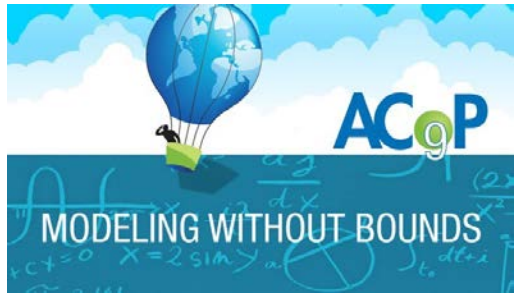


Overview of GDUFA-funded Modeling and Simulation Grants/Contracts

Liang Zhao, PhD

Division of Quantitative Methods & Modeling

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

ACoP 9, San Diego, CA
October 10th, 2018

Modernize ANDA Program to Ensure Timely Availability of High Quality Generic Products

- Increase first cycle approval rate; decrease number of review cycles
- Shorten drug development timeline
- Develop sensitive and efficient bioequivalence methods
- Reduce exposure of human subjects to unnecessary studies

- ***All of the above are especially important for locally acting, complex, and modified release products.***

Modeling & Simulation for Generics

- Cover a broad spectrum of toolsets including physiologically-based PK models and quantitative clinical pharmacology approaches
- Are employed for the development of novel BE methods, in vitro only BE approaches, and risk based evaluations
  - Complex generics are becoming more critical to patient care but generic versions are generally more difficult to develop due to lack of standards and tools that establish equivalency
- Are applied by the U.S. Food and Drug Administration (FDA) to facilitate generic drug development and review
  - Critical role in the modernization of bioequivalence (BE) assessment, especially for locally acting drug products, complex products of other types, and modified-release solid oral dosage forms

18 Topic Areas with Various Levels of M&S Involvement during GDUFA I (FY2013-2017)

- Complex Mixtures and Peptides
- Database and Knowledge Management
- Drug-Device Combinations
- Drug Products that Incorporate Nanotechnology
- Generic Drug Utilization and Substitution
- Locally-Acting Gastrointestinal Drugs
- Locally-Acting Orally Inhaled and Nasal Drug Products
- Long-Acting Injectables and Implants
- Modified Release Drug Products
- Ophthalmic Products
- Oral Abuse-deterrent Opioid Products
- Patient Substitution Studies
- Perceptions of Generic Drugs
- Pharmacokinetic/Pharmacodynamic Models and Pharmacometrics
- Physiologically-Based Absorption and Pharmacokinetic Models for Non-Oral Routes
- Predictive Dissolution and Physiological Models of Oral Absorption
- Topical Dermatological Drug Products
- Transdermal Drug Products

GDUFA: Generic Drug User Fee Amendments

Quantitative Methods & Modeling (QMM) Related Grants/Contracts Funded in GDUFA I (1)

	Grants/Contracts	Institute
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
	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA
	Bioequivalence Study of Lamotrigine Extended Tablets in Healthy Subjects	Vince & Associates Clinical Research
	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University
	Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus products in high risk Transplant Recipients	University of Cincinnati
	Evaluation of in vitro release methods for liposomal amphotericin B	ZoneOne Pharma
	Assessing Clinical Equivalence for Generic Drugs Approved By Innovative Methods	Brigham & Women's Hospital
	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns	University of Michigan
	Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification	University of Michigan
New BE metrics	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah
	Pharmacokinetics study of opioid drug product following insufflation of milled drug products	Vince & Associates Clinical Research
	Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital
	Pharmacometric modeling of immunosuppressant for evaluation of bioequivalence criteria	University of Utah
	BE and Characterization of Generic Drugs: Methylphenidate and Warfarin	Vince & Associates Clinical Research
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.
	Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	Simcyp, Ltd
	Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	University of South Australia
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University
	A cluster-based assessment of drug delivery in asthmatic small airways	University of Iowa
	Novel Method to Evaluate Bioequivalence of Nanomedicines	Nanotechnology Characterization Lab
	Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action	University of Florida
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation
	PBPK modeling and simulation for ocular dosage forms	Simulations Plus

QMM: Quantitative Methods and Modeling; BE: Bioequivalence

QMM Related Grants/Contracts Funded in GDUFA I (2)

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

QMM: Quantitative Methods and Modeling; NTI: Narrow Therapeutic Index

Outcomes and Regulatory Impacts of the Research Programs

- Research activity report for five areas have been published

  https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm

- All outcomes reported in this presentation are for the period between Oct 1, 2012 and Sept 30, 2017

- Some highlights will be demonstrated in the following slides

Disclaimer: All numbers related to research projects and outcomes are preliminary and subject to final verification.

Tools in Quantitative Clinical Pharmacology: PK/PD, Exposure-Response, and Model based BE Assessment

Without new in vivo data generated:

- Clinical practice data to aid NTI drug classification
  Site PI: John M. Michnowicz (Duke University)
  Grant #: 1U01FD004858; Start date: 09/15/2013
- Therapeutic index evaluation for tacrolimus and levetiracetam and Optimization of Pulmonary Drug Delivery
  Site PI: (Johns Hopkins University)
  Grant #: 1U01FD004859; Start date: 09/15/2013
- Population PK/PD dose-toxicity modeling and simulation for NTI drugs
  Site PI: Joga Gobburu (University of Maryland)
  Grant #: 1U01FD0005188; Start date: 09/14/2014
- Pharmacometric M&S for a generic drug substitutability evaluation and post-marketing risk assessment
  Site PI: (University of Maryland)
  Grant #: 1U01 FD0005192; Start date: 09/10/2014
- Pharmacometric M&S for a generic drug substitutability evaluation and post-marketing risk assessment
  Site PI: (University of Florida)
  Grant #: 3U01FD005210-03S1; Start date: 09/10/2014
- Evaluation of MBBE Statistical Approaches for Sparse Design PK Studies
  Site PI: (University Paris Diderot and INSERM)
  Contract #: HHSF223201610110C; Start date: 09/29/2016
- Evaluation and Development of MBBE Analysis Strategies
  Site PI: (Uppsala University)
  Contract #: HHSF223201710015C; Start date: 04/2017

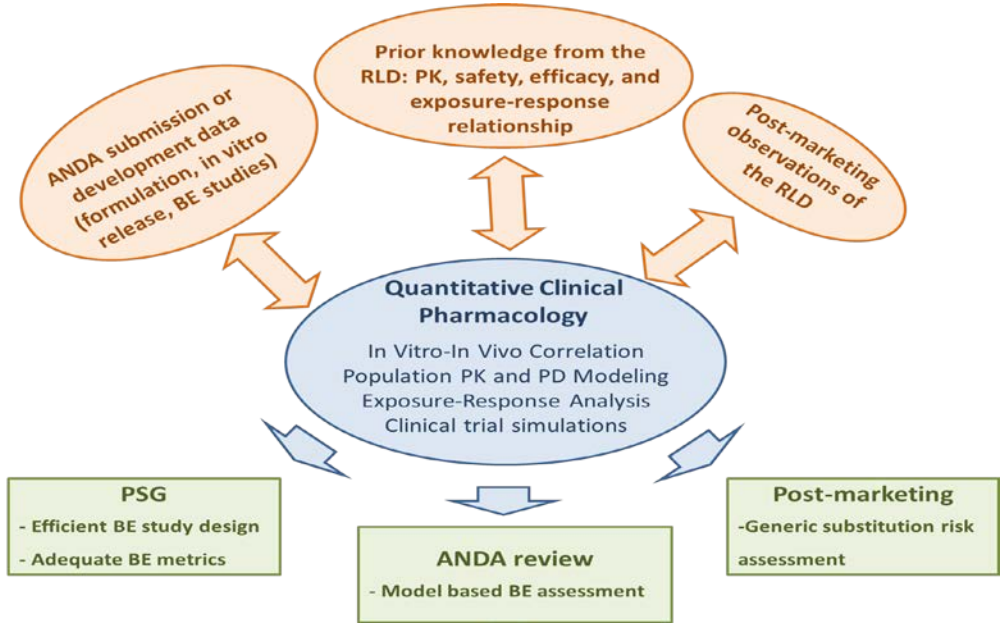
With new in vivo data generated:

