U.S. FOOD & DRUG ADMINISTRATION

Quantitative Methods and Modeling to Support GDUFA Regulatory Science Research Program

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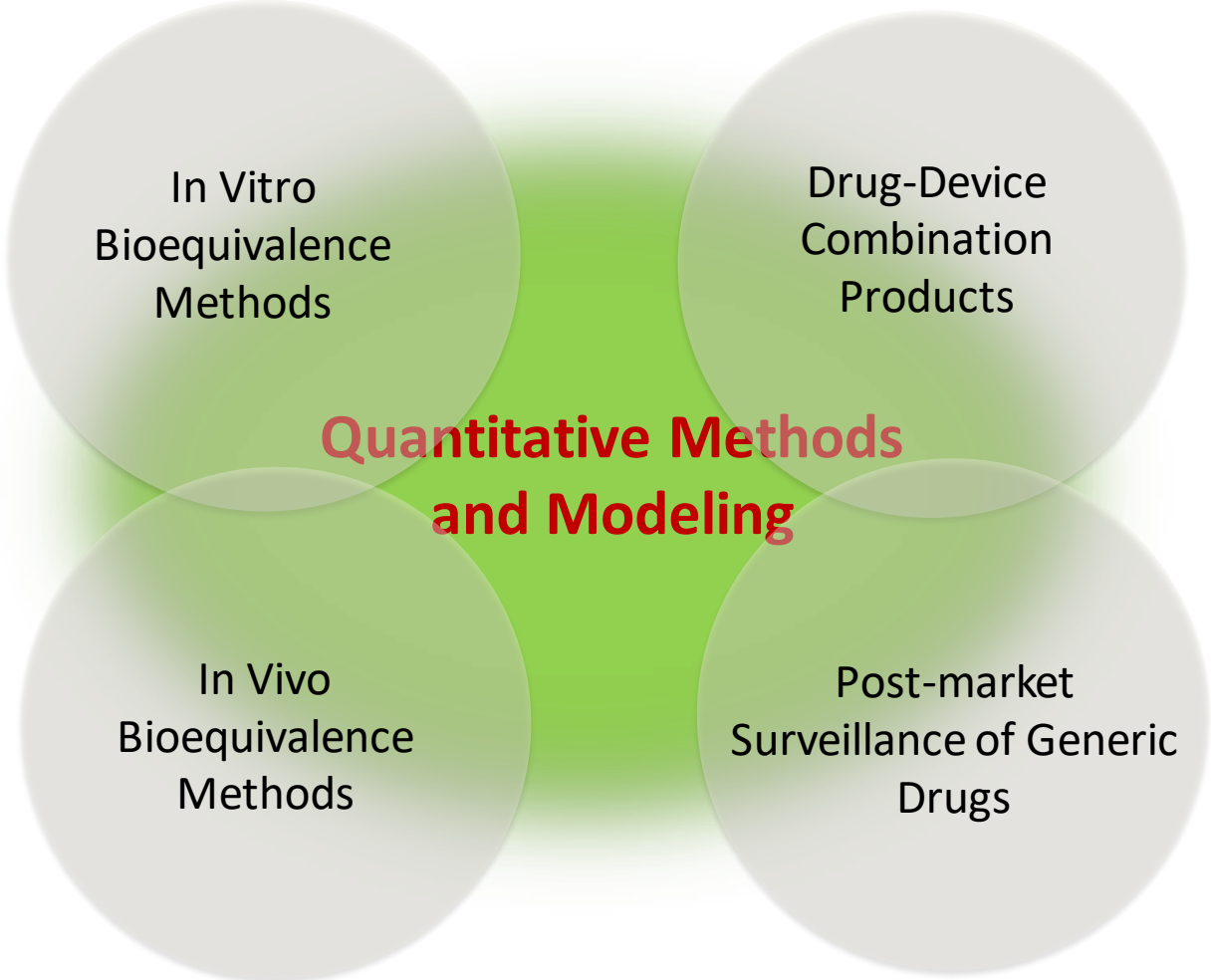
Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval

