MODEL-INFORMED DRUG DEVELOPMENT (MIDD): OPPORTUNITIES AND CHALLENGES

Shiew-Mei Huang, PhD  for Issam Zineh, PharmD, MPH
Office of Clinical Pharmacology | Office of Translational Sciences
Center for Drug Evaluation and Research | US FDA

Pharmaceutical Science and Clinical Pharmacology Advisory Committee
March 15, 2017
The State of Pharmaceutical R&D

Average time to develop a drug = **10 to 15 years**
Percentage of drugs entering clinical trials resulting in an approved medicine = less than **12%**

**RESEARCH AND DEVELOPMENT (R&D)**

**KEY DRIVERS of increasing R&D costs:**
- increased clinical trial complexity
- larger clinical trial sizes
- greater focus on targeting chronic and degenerative diseases
- higher failure rates for drugs tested in earlier phase clinical studies

**Average Cost to Develop One New Approved Drug—Including the Cost of Failures (in Constant 2013 Dollars)**

- **1970s**: $179M
- **1980s**: $413M
- **1990s-early 2000s**: $1.0B
- **2000s-early 2010s**: $2.6B
Regulatory Science
Science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products

Vision
FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.
FDA Science Priority Areas

1. **Modernize toxicology to enhance product safety**

2. **Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes**

3. Support new approaches to improve product manufacturing/quality

4. Ensure FDA readiness to evaluate innovative emerging technologies

5. **Harness diverse data through information sciences to improve health outcomes**

6. Implement a new prevention-focused food safety system

7. **Facilitate development of MCM to protect against threats to health**

8. Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products

*UNDERLINED* denotes priority area for which implementation plan has specific model-based strategies
Increased Focus on Advancing Regulatory Science

1993-1997: PDUFA I
- Review backlog

1998-2002: PDUFA II
- Review times and procedures

2003-2007: PDUFA III
- Increased interaction; support for post-market safety

2008-2012: PDUFA IV
- Enhance pre-market review; modernize post-market safety system

2013-2017: PDUFA V
- Review+ comms enhancement; strengthen regulatory science & post-market safety; electronic data standards

2018-2021: PDUFA VI
- Program/process enhancement; HR; IT; enhance regulatory science & promote innovative tools

More info @ http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm | Modified from J. Barton, OSP/CDER/FDA
Model-Informed Drug Development

• “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)

<table>
<thead>
<tr>
<th>Indication</th>
<th>MBDD approach adopted</th>
<th>Efficiencies gained over historical designs and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design</td>
<td>2,750 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Model-based dose–response relationship</td>
<td>1,000 Fewer patients</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Prior data supplementation, model-based dose–response relationship, sequential design</td>
<td>760 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Prior data supplementation, model-based dose–response relationship</td>
<td>120 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Model-based dose–response relationship</td>
<td>1,025 Fewer patients</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Model-based dose–response relationship</td>
<td>437 Fewer patients, increased probability of success</td>
</tr>
<tr>
<td>Global anxiety disorder</td>
<td>Omit phase IIb</td>
<td>260 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
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</tbody>
</table>

MBDD, model-based drug development.

• FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty

Physiologically-based PK Modeling
## PBPK Modeling for New Drugs: Current Status

<table>
<thead>
<tr>
<th>Applications</th>
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<td>Tissue concentration, drug delivery for locally-acting products</td>
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Wagner 2015 [PMID 26225246] | Slide courtesy of P. Zhao (OCP) and L. Zhao (OGD)
Increasing interest in using PBPK models to support regulatory evaluation in the realm of generic drug development

Modified from L. Zhao (OGD, CDER, FDA)
Safety-Related Attrition

Adapted from Redfern (2010) and Koistinen (www.imi-safe-t.eu/files/files-inline/Safety_Biomarkers.pdf)
PMRs for New Drug Approvals: 2012-2016

Data courtesy S. Pepe, Office of Translational Sciences, FDA
**Comprehensive in vitro Proarrhythmia Assay (CiPA)**

**Goal:** Develop a new *in vitro* paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential.

|---|---|---|---|

**Graphs and Formulas:**

1. $I_{Na}$, $I_{NaL}$, $I_{Ca,L}$, $I_{to1}$, $I_{Kr}$, $I_{Ks}$, $I_{K1}$

2. $I_{stim} = C \frac{dV}{dt} + I_m$

3. Image of ventricular cardiomyocytes

4. Image of ECG tracings

*Modified from Hoekstra et al., 2012*
MIDD Challenges

• Best practices for determining a model is fit-for-purpose (validation, performance/sensitivity metrics, platform independence)
• Identification and transparent communication of knowledge gaps
• Data/knowledge warehouses
• Varying degrees of comfort by end-users
• Clarity on regulatory expectations
PBPK
Advisory Committee Questions