- **Pharmacometric M&S for pAUC**
  Site PI: (University of Utah)
  Grant #: 1U01FD0005191; Start date: 09/10/2014
- **Pharmacometric M&S and Statistical Analysis for LAI Microsphere**
  Site PI: (University of Utah & University of Massachusetts)
  Grant #: 1U01FD005442 & 1U01FD005444; Start date: 09/15/2015
- **PK/PD studies of cardiovascular drugs in hypertensive patients**
  Site PI: (the University of Florida)
  Grant #: 1U01FD005235; Start date: 09/10/2014
- **PK/PD studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder (ADHD) patients**
  Site PI: (Massachusetts General Hospital)
  Grant #: 1U01FD005240; Start date: 09/10/2014
- **BE and characterization of generic drugs: methylphenidate hydrochloride extended release tablets**
  Site PI: (Vince and Associates Clinical Research)
  Contract #: HHSF223201210030I/HHSF22301001T; Start date: 09/15/2014
- **BE study of lamotrigine extended release tablets in healthy subjects**
  Site PI: (Vince and Associates Clinical Research)
  Contract #: HHSF223201210030I/HHSF22301003T; Start date: 09/15/2015
- **Evaluation of formulation dependence of drug-drug interaction (DDI) with proton pump inhibitors (PPIs) for oral extended release drug products (nifedipine)**
  Site PI: (BioPharma Services)
  Contract #: HHSF223201610004I; Start date: 09/19/2016

Close integration between experiment and M&S improves the models faster

GDUFA I Outcomes: 41 Product Specific Guidances; 6 publications; 12 external presentations; 8 external posters

Tools in Quantitative Clinical Pharmacology: PK/PD, Exposure-Response, and Model based BE Assessment



Type	Number	Examples
ANDA reviews	29	• Clinical trial simulations to extrapolate the clinical outcome at timepoints that were not studied • M&S to evaluate alternative BE study designs
Citizen petitions and other consults	15	• PK/PD M&S to evaluate alternative BE metrics for extended-release oxcarbazepine and dalfampridine tablets
BE guidances	46	• M&S to evaluate PK and/or clinical endpoint BE study design, feasibility and sensitivity, and BE metrics and criteria
Regulatory Research studies	67	• PKPD modeling of abuse-deterrent products • M&S on BE criteria evaluation of NTI drug products • M&S for generic substitutability evaluation

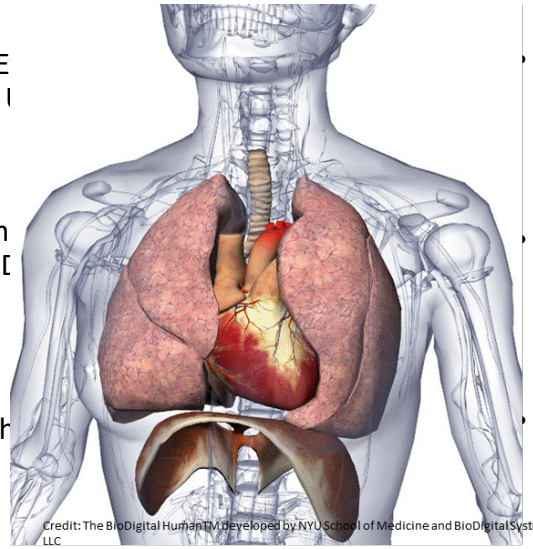
- Quantitative analysis of PK/PD relationship of abuse-deterrent opioid products
  - The preliminary results suggest that early pAUCs (e.g., pAUC0-3 hr) may be associated with maximum Drug Liking Visual Analogue Scale (VAS)
  - Early pAUCs are recommended in addition to conventional PK metrics (e.g., Cmax, AUCt and AUCinf) to assess whether a generic abuse-deterrent opioid product is no less abuse-deterrent than its reference product
- Clinical trial simulation for comparative clinical endpoint BE studies for locally acting drug products -- Ivermectin Case
- M&S approach to assess clinical efficacy BE at unstudied time points --Brimonidine
- Alternative BE approach and improvement
- Use of PK/PD M&S for assessment of post-market risk

Physiologically-Based Absorption and Pharmacokinetic Models for Non-Oral Routes

- Predictive Lung Deposition Models for Safety and E
  Site PI: P. Worth Longest (Virginia Commonwealth
  Grant #: 1U01FD004570; Star
  Start date: 09/14/2012

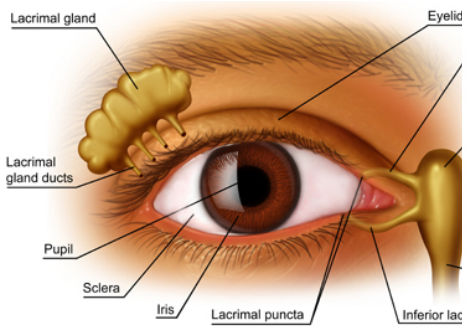
- A Predictive Multiscale Computational Tool for Sim
  Pharmacokinetics and Optimization of Pulmonary D
  Site PI: Peng Gou (CFD Research Corporation)
  Grant #: 1U01FD005214-01
  Start date: 09/10/2014

- A cluster-based assessment of drug delivery in asth
  Site PI: Ching-Long Lin (University of Iowa)
  Grant #: 1U01FD005837
  Start date: 09/10/2016



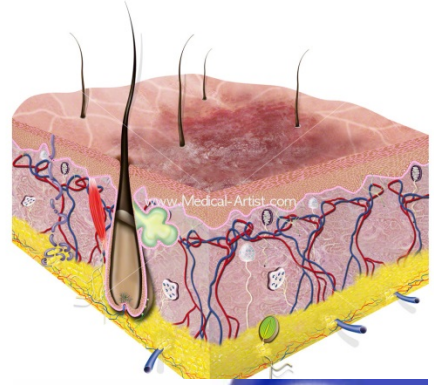
- PBPK Modeling and Simulation for Ocular Dosage Forms
  Site PI: Michael B Bolge
  Grant #: U01FD005211
  Start date: 09/11/2014

- An Integrated Multiscal
  Delivery with Whole-Bo
  Site PI: Kay Sun (CFD Re
  Grant #: 1U01FD005219
  Start date: 09/10/2014



- Physiologically Based Biopharmaceutics and Pharm
  Products for Dermal Absorption in Humans
  Site PI: Michael Roberts (University of South Austr
  Grant #: 1U01FD005232
  Start date: 09/11/2014

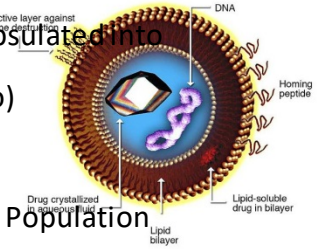
- Development and Validation of Dermal PBPK Mode
  Virtual BE Assessment Considering Population Vari
  Site PI: Sebastian Polak (SimCYP)
  Grant #: 1U01FD005225
  Start date: 09/10/2014



- Development of Hybrid CFD-PBPK Models for Absc
  Corticosteroids
  Site PI: Jeff Schroeter
  Grant #: 1U01FD005201-01
  Start date: 09/14/2014

- Development of PBPK Simulation for LAI Microspher
  Site PI: Viera Lukacova (Simulations Plus)
  Grant #: 1U01FD005463
  Start date: 09/15/2015

Liposome for Drug Delivery



Physiologically Based Pharmacokinetic Model for Drugs Encapsulated into Liposomes
Site PI: Yanguang Cao (State University of New York at Buffalo)
Grant #: 1U01FD005206
Start date: 09/10/2014