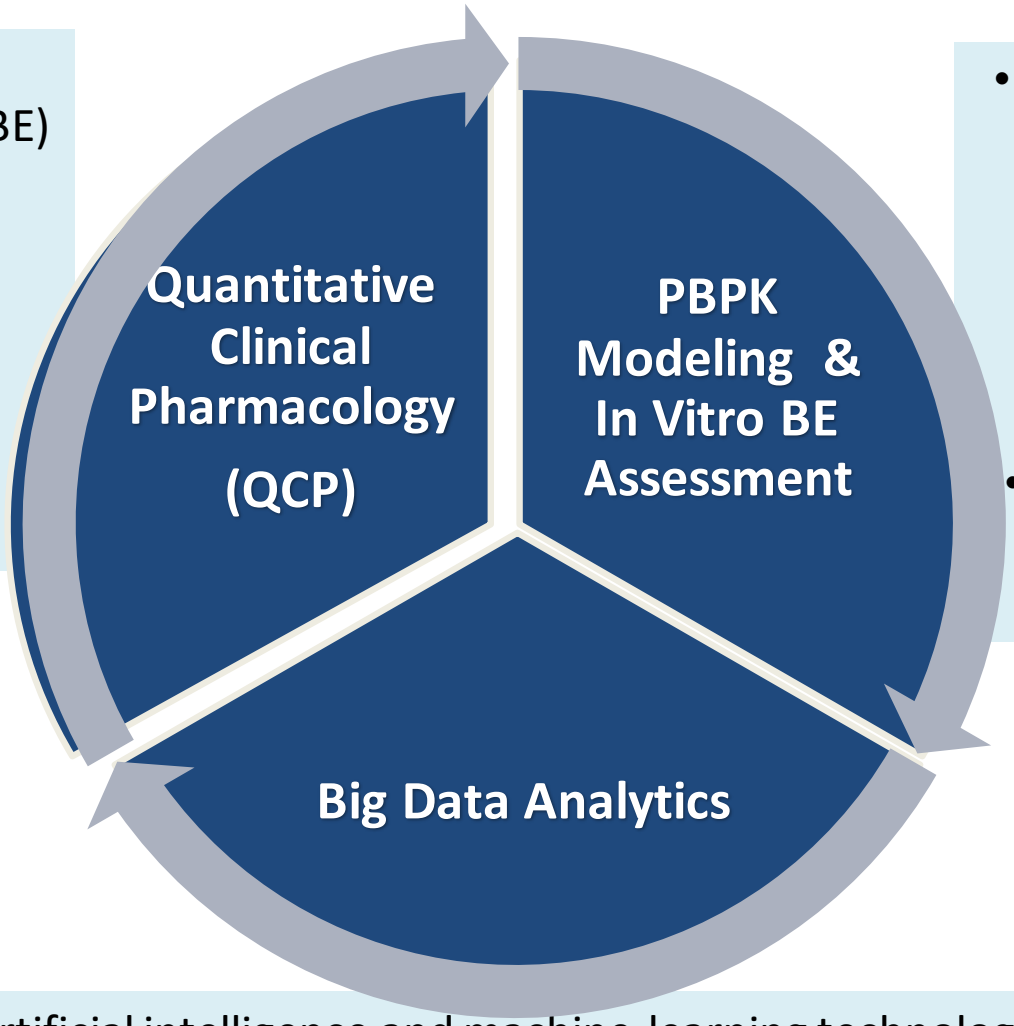


QMM is a quantitative summary of knowledge and data that can

- Drive a smart development program
- Serve as critical information or evidence for generic drug approval

Highlights of QMM Impact

- Efficient bioequivalence (BE) study design
- Pharmacokinetic (PK) metrics determination
- Evaluation of alternative BE approaches



- Physiologically based PK (PBPK) model as alternative approach
- Clinical relevancy of in vitro BE studies
- Spec. determination for in vitro characterization

- Leveraging artificial intelligence and machine-learning technologies in abbreviated new drug application (ANDA) review
- In vitro BE method development
- Post-marketing surveillance

Modeling and Simulation Impact Various Regulatory Activities in the Office of Generic Drugs (CY 2019)

