Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review from the FDA perspective

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Latest Messages for Quantitative Methods and Modeling (QMM)

Commissioner Dr. Gottlieb

In silico clinical trials use computer models and simulations to develop and evaluate devices and drugs. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs

-- 7/7/2017 Blog

This starts with better use of more advanced computing tools, and more sophisticated statistical and computational methodologies, as part of the drug development and the drug review process. This includes more widespread use of modeling and simulation, and high performance computing clusters inside FDA

-- 9/11/2017 to the Regulatory Affairs Professionals Society (RAS) 2017 Regulatory Conference

on that pre-ANDA area ... And we would expect that they have done modeling in order to have that meeting and have an informed conversation and discussion."

-- 3/15/2017 to the Pharmaceutical Science and Clinical Pharmacology Advisory Committee

OGD director Dr. Uhl

Modernize ANDA Program to Make High Quality Generic Products Quickly Accessible

- Increase first cycle approval rate; decrease number of review cycles
- Shorten drug development timeline
- Reduce costly but insensitive in vitro/in vivo studies
- Reduce chance of exposing human subjects to otherwise unnecessary studies
- Ensure timely availability of high quality and affordable generics for patients
- ***The above goals are especially important for locally acting, complex, and modified release products***

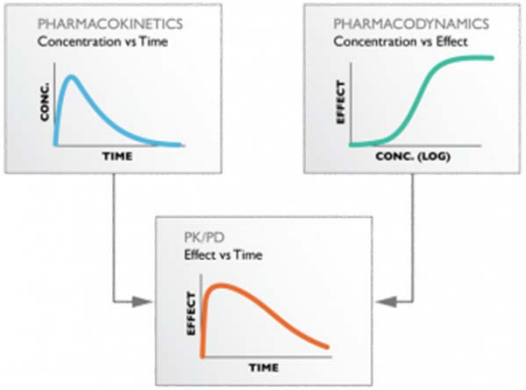
Core Tool Sets

Non-Oral Drug

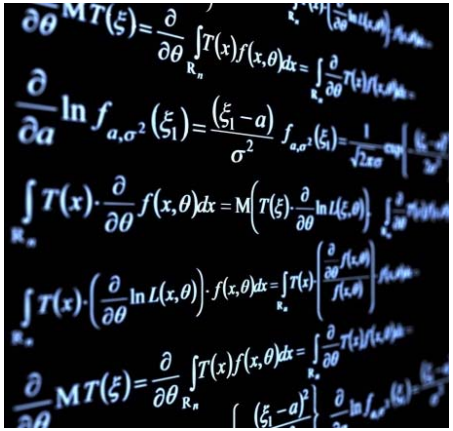
Oral Drug

Our Goal is to facilitate

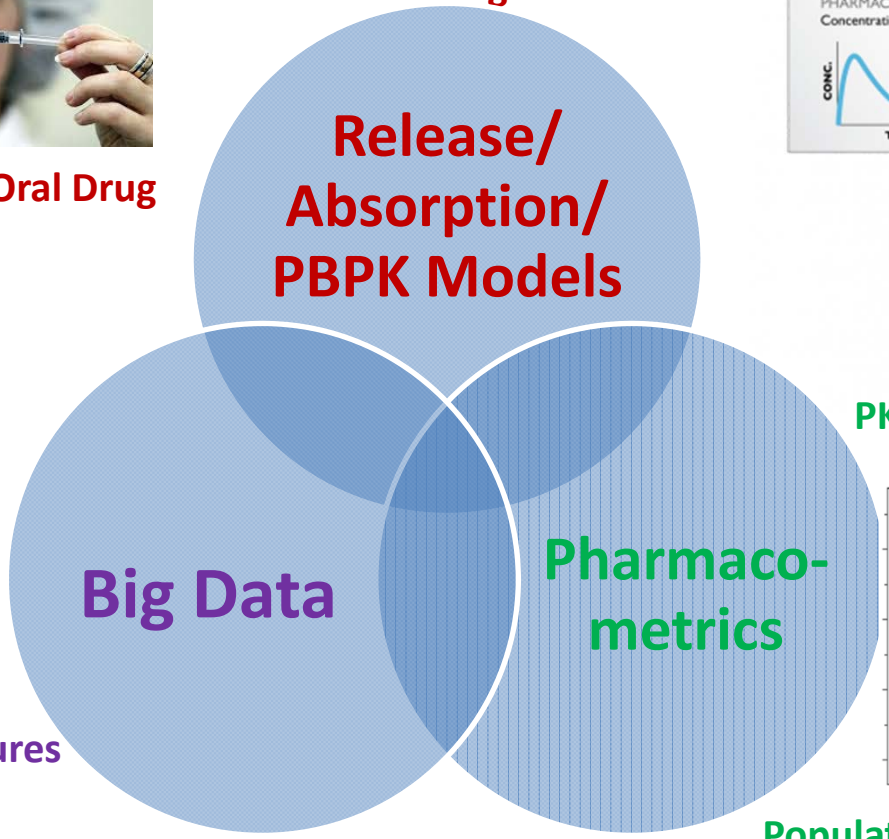
- Generic drug development/review
- Policy development
- Regulatory decisions