Enhancing the Reliability, Efficiency, and Usability of Bayesian Population PBPK Modeling
Site PI: Brad Reisfeld (Colorado State University)
Grant #: 1U01FD005838
Start date: 09/10/2016

Outcomes: 18 publications; 11 external presentations; 23 external posters

Locally-Acting Orally Inhaled and Nasal Drug Products

Process, packaging, in vitro dissolution, testing, and performance

- Development of Clinically Relevant in Vitro Performance Test for Generic OIDPs
  Site PI: Michael Hindle (Virginia Commonwealth University)
  Grant #: 1U01FD005231-01; Start date: 09/10/2014- 09/30/2018

- Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance
  Site PI: Guenther Hochhaus (University of Florida)
  Grant #: 1U01FD004943-01, 5U01FD004943-05; Start time: 09/15/2013, 9/01/2015

- An Optimized Dissolution Test System for Orally Inhaled Drugs: Development and Validation
  Site PI: Guenther Hochhaus (University of Florida)
  Grant #: 1U01FD004950-01; Start date: 09/15/2013

- Pharmacokinetic Research Study on the Effects of Different Protective Packaging on the Stability of Fluticasone Propionate Capsules for Inhalation
  Study PI: Guenther Hochhaus (University of Florida)
  Contract #: HHSF223201300479A; Start date: 09/30/2013-12/31/2016

New in vivo studies

- PK Comparison of Locally Acting Orally Inhaled Drug Products
  Study co-PI: Guenther Hochhaus (University of Florida)
  Study co-PI: Robert Price, Jag Shur (University of Bath)
  Contract #: HHSF223201110117A; Start date: 09/16/2011

- Pharmacokinetic Comparison of Locally Acting Orally Inhaled Drug Products
  Study PI: Juergen Bulitta (University of Florida)
  Contract #: HHSF223201610099C; Start date: 09/22/2016

- In Vitro Fluid Capacity-limited Dissolution Testing and Its Kinetic Relation to in Vivo Clinical pharmacokinetics for orally inhaled drug products
  Site PI: Masahiro Sakagami (Virginia Commonwealth University)
  Grant #: 1U01FD004941-01; Start date: 09/15/2013

- Study to investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action
  Site PI: Guenther Hochhaus (University of Florida)
  Contract #: HHSF223201310220C; Start date: 09/30/2013

- Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance
  Site PI: Guenther Hochhaus (University of Florida)
  Grant #: 5U01FD004943-05; Start date: 09/01/2015

- Development of in Vivo Predictive Dissolution Technique to Understand the Clinical Based
  Site PI: Robert Price (University of Bath)
  Grant #: 1U01FD004953-01; Start date: 09/15/2013

- Study to Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical properties of the active in suspension nasal products for local action
  Study PI: Guenther Hochhaus (University of Florida)
  Contract #: HHSF223201310220C; Start date: 09/30/2013- 09/30/2018

Modeling and simulation studies

- **A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery**
  Site PI: Peng Gou (CFD Research Corporation)
  Grant #: 1U01FD005214-01; Start date: 09/10/2014; The project's goal is to create and develop a lung model which can accurately predict deposition, distribution, absorption, metabolism, and excretion of OIDPs, using a combined approach with computational fluid dynamics (CFD) and physiologically-based PK (PBPK) methods.

- **Predictive Lung Deposition Models for Safety and Efficacy of Orally Inhaled Drugs**
  Site PI: P. Worth Longest (Virginia Commonwealth University)
  Grant #: 1U01FD004570; Start date: 09/14/2012; The goal was to develop computational fluid dynamics (CFD) models of orally inhaled drug product (OIDP) delivery to human lungs, where these predictions would be used to evaluate the impact of certain drug product and physiological characteristics on total and regional lung deposition.

- **A cluster-based assessment of drug delivery in asthmatic small airways**
  Site PI: Ching-Long Lin (University of Iowa)
  Grant #: 1U01FD005837; Start date: 09/10/2016; The main focus of this work is to incorporate the effects of inter-subject variability on small airways deposition of MDI drug delivery, based on data collected from computerized tomography (CT) scans of a large population of asthmatic patients (n=248).

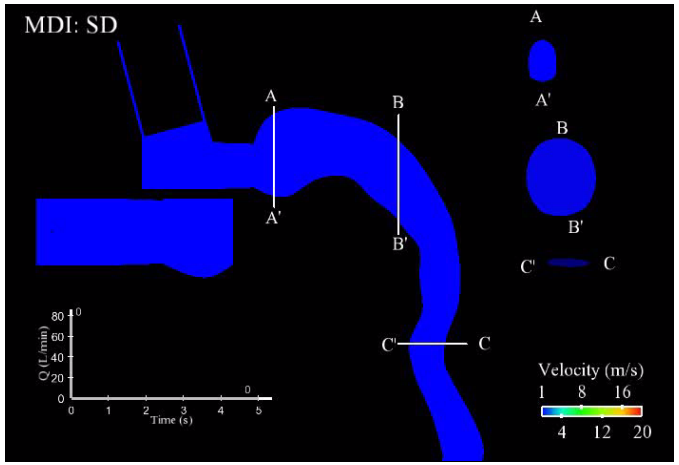
- **Development of Hybrid CFD-PBPK Models for Absorption of Intranasal** Corticosteroids
  Site PI: Jeff Schroeter
  Grant #: 1U01FD005201-01; Start date: 09/14/2014; The goal is to develop a model which can predict deposition, distribution, and absorption of intranasal corticosteroids, using a combined approach with computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) methods

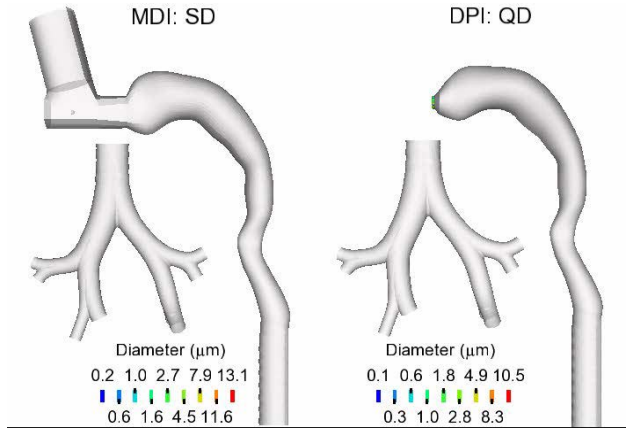
Outcomes: 33 Product specific guidances; 42 publications; 6 external presentations; 25 external posters;

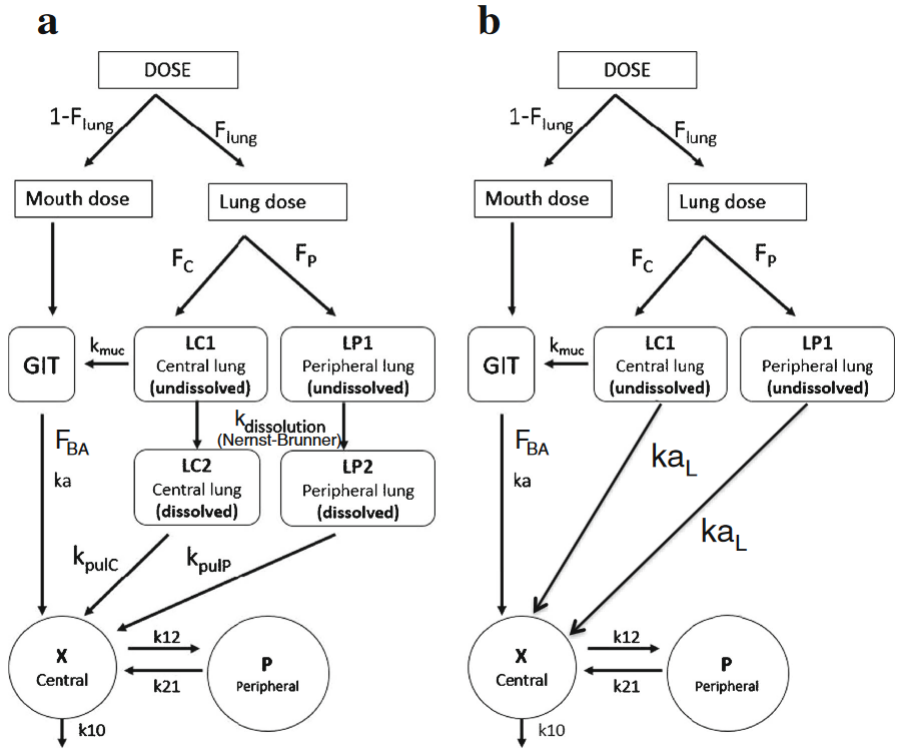
Value Proposition: Computational Modeling in Orally Inhaled Product Development