Type	No.	Examples
ANDA Review Consults	9	❖ Evaluation of clinically relevant PK metrics for BE assessment ❖ Evaluation of various alternative BE approaches to the CE study (e.g., reference scaling BE approach) ❖ In vitro BE evaluations (e.g., particle size distribution)
Pre-ANDA Meetings (excluding CC)	37	
BE Guidance (General & PSGs)	31	❖ General guidance development; BE metrics for modified release products
Internal Regulatory Research Projects*	44	❖ Investigation of novel BE study design (e.g., Bayesian estimation, adaptive design) ❖ Sensitivity of pharmacodynamic endpoints on BE evaluation ❖ BE methods (e.g., baseline corrections, highly variable drugs)
New Contracts and Grants in GDUFA II since 10/2017	28	❖ Model-based BE assessment for PK and performance ❖ Development of a Machine Learning model to enhance PSG review efficiency ❖ Development of PBPK model for locally-acting drug products

ANDA: abbreviated new drug application; BE: bioequivalence; CC: controlled correspondence; CE, clinical endpoint; PK, pharmacokinetic; PBPK, physiologically based PK. *Internal research projects, 44 (FY19); PSG, product-specific guidance

Quantitative Clinical Pharmacology (QCP)

- BE study design and data analysis
  - Pharmacokinetic (PK) endpoints
    - Sparse PK sampling: model-informed optimal BE study design and model-based BE analysis
    - Endogenous baseline correction: appropriate BE metrics and criteria
    - Patient PK study: long-acting injectables
  - Pharmacodynamic (PD) endpoints
    - Dose-scale analysis
    - Endpoint sensitivity assessment
    - Alternative study design
  - Comparative Clinical endpoints
    - Clinical trial simulation platform
- PK/PD analysis to support BE recommendations and analysis
    - Narrow therapeutic index (NTI) classification and BE criteria
    - Partial AUC as additional BE metric
    - Model-based BE assessment

Highlights of QCP Impact

Category	Impact on Regulatory Decision Making	Example Drug
BE Study Design	▪ Recommendation on using **a reference-scaled average BE (RSABE) approach**	ANDA consults
	▪ Evaluation of the adequacy of **a group sequential study design (adaptive design)** in BE evaluation	Inhalation product
	▪ Recommendation **of a 1-year in vivo BE study against a 5-year in vivo BE study**	Levonorgestrel
	▪ Evaluation and feedback on Model-Integrated Study Design for BE assessment of Long-Acting Injectable products	Risperidone
BE Endpoint Assessment	▪ Evaluation on adequacy of **truncated AUC** ($AUC_{0\text{-}72h}$ or $AUC_{0\text{-}96h}$) for BE study analysis	ANDA consult
	▪ PSG revision on changing **partial AUC** parameters	Scopolamine
	▪ Evaluation and feedback on proposals with **PD endpoints,** e.g., chromameter in lieu of clinical endpoint	PSG development
Data Analysis	▪ Evaluation on acceptability of **ANCOVA analysis for the BE study**	Inhalation products
	▪ Evaluation of **a Dose-Scale Analysis**	ANDA consults
	▪ Evaluation of **Model Based/Integrated BE approaches**	Long-acting injectables
BE Assessment	▪ Sensitivity analysis on the aberrant observations	ANDA review consults
	▪ **Risk assessment for BE inequivalence**	Intra-nasal product
	▪ Evaluate the impact of Tmax differences on PD	ANDA consults

BE, bioequivalence; AUC, area under the curve; PK, pharmacokinetics; DLS, dynamic light scattering; ANCOVA, analysis of variance

Physiologically Based Pharmacokinetic (PBPK) for Systemically and Locally Acting Products