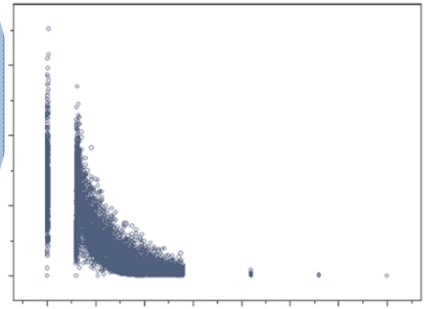


PK-PD model



Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





Population based model

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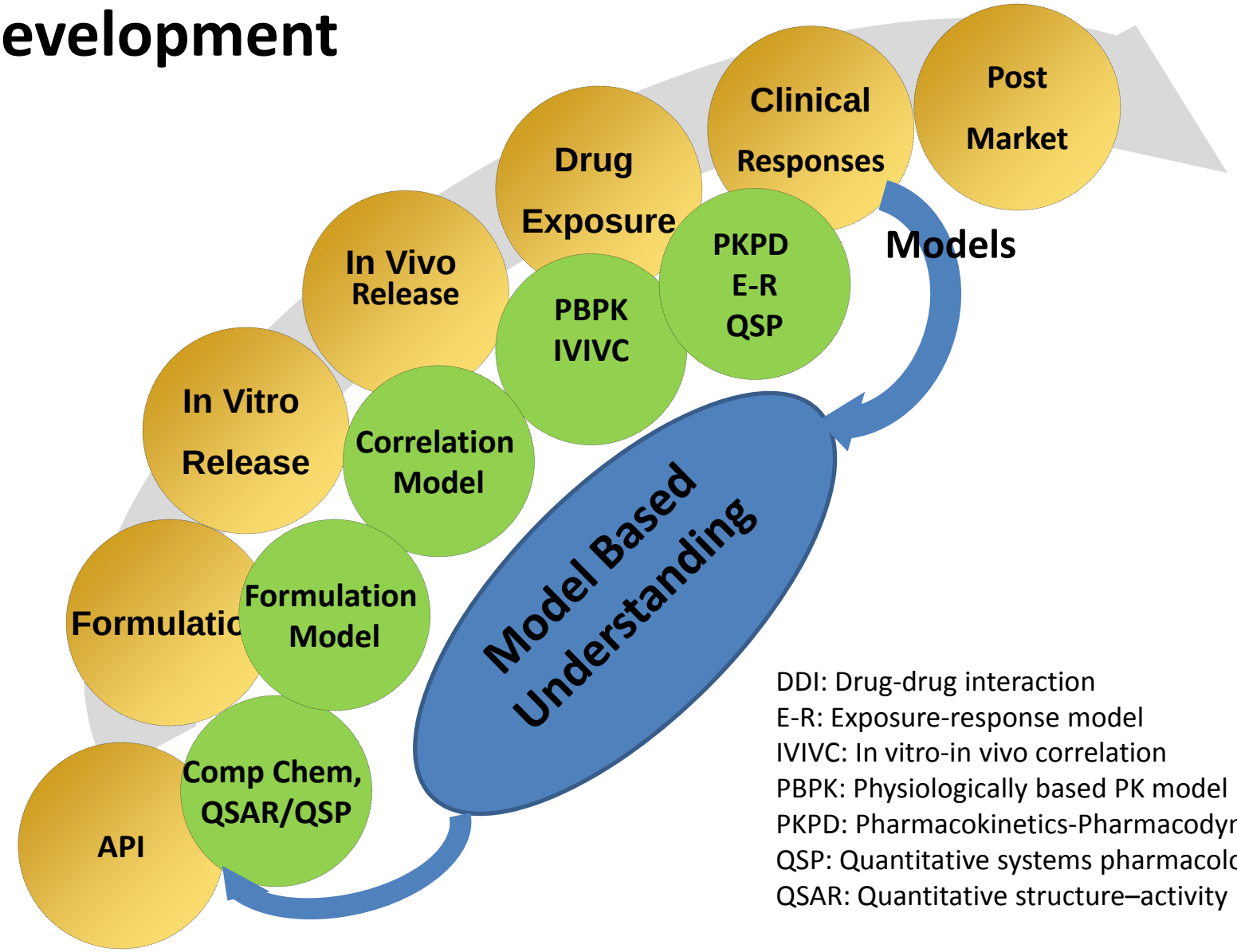
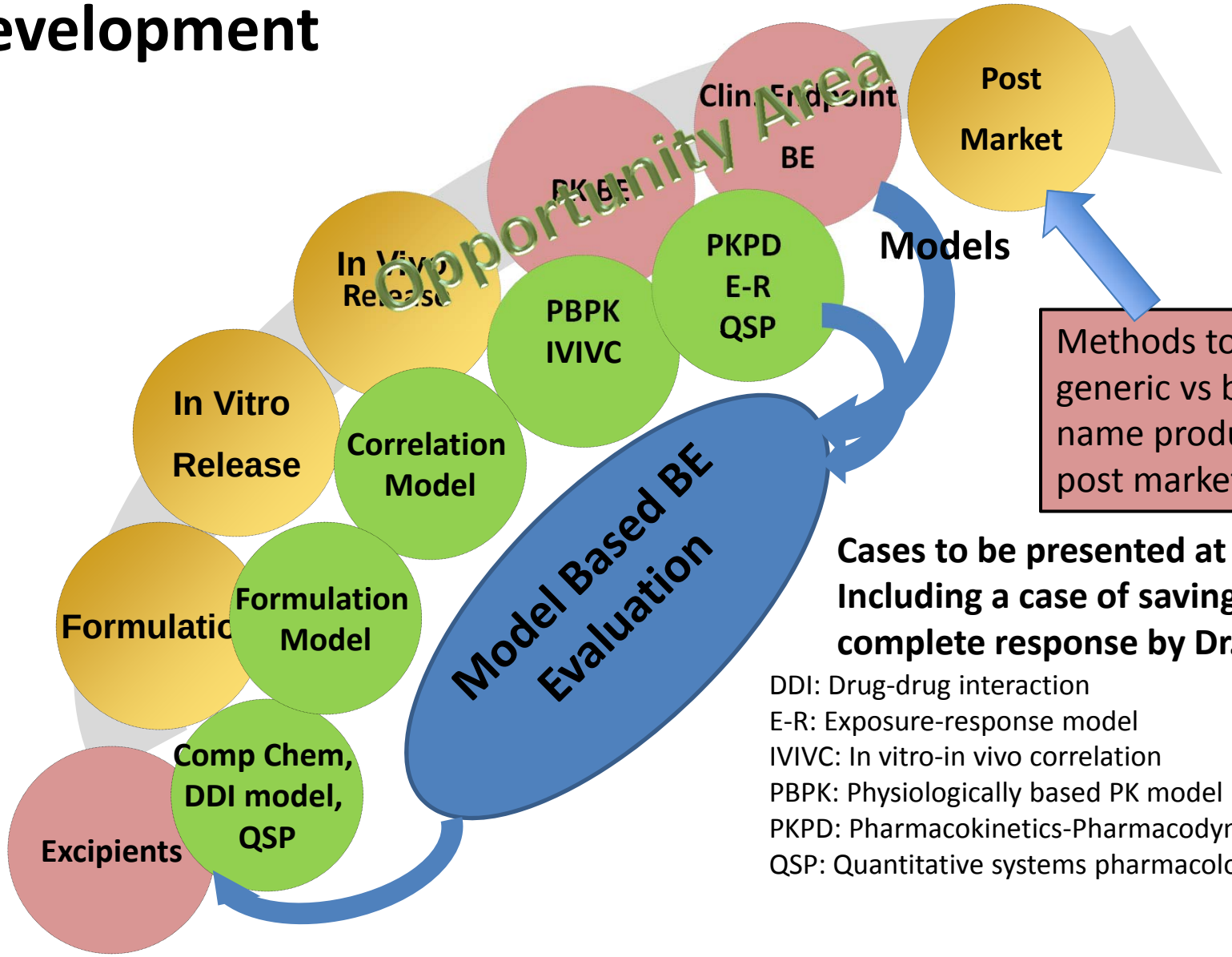
An Integrated Modeling System for New Drug Development



DDI: Drug-drug interaction
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

An Integrated Modeling System for Generic Drug Development



Methods to compare generic vs brand name products in the post marketing stage

Cases to be presented at Session II Including a case of saving a drug from complete response by Dr. Fang

DDI: Drug-drug interaction
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology

GDUFA Research

- GDUFA I supported the build out of the modeling and simulation tool chain for generic drugs
- GDUFA II will continue to build on the toolset and capitalize on the GDUFA regulatory science program

QMM Related GDUFA Funded Grants/Contracts (1)

	Grants/Contracts	Institute	Start	End	Status
BE investigations	Wireless Sampling Pill to Measure in Vivo Drug Dissolution in GI Tract and Computational Model To Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients	University of Michigan	9/2015	9/2018	Ongoing
	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland	9/2015	9/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Bioequivalence Study of Lamotrigine Extended Tablets in Healthy Subjects	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University	9/2013	8/2017	Completed
	Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus products in high risk Transplant Recipients	University of Cincinnati	9/2013	3/2017	Completed
	Evaluation of in vitro release methods for liposomal amphotericin B	ZoneOne Pharma	9/2014	9/2016	Completed
	Assessing Clinical Equivalence for Generic Drugs Approved By Innovative Methods	Brigham & Women's Hospital	9/2013	9/2015	Completed
	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns	University of Michigan	9/2013	11/2015	Completed
	Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification	University of Michigan	9/2013	9/2015	Completed
New BE metrics	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah	9/2015	8/2018	Ongoing
	Pharmacokinetics study of opioid drug product following insufflation of milled drug products	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital	9/2014	8/2017	Completed
	Pharmacometric modeling of immunosuppressant for evaluation of bioequivalence criteria	University of Utah	9/2014	2019	Ongoing
	BE and Characterization of Generic Drugs: Methylphenidate and Warfarin	Vince & Associates Clinical Research	9/2014	12/2016	Completed
Physiologically based models for systemic and locally acting products	Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug Products	Simcyp, Ltd.	9/2016	8/2018	Ongoing
	Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	Simcyp, Ltd	9/2014	8/2018	Ongoing
	Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	University of South Australia	9/2014	8/2018	Ongoing
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University	9/2016	8/2018	Ongoing
	A cluster-based assessment of drug delivery in asthmatic small airways	University of Iowa	9/2016	9/2018	Ongoing
	Novel Method to Evaluate Bioequivalence of Nanomedicines	Nanotechnology Characterization Lab	5/2016	4/2018	Ongoing
	Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action	University of Florida	9/2013	11/2017	Ongoing
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation	9/2014	8/2017	Completed
	PBPK modeling and simulation for ocular dosage forms	Simulations Plus	9/2015	8/2017	Completed

QMM Related GDUFA Funded Grants/Contracts (2)

	Grants/Contracts	Institute	Start	End	Status
Model based BE assessment for PK and performance	Evaluation and development of model-based bioequivalence analysis strategies	Uppsala University	6/2017	6/2019	Ongoing
	Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	University of Paris	9/2016	9/2018	Ongoing
	Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	University of Massachusetts	9/2015	8/2018	Ongoing
	Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs	University of Florida	9/2014	8/2018	Ongoing
	Computational drug delivery: leveraging predictive models to develop bioequivalent generic long-acting injections	Qrono, Inc.	9/2015	9/2018	Ongoing
	In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence (BE) Regulation	University of Michigan	9/2015	9/2018	Ongoing
	Prediction of In Vivo Performance for Oral Solid Dosage Forms	University of Michigan	9/2013	11/2017	Ongoing
	Correlation of Mesalamine Pharmacokinetics with Local Availability	University of Michigan	9/2013	9/2015	Completed
Post market evaluation	Generic drug substitution in special populations	Auburn University/ IMPAQ International	9/2016	8/2018	Ongoing
	Comparative Surveillance of Generic Drugs by Machine Learning	Marshfield Clinic, Inc.	9/2015	9/2018	Ongoing
	Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	9/2015	8/2018	Ongoing
	Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	9/2015	8/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	University of Maryland	9/2014	2/2018	Ongoing
	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/2014	8/2018	Ongoing
	Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants	Arbor Research Collaborative for Health	9/2014	8/2017	Completed
	Post-market authorized generic evaluation (PAGE)	Auburn University	9/2014	8/2017	Completed
	Effect of Therapeutic Class on Generic Drug Substitutions	Johns Hopkins University	9/2014	4/2017	Completed
	Assessing the post-marketing safety of authorized generic drug products	Brigham & Women's Hospital	9/2014	6/2017	Completed
	Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns	University of Maryland	9/2013	10/2015	Completed
NTI classification	Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	University of Maryland	9/2014	8/2018	Ongoing
	Clinical practice data to aid narrow therapeutic index drug classification	Duke University	9/2013	9/2016	Completed
	Therapeutic index evaluation for tacrolimus and levetiracetam	Johns Hopkins University	9/2013	3/2015	Completed