- Bioequivalence assessment of orally inhaled product presents a challenge since systemic (blood) drug exposure may not reflect local drug concentration at site of action
- Computational modeling provides a connection between in vitro parameters (e.g., spray angle and plume geometry) and lung regional deposition and absorption of orally inhaled aerosols
- Quantitative methods and modeling can inform regulatory decision-making otherwise difficult to make with available in vitro or in vivo data, by predicting:
  - Regional deposition of aerosolized drug within individual branches/lobes of the airway
  - Local bioavailability and its relationship with systemic pharmacokinetics
- Computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK), in combination, present the next generation modeling toolset that can offer an opportunity to preclude conducting PD endpoint BE studies

PBPK Predictions of Orally Inhaled Drug Absorption







Compartmental model schemes for dry powder inhaler drug delivery from Bhagwat et al. (2017)

Right: Bhagwat S, Schilling U, Chen MJ, Wei X, Delvadia R, Absar M, Saluja B, Hochhaus G. Predicting Pulmonary Pharmacokinetics from In Vitro Properties of Dry Powder Inhalers. Pharm Res. 2017 Dec;34(12):2541-2556.
Left: Longest, P. W., Tian, G., Walenga, R. L., and Hindle, M. (2012) Comparing MDI and DPI Aerosol Deposition Using in Vitro Experiments and a New Stochastic Individual Path (SIP) Model of the Conducting Airways. Pharmaceutial Research, 29(6), 1670-1688

Ophthalmic Products

In vitro characterization (IVRT, Dissolution testing, IVIVC)

- Topical Ophthalmic Suspensions: New Methods for Bioequivalence Assessment
  Site PI: Dr. Arto Urtti (University of Eastern Finland)
  Grant #: 1U01FD005180 ; Start date: 09/15/2014
- Dissolution Methods for Topical Ocular Emulsions
  Site PI: Srinath Palakurthi (Texas A&M University)
  Grant #: 1U01FD005184; Start date: 09/15/2014
- Modeling of the Vitreous for In Vitro Prediction of Drug Delivery of Porous Silicon Particles and Episcleral Plaques
  Site PI: Michael Sailor (University of San Diego)
  Grant #: 1U01FD005173; Start date: 09/15/2014
- Evaluation and Development of Dissolution Testing Methods for Semisolid Ocular Drug Products
  Site PI: Diane Burgess (University of Connecticut Storrs)
  Grant #: 1U01FD005177; Start date: 09/15/2014
- Dissolution Methods for Predicting Bioequivalence of Ocular Semisolid Formulations
  Site PI: Xiuling Lu (University of Connecticut Storrs)
  Grant #: 1U01FD005174; Start date: 09/15/2013
- Pulsatile Microdialysis for In Vitro Release of Ophthalmic Emulsions
  Site PI: Robert Bellantone (Physical Pharmaceutica, LLC)
  Contract #: HHSF223201610105C; Start date: 09/16/2016
- In Vitro In Vivo Correlations of Ocular Implants
  Site PI: Uday Kompella (University of Colorado, Denver)
  Grant #: 1U01FD004929; Start date: 09/15/2013
- An IVIVC System to Facilitate the Development of a Generic Vitrasert
  Site PI: Thomas Smith (Auritec Pharmaceuticals)
  Grant #: 1U01FD004927; Start date: 09/15/2013-09/30/2015
- Effect of Physicochemical Properties of Ophthalmic Formulations on Ocular Bioavailability
  Site PI: Uday Kompella (University of Colorado, Denver)
  Grant #: 1U01FD004719; Start date: 09/15/2012

- **An Integrated Multiscale-Multiphysics Modeling and Simulation of Ocular Drug Delivery with Whole-Body Pharmacokinetic Response**
  Site PI: Kay Sun (CFD Research Corporation)
  Grant #: 1U01FD005219; Start date: 09/10/2014; The goal was to develop a model which can predict delivery, distribution, and absorption of ophthalmic drug products using a combined approach with computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) methods in human and animal subjects.
- **PBPK Modeling and Simulation for Ocular Dosage Forms**
  Site PI: Dr. Michael B Bolger (Simulations Plus)
  Grant #: 1U01FD005211; Start date: 09/11/2014; The goals of this project were to advance the field of ocular PBPK and mechanistic absorption modeling (MAM) software

- A two dimensional CFD model has been developed to provide an enhanced understanding of fluid transport between the different regions in the eye. This tool will be useful to OGD for identifying the influence of various physicochemical properties and formulation variables (e.g., particle size, pH, and viscosity) on local and systemic ophthalmic drug absorption
- The main result expected is the development of a rabbit Ocular Compartmental Absorption and Transit™ (OCAT™) MAM/PBPK model within the GastroPlus™ software program, which may be used to predict ocular and systemic PK

Outcomes: 11 Product specific guidances; 6 publications; 7 external presentations; 18 external posters

Topical Dermatological Drug Products

In vitro testing, in vivo PK, IVPT, and IVIVC

- Novel Methodologies and IVIVC Approaches to Assess Bioequivalence of Topical Drugs
  Site PI: Frank Sinner; Joanneum Research
  Grant #: 1U01FD004946; Start date: 09/15/2013
- Bioequivalence of Topical Drug Products: In Vitro – In Vivo Correlations
  Site PI: Audra Stinchcomb (University of Maryland)
  Grant #: 1U01FD004947; Start date: 09/01/2013
- Characterization of Critical Quality Attributes for Semisolid Topical Drug Products
  Site PI: Michael Roberts (University of South Australia)
  Grant #: 1U01FD005226; Start date: 09/10/2014
- Topical Products and Critical Quality Attributes
  Site PI: Sathyanarayana Murthy (University of Mississippi)
  Grant #: 1U01FD005233; Start date: 09/10/2014
- Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations
  Site PI: Paul Lehman (QPS, LLC)
  Contract #: HHSF223201610125C; Start date: 09/29/2016-12/31/2017

PK by microdialysis or microperfusion techniques

- Development of a Universal Bioequivalence Test Method for Topical Drugs using dOFM
  Site PI: Frank Sinner; Joanneum Research
  Grant #: 1U01FD0045861; Start date: 09/15/2016
- Benchmark of Dermal Microdialysis to Assess Bioequivalence of Topical Dermatological Products
  Site PI: Grazia Stagni (Long Island University)
  Grant #: 1U01FD005862; Start date 09/15/2016

PBPK Modeling and Simulation

- **Physiologically Based Biopharmaceutics and Pharmacokinetics of Drug Products for Dermal Absorption in Humans**
  Site PI: Michael Roberts (University of South Australia)
  Grant #: 1U01FD005232; Start date: 09/11/2014
- **Development and Validation of Dermal PBPK Modelling Platform Towards Virtual BE Assessment Considering Population Variability**
  Site PI: Sebastian Polak (SimCYP)
  Grant #: 1U01FD005225; Start date: 09/10/2014