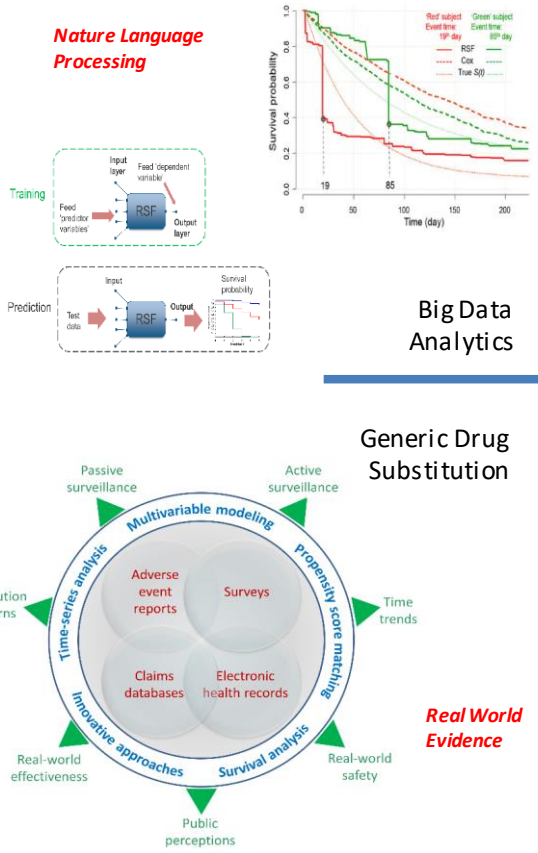
- Use of PBPK modeling to applicants to support drug product development
  - E.g., pre-ANDA /ANDA to use PBPK modeling package to support not conducting comparative clinical endpoint (CE) or PD endpoint BE studies
  - Review of regulatory submissions containing PBPK and/or computational fluid dynamic modeling – pre-ANDA meetings and ANDA consults
  - Identification of critical quality attribute and bio-predictive dissolution method
- Advance in vitro approaches to BE for locally acting products (i.e., product-specific guidances) in lieu of conducting a comparative PD/CE BE study
  - Determine appropriate BE metrics on systemic PK to ensure local equivalence
  - Simulate virtual BE studies on local PK based directly on formulation inputs
  - Identification of quality attributes with clinical relevance
  - Justify differences in quality attributes from RLD
  - Guide selection of clinically relevant in vitro tests for BE

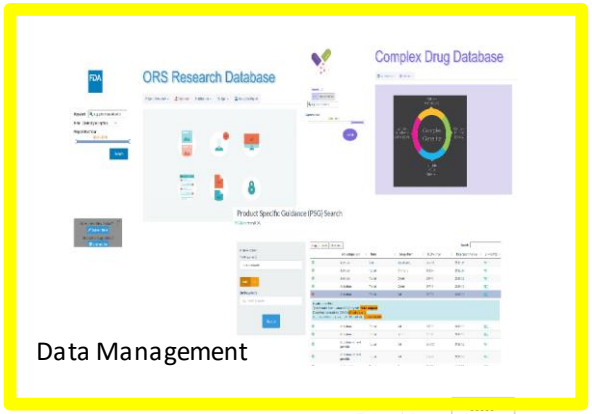
Highlights of PBPK Impacts

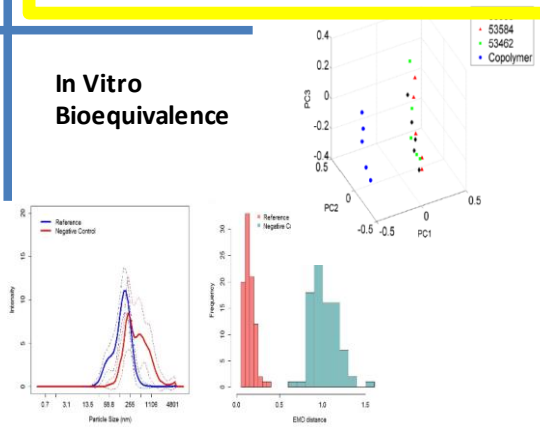
Category	Impact on Regulatory Decision Making	Example Drug
Alternative Approach to the CE study	• Evaluation on **a PBPK modeling approach as an alternative approach** in lieu of a CE study (a dermal PBPK model)	Diclofenac (topical)
	• Evaluation of CFD modeling for BE evaluation	Inhalation product
	• Assessment of dOFM study design, including dose selection • Assessment of the discriminatory power of dOFM	Topical dermatological products
In Vitro Characterization	• Evaluation on whether the **in vitro comparative dissolution study** serves as supportive information or as a critical determinant of BE	Mesalamine
	• Evaluation on an alternate requirement for the comparative drug particle size distribution (ophthalmic product)	Ophthalmic product
Utilization of Model to Support Information	• Utilizing modeling and simulation approaches to study the **role of formulation physical attributes on IVPT and local (skin)** bioavailability	Topical dermatological product