1. What information should be included in a PBPK submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?

2. Based on the proposed workflows as examples, please discuss:
   a. What criteria should be used to determine that the model is adequately verified for the intended purpose?
   b. When a model needs modification, what considerations should be given related to modifications of model structure, and/or parameter estimates?
Mechanistic Safety (CiPA)
Advisory Committee Questions

1. For a QT prolonging drug, will this mechanistic, model-based approach be fit for the following 2 applications:
   a. Determining whether ECGs need to be collected in Phase 3?
   b. Informing proarrhythmic risk language in drug labeling?

2. Does the AC agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate, and high risk by an expert panel? If not, what else should be done?

3. As this new mechanistic, model-based approach is implemented, should FDA collect the world’s experience (i.e. digital waveform data from in vitro experiments) to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?
Overview of the Day

• **Session 1: Role for PBPK M&S in Drug Development and Regulation**
  - Overview of multi-regional regulatory experience and issues
  - Drug development point of view

• **Session 2: Mechanistic Model-informed Safety Evaluation: CIPA as an Example**
  - Motivation, progress, and outstanding issues with model-informed dysrhythmia assessment

• **Concluding Remarks**
  - Dr. Kathleen Uhl, Director, Office of Generic Drugs (FDA)
Towards Consistent Regulatory Assessment of Physiologically-based Pharmacokinetic Modeling to Support Dosing Recommendations

Ping Zhao, PhD
Division of Pharmacometrics, Office of Clinical Pharmacology
Office of Translational Sciences, CDER, FDA

FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting
March 15, 2017, Washington, DC
Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

A. Intrinsic/extrinsic Factors

B. PBPK Model components

Predict, Learn, Confirm → Apply

Individual or combined effects on human physiology

Degree of complexity of the PBPK model can vary according to the need

Huang and Temple, 2008

System component (drug-independent)

Drug-dependent component

Lung

Rapidly perfused organs

Blood

Slowly perfused organs

Kidney

Liver

Intestines

ADME, PK, PD and MOA

Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding
PBPK submissions to the FDA since 2004

<table>
<thead>
<tr>
<th>As of June, 2014</th>
<th>As of Aug, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 96 (60% DDI)</td>
<td>n = 217 (60% DDI)</td>
</tr>
</tbody>
</table>

Sinha, MHRA Workshop, 2014
Zhao, EMA Workshop, 2016

DDIs: Drug-drug Interactions

PBPK supporting dosing recommendations in US prescribing information (38 cases 2009-2016)

Greater confidence in predicting DDIs

Examples in backgrounder
Outline

• Evidence based establishment of predictive performance and workflow for intended uses

• Policy development towards consistent assessment of PBPK submissions
Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

**PBPK Model Describes the Effects of Comedication and Genetic Polymorphism on Systemic Exposure of Drugs That Undergo Multiple Clearance Pathways**

MdLT Vieira¹, M-J Kim¹, S Apparaju¹, V Sinha¹, I Zineh¹, S-M Huang¹ and P Zhao¹

*Clin Pharmacol Ther, 2014*

**Predicting the Effect of Cytochrome P450 Inhibitors on Substrate Drugs: Analysis of Physiologically Based Pharmacokinetic Modeling Submissions to the US Food and Drug Administration**

Christian Wagner · Yuzhuo Pan · Vicky Hsu · Joseph A. Grillo · Lei Zhang · Kellie S. Reynolds · Vikram Sinha · Ping Zhao

*Clin Pharmacokinet 2015*

**Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic (PBPK) Modeling: An Analysis of PBPK Submissions to the US FDA**

Christian Wagner¹ · Yuzhuo Pan² · Vicky Hsu¹ · Vikram Sinha¹ · Ping Zhao¹

*Clin Pharmacokinet 2016*
Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

\[ R_{pred/obs} = \frac{Pred.Exposure Ratio}{Obs.Exposure Ratio} \]

Exposure ratio: AUC or Cmax ratio (w/wo modulator)