- Research outcomes from the grants/contracts lead to insightful understanding of the formulation characteristics of the product and their interaction with physiological environment of the skin
- The University of South Australia (UniSA) award leads to the development of different models to predict drug concentrations at or near the local site of action in the skin
  - The models utilized either a Laplace domain approach based on diffusion processes
  - A compartmental representation of dermal absorption transport
  - A three dimensional (3D) numerical simulation approach based on actual stratum corneum and viable epidermis geometry and processes of diffusion, convection, and binding occurring in the skin
- The Simcyp award approached the development of a PBPK model by incorporating considerations for the drug, the formulation characteristics, the underlying local skin and systemic physiology, and in vivo sources of variability
  - The intent was to be able to predict the local and/or systemic PK and PD response for a population including inter-individual variability.
  - Simcyp has completed the development of a novel multi-phase-multi-layer MechDermA model which incorporates an exhaustive survey of data on healthy skin physiology, including data on key parameters like skin pH, skin thickness, etc. which can affect the inter-subject variability component of model predictions.
  - **The updates have been implemented successfully in Simcyp Simulator release version 16**
  - **Simcyp is currently working on the incorporation of pediatric and geriatric populations in the model, in addition to different ethnic groups and diseased skin models in the next release (version 17) as well as enhancing the manner in which characteristics of the formulation are incorporated in the model**

Outcomes: 20 Product Specific Guidances; 7 publications; 42 external presentations; 42 external posters

Locally-Acting Gastrointestinal Drugs

PK studies

- Correlation of Mesalamine Pharmacokinetics with Local Availability
  Site PI: Duxin Sun (University of Michigan)
  Contracts #: Contract HHSF223201000082C and HHSF223201300460A
  09/15/2010, 9/13/2013- 09/12/2015

In vitro and MRI in GI

- In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence
  Study co-PI: Gordon L. Amidon (University of Florida)
  Contract #: HHSF223201510157C
  08/24/2015-08/31/2020
- In vitro evaluation of sucralfate performance
  Study PI: Office of Testing and Research
- In vitro dissolution performance of fidaxomicin tablet under different conditions
  Study PI: Office of Testing and Research
- Product Characterization and In vitro Dissolution of Rifaximin Tablets
  Study PI: Office of Testing and Research

M&S learnings from these research efforts critically impacted on

- Addressing 8 citizen petitions for mesalamine modified release products, budesonide extended release product, rifaximin tablet, fidaxomicin tablet
- The pAUC recommendation for BE establishment of mesalamine products
- Addressing 9 pre-ANDA meeting requests

Outcomes: 23 Product Specific Guidances

Advances in Predictive Dissolution and Physiological Models of Oral Drug Absorption

In vitro testing and characterization, GI physiology

- Formulation, processing and performance interrelationship for amorphous solid dispersions
  Site PI: Lynne Taylor (Purdue University)
  Grant #: 1U01FD005259; Start date: 09/10/2014

- Wireless Pharmaceutical Analysis Device and Computational Model to Determine in Vivo Drug Dissolution in GI Tract for Distinguishing Meaningful Product Differences and Ensuring Bioequivalence
  Site PI: Duxin Sun (Regents of the University of Michigan)
  Contract #: HHSF223201510146C; Start date: 09/30/2015

Excipient effects on transporter and off targets

- Interactions of Excipients with Intestinal Uptake and Efflux Transporters
  Site PI: Kathy Giacomini (The University of California, San Francisco)
  Grant #: 3U01FD004979-02S3 ; Start date: 04/01/2015

- Prediction & testing of excipient molecular targets
  Site PI: Brian Shoichet (The University of California, San Francisco)
  Grant #: 3U01FD005978; Start date: 04/01/2015

New PK and BE studies

- Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors for oral extended-release drug products
  Site PI: David Moreton (BioPharma Services Inc.)
  Contract #: HHSF223201610004I
  09/08/2016- ongoing

- BE and Characterization of Generic Drugs: Warfarin
  Site PI: Bradley Vince (Vince and Associates Clinical Research, Inc)
  Contract #: HHSF223201210030I/HHSF22301001T; Start date: 09/24/2012

Predictive modeling

- Prediction of In Vivo Performance for Oral Solid Dosage Forms
  Site PI: Gordon Amidon (Regents of the University of Michigan)
  Contract #: HHSF223201310144C; Start date: 09/25/2013; , a multi-faceted approach was utilized to focus on both aspects by developing fundamental mechanistic in vitro and in silico modeling methodologies that will predict in vivo performance using state of art computational methods, GI measurements, in vitro measurement, and mathematical modeling.

- Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling
  Site PI: Brad Reisfeld (Colorado State University)
  Grant #: 1U01FD005838; Start date: 09/10/2016; incorporate population PK modeling aspects in PBPK models to allow for parameter estimation at the individual data level

- In Vivo Predictive Dissolution to Advance Oral Product Bioequivalence
  Site PI: Gordon Amidon (Regents of the University of Michigan)
  Contract #: HHSF223201510157C; Start date: 09/30/2015; Modeling work in combined with the generation of new in vivo data via MRI studies of the GI tract

- Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic Framework for the Prediction of the In Vivo Behaviour of Supersaturating Drug Products
  Site PI: Dr. David Barnes Turner (Simcyp Limited)
  Grant #: 1U01FD005865; Start: 09/10/2016; Develop state-of-the art mechanistic models and workflows to predict and simulate the behavior of supersaturating orally-dosed drug products in the human gastrointestinal (GI) tract

Outcomes: 9 Product specific guidances; 18 publications; 14 external presentations; 22 external posters

Modified-Release Drug Products: Therapeutic Equivalence between Brand-Name Drugs and Generics

NTI Investigation based on clinical data

- Clinical practice data to aid NTI drug classification
  Site PI: Michael Cohen-Wolkowiez (Duke University)
  Grant #: 1U01FD004858; Start date: 09/30/2013
- Therapeutic index evaluation for tacrolimus and levetiracetam
  Site PI: William A. Clarke (Johns Hopkins University)
  Grant #: 1U01FD004859; Start date: 09/30/2013

New PK and BE studies

- Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification
  Site PI: Duxin Sun (University of Michigan)
  Contract #: HHSF223201310183C; Start date: 09/10/2013
- Pharmacokinetic study of bupropion hydrochloride products with different release patterns
  Site PI: Duxin Sun (University of Michigan)
  Contract #: HHSF223201310164C; Start date: 09/24/2013
- Bioequivalence and clinical effects of generic and brand bupropion hydrochloride
  Site PI: Evan Kharasch (Washington University)
  Grant #: 1U01FD004899-01; start date: 09/10/2013
- BE and characterization of generic drugs (methylphenidate)
  Site PI: Bradley Vince (Vince and Associates)
  Contract #: HHSF223201210030I, HHSF22301001T; Start date; 09/15/2015, 09/15/2015
- A pharmacokinetic/pharmacodynamic study of methylphenidate formulations in pediatric attention-deficit/hyperactivity disorder (ADHD) patients in a laboratory classroom
  Site PI: Thomas Spencer (Massachusetts General Hospital)
  Grant #: 1U01FD005240-01; Start date: 09/10/2014
- Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs in hypertensive patients" (Metoprolol ER Tablets)
  Site PI: Larisa Cavallari (University of Florida)
  Grant #: 1U01FD005235-01; Start date: 09/15/2013
- Bioequivalence study of lamotrigine extended release tablets in healthy subjects
  Study PI: Bradley Vince (Vince and Associates)
  Contract #: HHSF223201210030I, HHSF22301003T
  Start date: 09/23/2015; 09/23/2015
- Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors (PPIs) for oral extended-release drug products
  Site PI: David Moreton (BioPharma Services Inc.)
  Contract #: HHSF223201610004I; Start date: 09/08/2016

Outcomes: 18 Product specific guidances; 15 publications; 14 external presentations; 11 external posters

Long-Acting Injectable Formulations

In vitro testing, IVIVC (animal):