CFD, computational fluid dynamics; CE, clinical endpoint; BE, bioequivalence; AUC, area under the curve; dOFM, dermal open flow microperfusion; IVPT, in vitro permeation testing

Data Analytics/Big Data







Highlights of Novel Techniques in Big Data Analytics

Category	Impact on Regulatory Decision Making	Example Case
Leveraging AI and Machine Learning Technologies to Enhance Review Process and Decision Making	• Prediction of the Time to the First ANDA Submission Referencing New Chemical Entities Product Using **Machine Learning Methodologies**	
	• Development of a BE Review Automation Tool to **Enhance Review Efficiency and Consistency** (ongoing)	
	• Development of a Data Analytic Tool Based on Text Analysis and **Machine Learning to Facilitate the PSG Review** (ongoing)	
Developing Data Analysis Method to Facilitate the In Vitro BE Assessment	• Evaluating equivalence of **particle size distribution profile** based on Earth Mover's Distance	Ophthalmic Emulsion
	• Assessing equivalence of mass spectrum using sparse **principle component analysis**	Glatiramer Acetate Injection
	▪ Multivariate Analysis Based Method to **Facilitate the Assessment of API Similarity** (ongoing)	Complex API
Post-marketing Surveillance for Generic Drug	• Generating Real-World Evidence to Compare Outcomes between Generic and Brand-name Drug Products Using Real-World data (ongoing)	G-computation based analysis method & The instrumental variable methodology
	• Exploring the utilization of Sentinel Tool for generic drug post-marketing surveillance	

AI, artificial intelligence; ANDA, abbreviated new drug application; BE, bioequivalence; PSG, Product-Specific Guidance; API, active pharmaceutical ingredients.

New Work for Complex Products

- Support development of in vitro (only) BE approaches

- Alternative metrics to replace comparative pharmacodynamic/clinical endpoint studies as appropriate
  - Correlate PK metrics based on systemic PK exposure to action site exposure and/or clinical response
- Platform for virtual BE simulations
  - Model as a platform to integrate all pre- and post-marketing information and knowledge of a product
  - Sufficiently verified and validated model to generate virtual BE results
  - Use of model integrated evidence for generic drug approval

New Work for Non-Complex Products

- PBPK approach to BCS 3 biowaivers
  - Bigger scope of applications
- PBPK use in lower strength waivers for modified release products
  - Potential expansion to current regulatory practice
- QCP use for assuring BE in different populations
  - Pediatric and geriatric

New Work on Data Analytics

- Novel in vitro BE methods
  - Equivalence assessment for complex active pharmaceutical ingredients
- Machine learning and natural language processing for knowledge management
  - Knowledge collection for reviewers
  - PK data warehouse
  - Tools to enhance review efficiency, consistency, and quality

Industrial Implementation and Use of Quantitative Methods and Modeling

- Sufficient communication between the agency and industry in terms of expectation in the modeling package

- Awareness of value creation by using modeling and simulation toolsets to support regulatory decision making

Seeking Your Input on Future Research under the GDUFA Regulatory Science Program, especially on:

- Challenges in industry implementing PBPK/absorption models to support more efficient BE methods (such as alternative to comparative clinical endpoint BE studies)
- Emerging QMM expertise/tools in implementing new BE approaches
- How to evaluate data from in vitro studies and which in vitro studies are clinically relevant

BACK-UP SLIDES

QMM Focused Grants/Contracts Funded During GDUFA II (1)

