraz A, Mullin J, Spires J, Lukacova V, Bolger MB, Woltosz WS

- Poster accepted for ACoP10
  Modeling and Simulation of the Local Tissue Response to Long-acting Injectable Formulations
  Azar Shahraz, James Mullin, Viera Lukacova
GastroPlus® PBPK Consulting: Regulatory Submissions

• Since 2016, our consulting team has built PBPK models for over 110 applications, some of which were used to support submissions to various regulatory agencies:
  – Preclinical development and First-in-Human predictions
  – Formulation optimization
  – DDI predictions
  – Virtual bioequivalence trial simulations
  – Pediatric population simulations and dose projections
  – Food effect modeling
  – Parent-metabolite and prodrug PBPK modeling
  – Pulmonary/dermal/oral cavity product assessment
  – Mechanistic IVIVCs to define product specifications
Key Points to be Addressed to Regulators

- Objective and intended regulatory purpose of the PBPK modeling
- Sufficient background information to place the PBPK modeling in its context in the clinical development of the drug
- Model validation and explicit/systematic discussion of the assumptions made in the submitted drug model and analysis, i.e. supportive data and biological plausibility and impact of the assumptions on the model and the outcome
- Sensitivity analysis, especially on the parameters that were fitted in the model
Questions?