- Dissolution Methods for Parenteral Sustained Release Implant Drug Products
  Site PI: Diane Burgess (University of Connecticut)
  Grant #: 1U01FD005169 ; Start date: 09/15/2013
- In Vitro-In Vivo Correlation of Parenteral Microsphere Drug Products
  Site PI: Diane Burgess (University of Connecticut)
  Grant #: 1U01FD004931; Start date: 09/15/2013
- In vitro-In vivo correlations of parenteral microsphere drug products
  Study PI: Steve Schwendeman (University of Michigan)
  Grant #: 1U01FD005014; Start date: 09/15/2013
- Development of hydrogel-based in vitro dissolution apparatus for microparticle formulations
  Study PI: Haesun Park (Akina, Inc.)
  Grant #: 1U01FD005168; Start date: 09/15/2014
- Dissolution Methods for Long-acting (LA) Periodontal Drug Products
  Site PI: Lisa Rohan (Magee-Women's Research Institute and Foundation)
  Grant #: 1U01FD005447; start date: 09/15/2015
- Dissolution Methods for Long-acting Levonorgestrel Intrauterine System
  Study PI: Diane Burgess (University of Connecticut)
  Grant #: 5U01FD005443-02; Start date: 09/15/2015
- Development of a Dissolution Method for Long-acting Periodontal Drug Products
  Site PI: Kevin Li (University of Cincinnati)
  Grant #: 1U01FD005446; Start date: 09/15/2015
- Evaluation of the ex vivo release profile of a long-acting biodegradable periodontal dosage form in a canine periodontal disease model
  Site PI: Joseph Araujo (InterVivo Solutions)
  Contract #: HHSF223201510771P; Start date: 09/15/2015

Material, Manufacturing, process and storage on quality

- Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on Release Performance of Long-acting Release Microsphere Products
  Site PI: Steve Schwendeman (University of Michigan)
  Contract #: HHSF223201510170C; Start date: 09/15/2015
- Investigation of Peptide-Polymer Interactions in PLGA Microspheres
  Site PI: Steve Schwendeman (University of Michigan)
  Grant #: 1U01FD005847; Start date: 09/15/2016
- Advanced analytical techniques for mixed polymer drug-delivery systems
  Site PI: Haesun Park (Akina, Inc.)
  Contract #: HHSF223201610091C; Start date: 09/15/2016

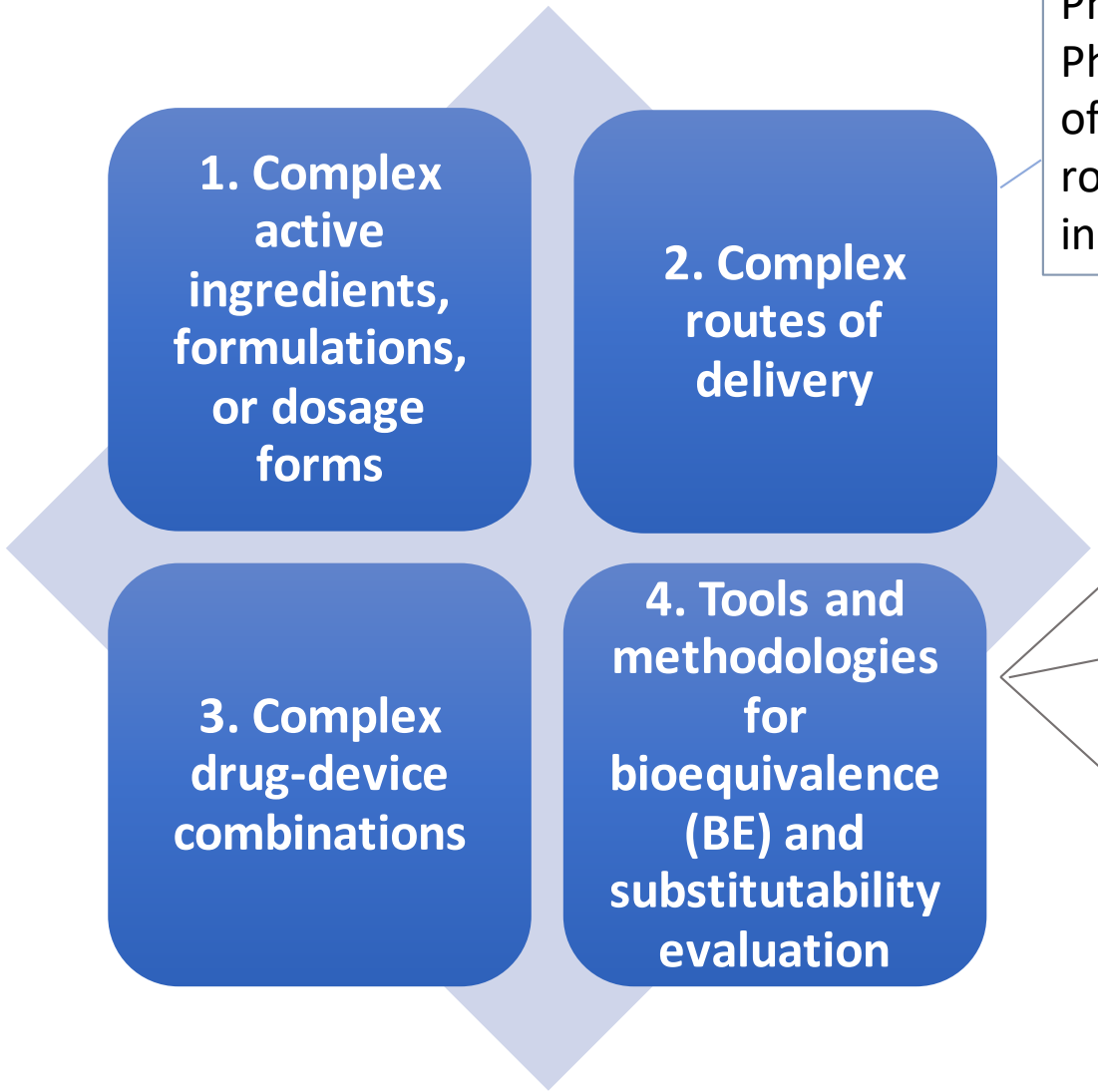
Modeling and Simulation

- **Computational Drug Delivery: Leveraging Predictive Models to Develop Bioequivalent Generic Long-acting Injections**
  Site PI: Sam Rothstein (Qrono, Inc.)
  Contract #: HHSF223201510102C; Start date: 09/15/2015; to compare a simulation-driven approach to bioequivalence formulation design with a more experimentally intensive approach based on the direct measurement of the reference product's critical quality attributes.
- **Development of PBPK Simulation for Long Acting Injectable Microspheres**
  Site PI: Viera Lukacova (Simulation Plus)
  Grant #: 1U01FD005463; Start date: 09/15/2015; To develop and validate general PBPK models for LAI products to relate CQAs to in vitro and in vivo performance and to evaluate BE criteria for LAI products.
- **Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection**
  Site PI: Catherine Mary Turner Sherwin (University of Utah)
  Grant #: 1U01FD005442; Start date: 09/15/2015; The purpose of this research grant is to conduct pharmacokinetics-pharmacodynamics (PK-PD) modeling and statistical analysis for LAI products to identify ways to reduce residual variability and identify appropriate PK metrics, enabling BE assessment in parallel BE studies with acceptable sample size.