<table>
<thead>
<tr>
<th></th>
<th>CYP Inhibition (Vieira, 2014)</th>
<th>CYP Inhibition (Wagner/Pan, 2015)</th>
<th>CYP3A Induction (Wagner, 2016)</th>
</tr>
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<tbody>
<tr>
<td>Substrates evaluated</td>
<td>4</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>DDI cases to predict (external verification)</td>
<td>20</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Organization</td>
<td>FDA</td>
<td>9 sponsors</td>
<td>6 sponsors</td>
</tr>
<tr>
<td>Substrate model predicts base PK (≤2-fold of observed clearance)</td>
<td>100%</td>
<td>87%</td>
<td>91%</td>
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<tr>
<td>(0.80 \leq R_{pred/obs} \leq 1.25)</td>
<td>72% AUC; 70% Cmax</td>
<td>81% AUC; 77% Cmax</td>
<td>77 % AUC; 83% Cmax</td>
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<tr>
<td>(0.50 \leq R_{pred/obs} \leq 2.00)</td>
<td>100%</td>
<td>100%</td>
<td>77% AUC; 92% Cmax</td>
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<tr>
<td>(R_{pred/obs} &gt; 2.00)</td>
<td>0</td>
<td>0</td>
<td>23% AUC; 8% Cmax</td>
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Cut-off values are arbitrary

- Under-prediction of induction using rifampicin model
- Rifampicin induces non-CYP3A pathways
Established predictive performance allows the use of PBPK to predict the effect of CYP modulation.

**Substrate Model**
- Build: in vitro + human single dose PK
- Verify: other PK; Consider nonlinearity

**Inhibitor/inducer Model**
- Build: DDI mechanisms
- Verify: DDI with probes

- Predict interactions
- Prioritize, plan and design the critical study

- Verify and modify (if necessary) substrate model

- Predict untested scenarios
- Support dose recommendations

Wagner, CPT-PSP, 2015
## PBPK applications: current status

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Updated from Wagner, CPT-PSP, 2015.
Pediatrics: PROSPECTIVE prediction relies on confidence in relevant system parameters

**PBPK model in adults**

- Drug parameters
- System parameters (Adults)

**PBPK model in children**

- Drug parameters
- System parameters (pediatrics)

**Intended uses**

- ✓ Optimize design of “first in pediatric” PK study
- ✓ Inform physiological model with pediatric PK data (Learning)
- x Inform dosing in pediatrics in lieu of PK study
Proposed workflow to predict drug PK in a specific population using PBPK

Drug model
- Verify drug model for healthy adult subjects
  - No
  - Does drug model account for key ADME processes of the investigational drug?
    - No
    - Yes

Physiological model
- Establish model for various physiological or disease stages
  - No
  - Does model account for changes relevant to ADME processes of the investigational drug?
    - No
    - Predict drug PK in a specific population

Modified from Zhao P, “The Readiness and Specific Paths of Using PBPK to Support Dosing Recommendation in Patients with Renal Impairment”, 2017 ASCPT Annual Meeting
Advisory committee questions

1. What information should be included in a physiologically-based pharmacokinetic (PBPK) submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?

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Outline

• Evidence based establishment of predictive performance and workflow for intended uses

• Policy development towards consistent assessment of PBPK submissions
Policy development on PBPK

2010

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

2012

Best Practice in the Use of Physiologically Based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Regulatory Questions

2014

Concept paper on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and analyses

2015

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

2015

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation
**PBPK guideline and guidance in 2016**

### Scope

<table>
<thead>
<tr>
<th>Question</th>
<th>EMA</th>
<th>FDA</th>
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<tbody>
<tr>
<td>How well can PBPK predict?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>How should PBPK submissions be prepared?</td>
<td>✓</td>
<td>✓</td>
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**European Medicines Agency (EMA)**

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

- **Draft agreed by Modelling and Simulation Working Group**: April 2016
- **Draft agreed by Pharmacokinetic Working Party**: May 2016
- **Adopted by CHMP for release for consultation**: 21 July 2016
- **Start of public consultation**: 29 July 2016
- **End of consultation (deadline for comments)**: 31 January 2017

**Keywords**: pharmacokinetics, modelling, simulation, qualification, predictive performance


**Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry**

DRAFT GUIDANCE

- **U.S. Department of Health and Human Services**
- **Food and Drug Administration**

FDA Draft PBPK Guidance

- To facilitate efficient, timely and consistent FDA review of applications using PBPK
- Does not address methodological considerations and best practices for the conduct of PBPK modeling and simulation, or the appropriateness of PBPK analyses for a particular drug or a drug product
- Received 10 comments from individual pharmaceutical companies, consortiums, regulatory agencies, and individuals within two months public comment period (Closed on Jan 31, 2017)

Summary

• PBPK analyses are routinely submitted to the FDA

• Confidence varies, depending on predictive performance for intended purposes

• Establishing confidence in physiological (drug independent) model is crucial for effective use of PBPK
Absorption PBPK Modeling and Applications to Support Formulation and Generic Drug Development

Liang Zhao, PhD
Division of Quantitative Methods & Modeling
Office of Research and Standards, Office of Generic Drugs
CDER, FDA

FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting
March 15, 2017, Washington, DC
Outline

• Focus of my presentation (absorption model)

• Case example to illustrate utilities of absorption models

• Summary
Advisory Committee Questions

1. What information should be included in a physiologically-based pharmacokinetic (PBPK) submission to the FDA to ensure adequacy of an analysis for its intended purpose? Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submissions will be used (e.g., to inform clinical study planning vs. labeling or regulatory decision making). What are the principles or criteria that should be considered?

