FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop

Breakout session 4:
Data Analysis and Model-Based Bioequivalence
Session summary

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Office of Research and Standards, Office of Generic Drugs, CDER, FDA

Expert Discussants

- **Liang Zhao, PhD** – FDA, CDER/OGD/ORS/DQMM, Session moderator
- **Amin Rostami, PhD** – University of Manchester, Centre for Applied Pharmacokinetic Research
- **Andrew Hooker, PhD** – Uppsala University, Department of Pharmaceutical Biosciences
- **Charlie DiLiberti** – Montclair Bioequivalence Services, LLC
- **Glenys Barber, PhD** – University of Manchester
- **Sandra Suarez-Sharp, PhD** – Simulations Plus, Inc.
- **Viera Lukacova, PhD** – Simulations Plus, Inc.
- **Stella C. Grosser, PhD** – FDA, CDER/OTS/OB (Office of Biostatistics)/DBVIII
- **Stephan Schmidt, PhD** – University of Florida, Center for Pharmacometrics & Systems Pharmacology
- **Sid Bhoopathy, PhD** – Absorption Systems
- **Raja Velagapudi, PhD** – Sandoz Pharmaceuticals, Clinical Development (US)
- **Lanyan (Lucy) Fang, PhD** – FDA, CDER/OGD/ORS/DQMM
- **All break out session participants**

Presentation

Speaker	Topics
Charlie DiLiberti	Modeling to Support Relaxation of Compositional/Microstructural Criteria to Qualify for Streamlined Bioequivalence Approaches
Sid Bhoopathy	Model Informed BE Expanding the Reach and Utility
Amin Rostami	Virtual BE: Requirement for Prudent Use of PBPK in Uncharted Territories
Andrew Hooker	Improved BE Assessment through Model-informed and Model-based strategies
Stephan Schmidt	A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution
Sandra Suarez-Sharp; Viera Lukacova	Comments to each question

Presentation Summary

- **Modeling and simulation can accelerate generic drug development and assessment**
  - Prior knowledge exists from new drug
  - Generating model integrated evidence for generic drug development and assessment

- **There are emerging quantitative methods and modeling expertise/tools in implementing new BE approaches for various purposes.**

Panel Discussions (1)

- **How to evaluate data from in vitro studies and which in vitro studies are clinically relevant**
  - Solid oral dosage forms: in vitro release/dissolution testing is the quality attribute that best represents the drug product performance
  - Using modeling methods to probe the impact of deviations from narrow compositional/microstructural criteria on expected product performance in vivo
  - BCS 3 waiver expansion for other “non-qualifying” oral drug products
    - Expanding the reach and utility of modeling supported BE to more product categories
    - Application of PBPK model

Panel Discussions (2)

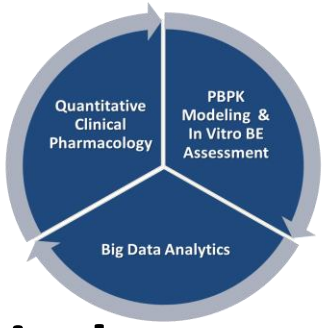
- **What are the challenges for industry in implementing PBPK/absorption models to support more efficient BE methods (such as alternatives to comparative clinical endpoint BE studies)?**
  - Improved understanding of the biological systems is needed
    - GI tract is dynamic + all levels of variability
    - Formulation-dependent interactions with GI tract
  - Uncertainty of the model which best describes the system; Bias or misspecification of model parameters
  - Global harmonization & regulatory guidance

Panel Discussions (3)

- **What are the emerging QMM expertise/tools in implementing new BE approaches?**
  - NLME modeling informed & based BE approaches
    - Virtual BE simulations
    - Optimal design methodology for BE studies
    - Model averaging to address model mis-specification
  - PBPK modeling
    - Using model to justify/qualify streamlined BE approaches
    - Usage of PBPK model to support alternative BE methods
    - Pharmacologically feasible aberrant observations
  - Combined Bio-informatics, PBPK and PKPD approach
    - Probe statistically significant and mechanism-plausible real-world signals

Final Remarks

- **Significant opportunities exist to apply modeling methods in generic drug development and assessment.**
  - Vision: Accelerate development and regulatory assessment of generic products by modeling and simulation
- **Division of Quantitative Methods and Modeling (DQMM)/ORS/OGD**
  - Quantitative Clinical Pharmacology (QCP)
  - PBPK for locally acting product
  - PBPK for orally administered drugs
  - Data Analytics