Modeling and Simulation Impact Various Regulatory Activities in OGD (Fiscal Year 2017)

Type	No.	Examples
ANDA Reviews & Citizen petitions	37	❖ Implement clinically relevant pharmacokinetics metrics for BE assessment (e.g., pAUCs) ❖ EMD profile analysis of particle size distribution ❖ Impact of dissolution failure
Pre-ANDA interactions (including CC)	15	❖ Trial simulations for alternative BE study designs ❖ Aerosol evaporation from solution-based metered dose inhalers
BE Guidances	15	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Studies	32	❖ Evaluation of post-marketing switching patterns ❖ Model-based BE assessment; Meta-analysis for opioid products with abuse deterrence properties ❖ Physiologically based pharmacokinetics platform development for non-oral routes

ANDA: abbreviated new drug application; BE: bioequivalence; CC: controlled correspondence; HVD: highly variable drugs; NTI: narrow therapeutic index; EMD: earth mover's distance; pAUC: partial area-under-curve

Highlights of Recent QMM Activities at OGD

- Applications for locally acting and complex drug development and review, eg,
  - *Efficacy extrapolation in the generic drug review– Cases by Dr. Fang in Session II*
  - *Other cases from industry and academia in Session II*
- Support for in vitro only BE assessment, eg,
  - BCSII-IV drugs– past FDA/CERSI workshops
  - *Physiologically based PK modeling for drug absorption in session II*
- Big data, eg,
  - *Informing generic research prioritization—Case by Dr. Hu in Session III*
- Post market signal evaluation tools
  - *External research projects by Dr. Dutcher in Session IV*
  - *Engagement with Sentinel in Session IV*
  - *Evaluating concept of real world study for post market performance evaluation in Session IV*
- Meta-analysis to support risk based BE standards, eg,
  - Product specific guidance for dabigatran
- In vitro BE methodologies, eg,
  - EMD for evaluating particle size distribution
- Outlier evaluations
- Tools for fraud detection

Received QMM Related Regulatory Questions

Questions from PreANDA meetings

- Modeling and simulation to waive a clinical endpoint study for a locally acting product?
- Quantitative BE assessment for long acting implant?
- Development strategy to use QMM to support in vivo options for inhalation products?

Questions from ANDA review consult

- Waiving four way crossover PK study via simulations based on two way crossover PK study result?
- How to implement the earth mover distance approach In vitro BE assessment for particle size distribution?
- Clinically relevant in vitro testing parameters for locally acting product?

Modernize QMM Principles/Toolsets for Product Development and Review

- **Time for global harmonization for QMM? On what?** Session I presentations

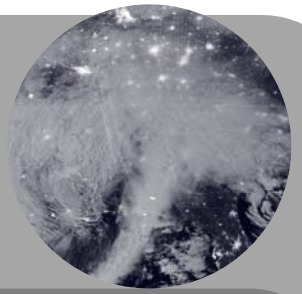
- **Time for Bayesian approach and how?** To be presented by Dr. Peck at Session III
- **How to transform generic drug development/review with QMM?** To be presented by Dr. Lionberger at Session III
- **Machine learning as one of next generation pharmacometrics toolsets?** Session III
- **What are the guiding principles for real world study**? Can it be applied to compare post marketing performance? See session IV
- **Model qualification/verification to inform regulatory decisions?** Workshops, Advisory Committee meetings

One of the Future Initiatives: Driving Decisions Based on Big Data

Big data

Social media

Commercial/Sales



NDA

Internet

Literature

Post Market

Data Mining/Selection

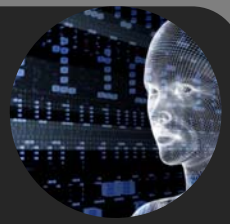
Proactively planned data collection

Secondary databases including Sentinel

Research/ Guidance Databases

Relational databases

Analytics including Artificial Intelligence



Work Load Optimization

(Case by Dr. Hu, Session III)

Generic Drug Competition

(Cases by Drs. Burnt and Conti, Session III)

Generic Drug Substitution

(Cases by Speakers at Session IV)

Take Home Messages

- Modernize generic drug review especially for locally acting, complex, and/or modified release products
  - Generic drug sponsors identify opportunities of leveraging QMM in pre-ANDA interactions and ANDA packages to shorten development timeline and cut cost
  - Office of Research Standard/Office of Generic Drugs uses QMM to modernize guidance development and product reviews to reduce regulatory burden
- Big data to aid product development, post-market evaluation, and workload management
- Global stakeholder engagement for QMM can greatly benefit the global generic enterprise as a whole

Thank you!