Outcomes: 2 Product specific guidances; 12 publications; 9 external presentations; 32 external posters

FY2018 GDUFA Research Science Priority Areas

15 priority areas under 4 broad categories



Physiologically-Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products

Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards

Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution and utilization patterns and drug safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

Take Home Message

- M & S critically impact on generic drug review and approval
  - Generating Model Integrated Evidence for Generic Drug Development and Assessment

- Looking into the future
  - More collaborations with the M&S community are expected to close scientific gaps for both generic and new drug development and approval!
  - GDUFA Regulatory Science Priorities for Fiscal Year 2018
  - Upcoming ASCPT preconference on PBPK for locally acting drug products in March 2019
  - February 2019 CPT theme issue for “Generic Drugs”

Acknowledgement

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OGD/ORS/DTP

OGD/OB

OPQ/OTR

OSE/OPE/DEPII

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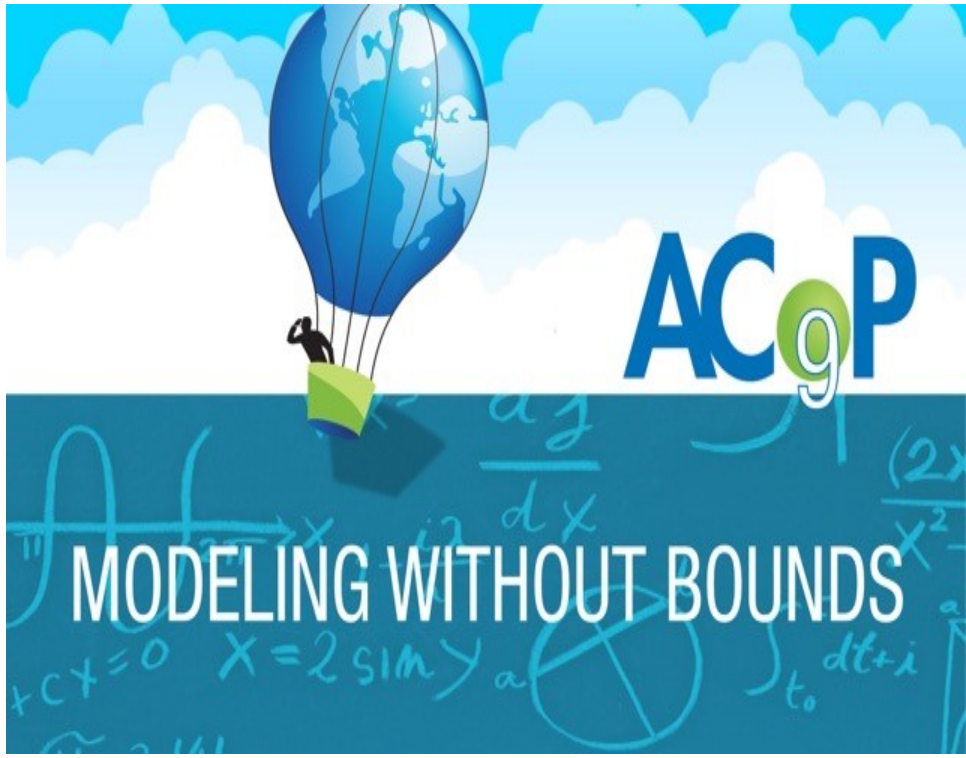
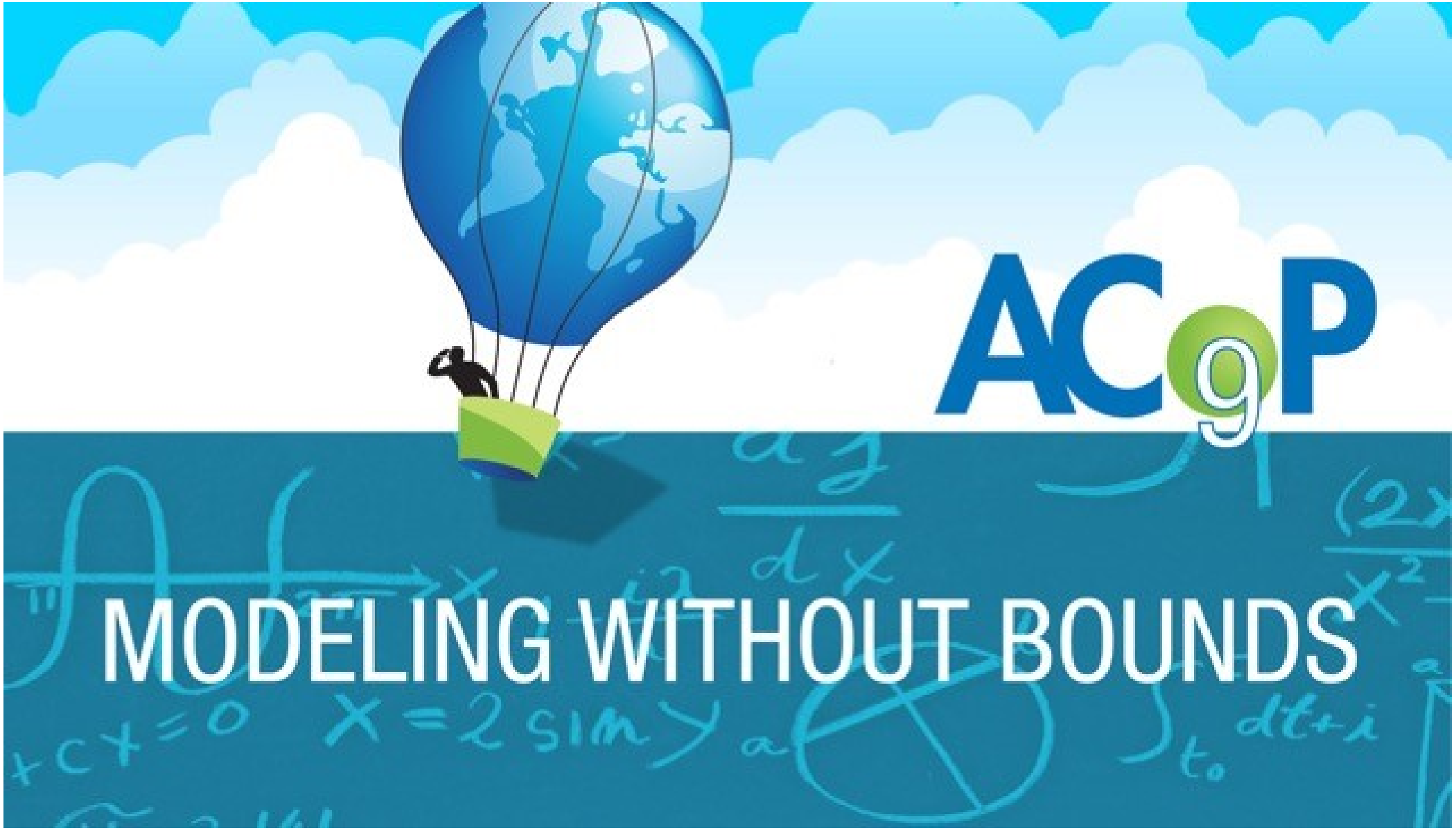


All FDA Grantees/Contractors!!