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## NDA vs. ANDA Review Process

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<th>Generic Drug ANDA Requirements</th>
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<tbody>
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<tr>
<td>3. Controls</td>
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<tr>
<td>4. Microbiology</td>
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</tr>
<tr>
<td>5. Biopharmaceutics</td>
<td>5. Biopharmaceutics</td>
</tr>
<tr>
<td>6. Preclinical Studies</td>
<td></td>
</tr>
<tr>
<td>8. Clinical Studies</td>
<td></td>
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**BE:** Is the drug delivered to the action site in the same way for different formulations?

If yes, brand product can be substituted by generics upon their approval.

ANDA: abbreviated new drug application; NDA: new drug application
Modeling and Simulation Impact Various Regulatory Activities in the Office of Generic Drugs (Calendar Year 2016)

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
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</tr>
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<tbody>
<tr>
<td>ANDA Reviews &amp; Citizen petitions</td>
<td>22</td>
<td>- Implement clinical relevant PK metrics for BE assessment</td>
</tr>
<tr>
<td>Pre-ANDA interactions (including CC)</td>
<td>26</td>
<td>- Development of BE criteria for analgesics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assessment of BE standards for GI locally acting products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Simulation of in vivo alcohol dose dumping studies</td>
</tr>
<tr>
<td>BE Guidances</td>
<td>31</td>
<td>- Simulations for the development of BE criteria for HVDs and NTI drugs</td>
</tr>
<tr>
<td>Regulatory Research Studies</td>
<td>30</td>
<td>- Pharmacokinetic(PK)/Pharmacodynamic (PD) modeling and simulation to determine the appropriate study design and evaluate clinical endpoint sensitivity for BE assessment</td>
</tr>
</tbody>
</table>

ANDA: abbreviated new drug application; BE: bioequivalence; CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.
Modeling and Simulation for Generic Drug Development

- OGD uses modeling and simulation to evaluate deviations from guidance or unusual review situations

- The generic industry could use Model-Informed Drug Development (MIDD) before they propose novel methods in an ANDA to support new BE approaches

- The committee questions are intended to inform industry and FDA on good model based submissions
Physiologically Based Models

Drug Substance Formulations
In Vitro Testing

Physiological System

In vivo Performance

Factors Affecting Oral Absorption

Source: Xinyuan (Susie) Zhang
Workflow of Oral Absorption Modeling

Construct the PK model: (1). If human PK data are available, deconvolute PK data from i.v. administration (ideally) and/or p.o. administration of the fastest dissolving formulation to obtain disposition model; (2). If no human data, predicted from in vitro or animal data.

Collect drug information: formulation information, physicochemical properties, gut and liver extraction ratio, and etc.

Fix the parameters with high confidence in the ACAT model and optimize the parameters with high uncertainty to fit PK data obtained from another formulation.

Validate the model with different PK data set(s): different dosing regimens, different formulations, and different food conditions, etc.

Does the model predict the trend? Do we have enough confidence about the model?

Yes

Model exploration: (1) perform PSA to identify the key parameters in the formulation under different conditions to guide the next formulation design to achieve the target PK profile; (2) deconvolution of PK data to obtain in vivo dissolution profile and to identify biorelevant dissolution conditions by comparing with in vitro dissolution profiles; (3) simulate different dosing regimens; (4) conduct virtual BE study; (5) connect the PK model with a PD model; etc.

PSA: parameter sensitivity analysis

What is a Virtual BE Study?