- **More collaborations among FDA, industry and academia are needed to close scientific gaps in the use of modeling and simulation in generic drug development and assessment.**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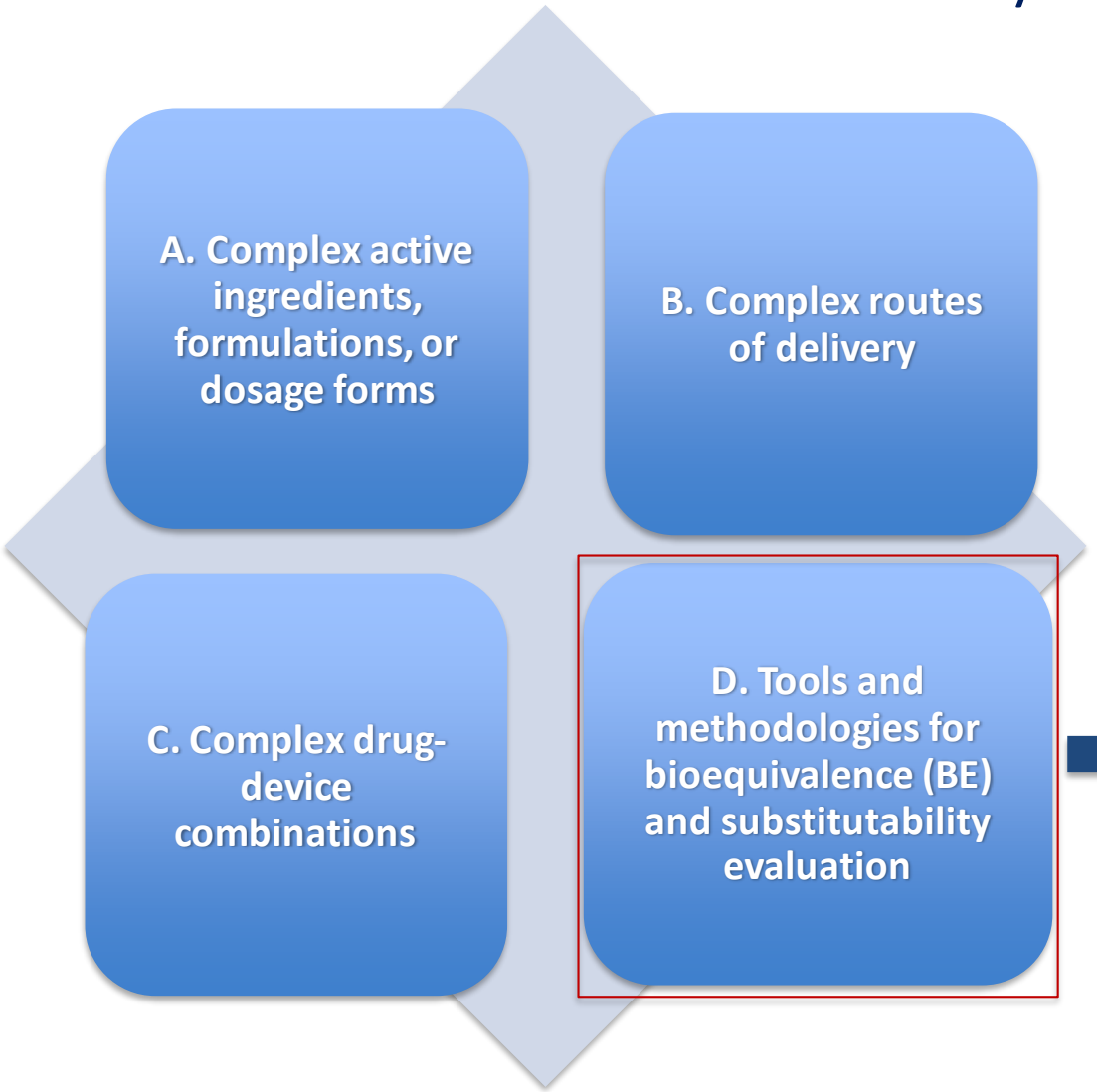
FY2020 GDUFA Research Science Priorities

that are most relevant to Data Analysis and Model-Based Bioequivalence



- D1. Improve **quantitative pharmacology and BE trial simulation** to optimize design of BE studies for complex generic drug products
- D2. **Integrate predictive dissolution, PBPK and Pharmacokinetic/Pharmacodynamic (PK/PD) models** establishing generic drug bioequivalence standards
- D3. Expand the scientific understanding of the role of excipients in generic drug products to support **the expansion of BCS Class 3 biowaivers** to drug products with differences in formulations larger than currently recommended in FDA guidance
- D4. **Develop methods and integrated technological solutions that will allow FDA to leverage large data sets** (such as bioequivalence study submissions, electronic health records, substitution/utilization patterns, drug safety data, and drug quality data) to support regulatory decisions and improve post-market surveillance of generic drug substitution

https://www.fda.gov/media/132370/download

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Team 1: Quantitative Clinical Pharmacology

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Yuqing Gong, PhD,
Xing Jing, PhD

Team 2: PBPK for Locally Acting Products

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Team Leader

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Mingliang Tan, PhD

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Team 3: Oral PBPK

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Science Lead

Team 4: Data Analytics

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