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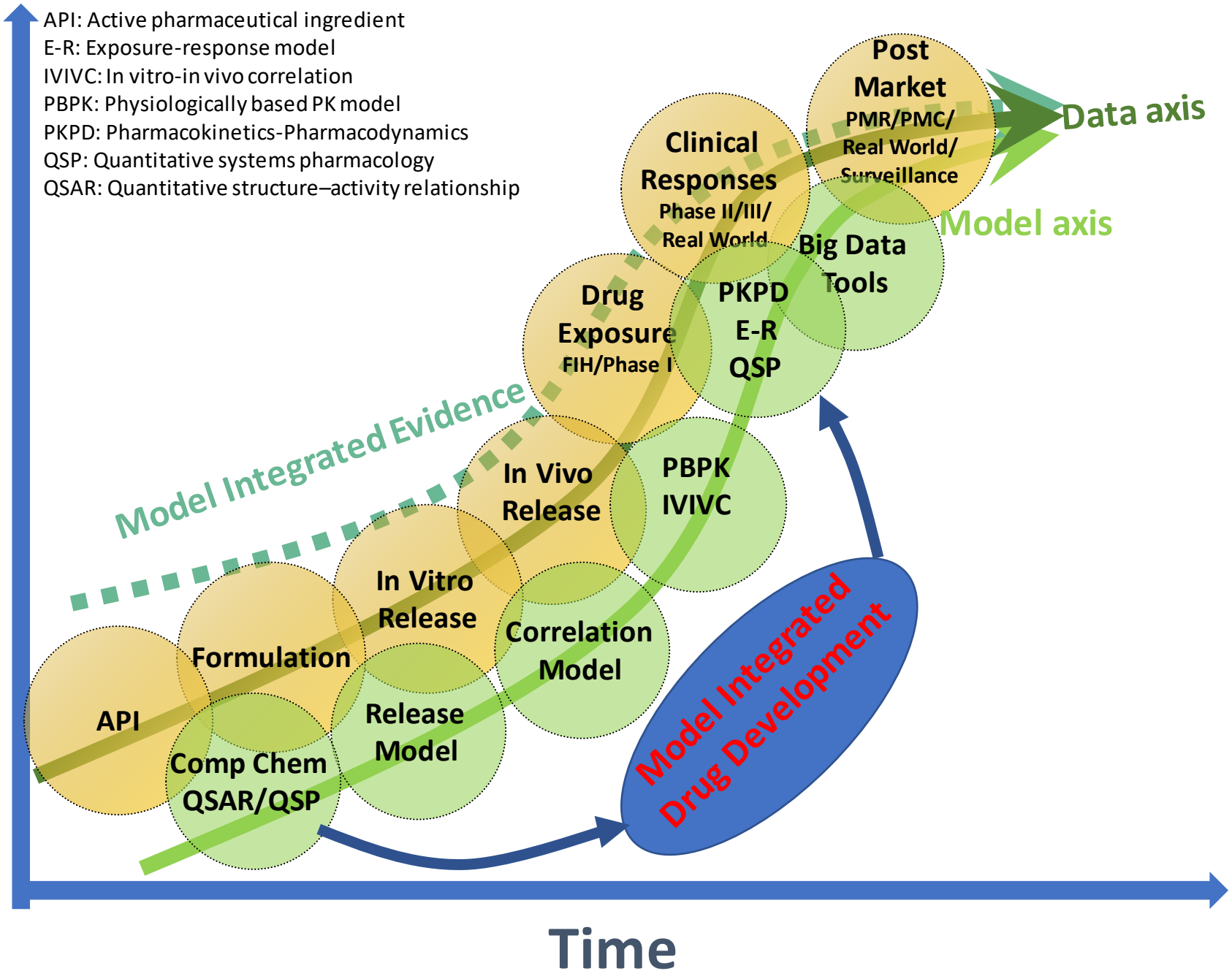
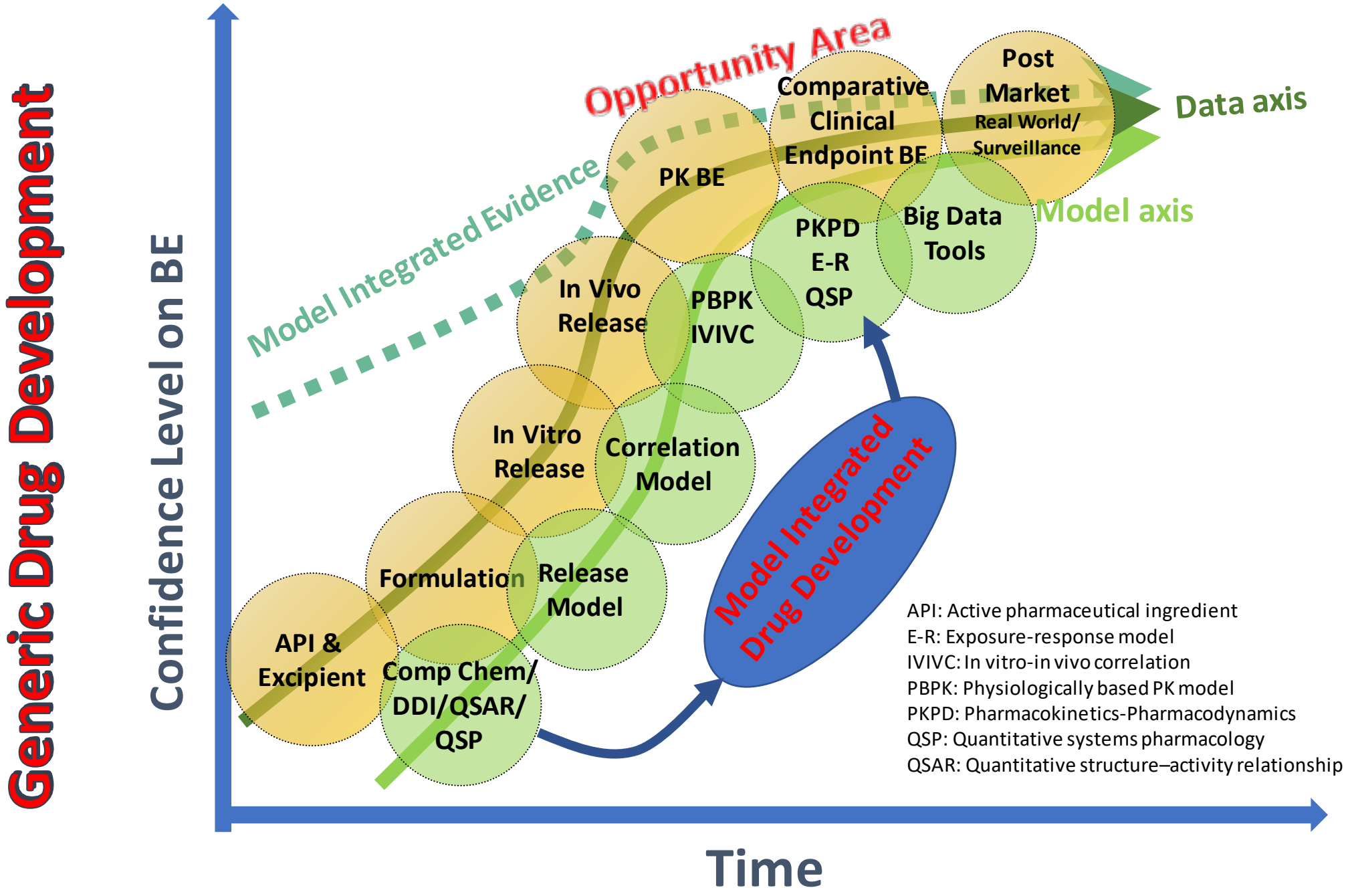
New Drug Development




Generic Drug Development
Confidence Level on BE
Time
Opportunity Area
Model Integrated Evidence
Data axis
Model axis
API & Excipient
Formulation
Comp Chem/ DDI/QSAR/ QSP
Release Model
In Vitro Release
Correlation Model
In Vivo Release
PBPK IVIVC
PK BE
Comparative Clinical Endpoint BE
PKPD E-R QSP
Big Data Tools
Post Market Real World/ Surveillance
Model Integrated Drug Development
API: Active pharmaceutical ingredient
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

~~The Generic Drug User Fee Amendments (GDUFA) Regulatory Science Program and Research Activities~~

- ~~The program supports the development of new methodologies and tools to help establish drug equivalence standards and the development of, and access to, generic drug products~~
- ~~GDUFA I (FY2013-2017) supported the build out of the modeling and simulation tool chain for generic drugs~~
- ~~GDUFA II (FY2018-2022) will continue to build on the toolset and capitalize on the GDUFA regulatory science program~~
- ~~During GDUFA I, Office Research & Standards awarded 36 research contracts and 69 grants for innovative research projects on generics, half of which are managed by Division of Quantitative Methods and Modeling and one third of them are focused on M&S~~
- ~~All outcomes reported in this presentation are for the period Oct 1 2012-Sept 30 2017~~