• Use of model to compare test and reference formulations

• The model must have a formulation variable that can be adjusted to represent the difference between T and R

• The model generates a population for BE study, compares T and R in that population
  – Simulate many studies to estimate probability of success or failure

BE: bioequivalence; T: test product; R: reference product
General PBPK Model Applications for Generic Products

- Dissolution
- Locally acting product assessment
- Product quality
- In vivo alcohol dose dumping simulation
- Waiver of in vivo studies
- GI local concentration
- Specific populations
- Mechanism change risks
- PPI - DDI

Increasing trends in using PBPK models to support regulatory decision makings in the realm of generic drug development

BE: bioequivalence; PPI: proton pump inhibitor; GI: gastrointestinal; DDI: drug-drug interaction
## Highlights of PBPK Impacts (Year 2016)

<table>
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<tr>
<th>Category</th>
<th>Example Drug</th>
<th>Impact on regulatory decision making</th>
</tr>
</thead>
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<tr>
<td>Dissolution</td>
<td>Fingolimod, Oxybutynin</td>
<td>Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths</td>
</tr>
<tr>
<td>Product quality</td>
<td>Prasugrel</td>
<td>Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI</td>
</tr>
<tr>
<td>Mechanism change risks</td>
<td>Venlafaxine</td>
<td>Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism</td>
</tr>
<tr>
<td>PPI effect</td>
<td>Several ER products</td>
<td>Risk assessment of changing drug release to a PH dependent mechanism</td>
</tr>
<tr>
<td>PK metrics determination</td>
<td>Mesalazine Suppositories</td>
<td>Determination of PK metrics for BE evaluation</td>
</tr>
<tr>
<td>Alcohol dose dumping</td>
<td>Metformin Hydrochloride ER Tablet</td>
<td>Assessment of alcohol dose dumping potential</td>
</tr>
<tr>
<td>Virtual simulation</td>
<td>Methylphenidate</td>
<td>Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE assessment</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor; ER: extended release
Case: Oxybutynin HCl ER Tablets

• Intended Purpose of the Model
  o To quantitatively describe the delay in oxybutynin absorption when oxybutynin is formulated as an enteric-coated matrix tablet compared to an OROS® tablet
  o To assess the risk of not conducting BE study for the lower strengths of oxybutynin extended release products

• Model Development and Parameter Estimation
  o In vivo dissolution
Oxybutynin Properties

- High solubility, High permeability
- pKa: 7.88 (base)
- logP: 4.87
- Half-life: 2-3 h
- Metabolized by CYP3A4 (gut, liver)
- Relief from urinary and bladder difficulties (frequent urination, inability to control urination)
- Extended release dosage forms (osmotic pump and enteric-coated matrix)
- No reported food effect

Certain properties are predictions from GastroPlus, ADMET Predictor v7.2.0.0
Prescribing Information Ditropan XL, Drugs@FDA
Benet et al. AAPS J 13, 519-547 (2011)
PBPK Absorption Modeling Approaches

Model was developed based on in vitro data (drug physicochemical properties and metabolism) and i.v. and oral PK data.

Fit in vitro dissolution profiles as model input-Weibull function and establish in vitro-in vivo correlations (IVIVC) or relationships (IVIVR).

Leverage human observed data obtained from bioequivalence studies evaluating osmotic pump and enteric-coated matrix delivery systems.

\[
\%\text{Drug Release} = Max \times \left( 1 - f_1 \times \exp\left[-\frac{(t-\text{lag})}{a_1}\right] - f_2 \times \exp\left[-\frac{(t-\text{lag})}{a_2}\right] \right)
\]

Perform simulations to answer specific questions utilizing the developed IVIVC/IVIVRs.

Source: Eleftheria Tsakalozou & Xinyuan (Susie) Zhang
Models Described Observed Data Reasonably Well

Dose level: 15 mg oxybutynin, PK data extracted from 5 ANDAs submitted to USFDA
Risk Assessment for Not Conducting In Vivo Studies in Lower Strength Oxybutynin Generic Products

**In vitro dissolution**

**Simulated PK profiles for different formulations under fasting and fed conditions**

**Bioequivalence evaluation of lower strengths osmotic pump oxybutynin drug products leveraging developed IVIVR.**
Case Conclusions

• In vitro dissolution does not appear to be predictive of in vivo drug release

• Developed mechanistic absorption pharmacokinetic models
  o described well oxybutynin disposition following administration of oxybutynin formulated as an OROS or enteric-coated matrix extended release formulations under fasting and fed conditions.
  o captured the multiple peak PK profile observed with enteric-coated matrix formulations.

• Established IVIVR
  o can be utilized for risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths.
Revisiting Model Qualification

Formulation Characteristics
Excipient target profiles

Fixed system parameters & variability

In vitro testing
Parameters to be fitted + variability

Model Building

Model qualification

BE data
In vivo studies

Qualification/Application

Regulatory decision making
Key Questions for Inputs

• Should model modification/verification be based on the intended purpose

• Based on the proposed workflows as described in AC briefing package, please discuss:
  – What criteria should be used to determine that the model is adequately verified for the intended purpose?
  – When the model needs modification, what considerations should be given related to modifications of model structure, and/or parameter estimates?