Classification	Study Title	Awardee	Start Date	Status
BE investigations	Phase behavior and transformation kinetics of a poorly water soluble weakly basic drug upon transit from low to high pH conditions	Purdue University	2017-09-29	Completed
	Evaluating relationships between in vitro nasal spray characterization test metrics for bioequivalence and nasal deposition in silico and in vitro	Virginia Commonwealth University	2018-09-28	On-going
	Agonist-antagonist combination products (Embeda) in vivo PK	Biopharma	2018-09-13	On-going
	formulation of hydrocodone bitartrate opioid tablet	NIPTE	2018-09-21	On-going
	Pharmacokinetic (PK) study of opioid drug products following oral ingestion of chewed products	BIOPHARMA SERVICES USA INC.	2019-09-17	On-going
	Batch-to-batch Variability: exploring solutions for generic BE pathway	UMD	2019-10-01	On-going
	Expanding BCS class 3 waivers for generic drugs to non-Q1/Q2	Absorption Systems	2019-09-30	On-going
Model-based BE assessment	An integrated multiscale-multiphysics modeling framework for evaluation of generic ophthalmic drug products	CFD Research Corporation	2018-10-01	On-going
	A multiscale computational framework for bioequivalence of orally inhaled drugs	CFD Research Corporation	2018-09-21	On-going
	Development of model-informed bioequivalence evaluation strategies for long-acting injectable products	Uppsala University	2019-05-20	On-going
	Computational fluid dynamics (CFD) and discrete element modeling (DEM) approach for predictions of dry powder inhaler (DPI) drug delivery	Princeton University	2018-09-01	On-going
	MIDD approach to identify critical quality attributes and specifications for generic nanotechnology products	IQSP - Institute of Quantitative Systems Pharmacology	2019-09-27	On-going
	Evaluation of model-based bioequivalence (MBBE) statistical approaches for sparse designs PK studies	INSERM	2019-09-23	On-going

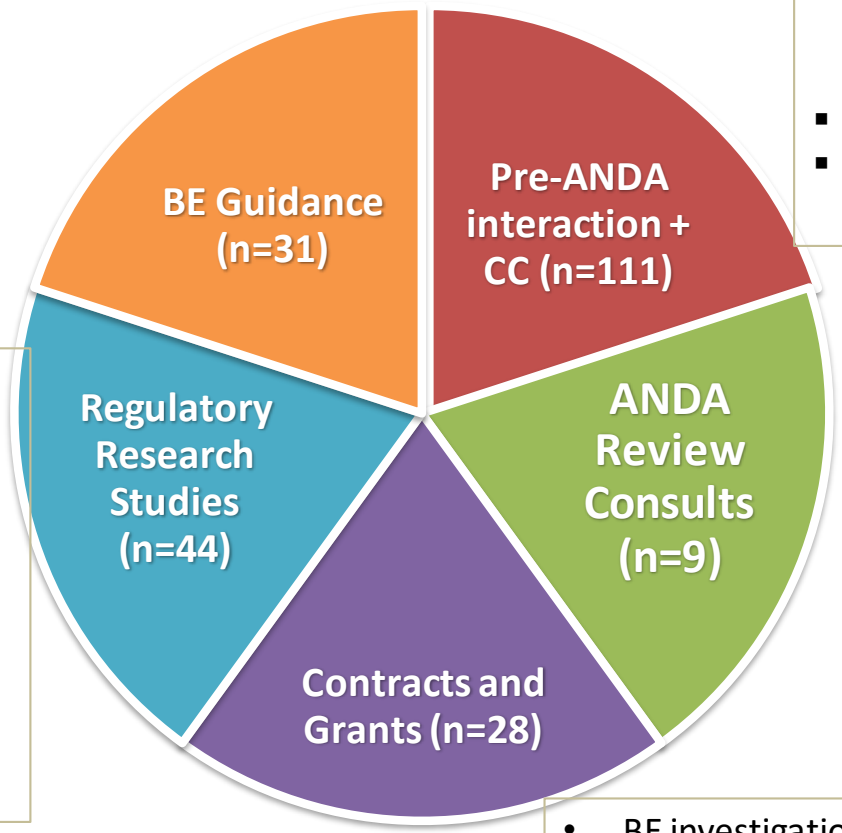
BE, bioequivalence; PK, pharmacokinetic

QMM Focused Grants/Contracts Funded During GDUFAII (2)

Classification	Study Title	Awardee	Start Date	Status
PBPK	Simulation plus ophthalmic ointment implementation	Simulations Plus, Inc.	2018-08-21	Complete
	PBPK and population modeling seamlessly linked to clinical trial simulation in an open-source software platform	Children's Hospital of Los Angeles	2018-09-01	On-going
	Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems	University of Queensland; Simulation Plus	2018-09-01	On-going
	Characterize skin physiology parameters utilized in dermal physiologically-based pharmacokinetic model development across different skin disease states	SIMCYP, LTD	2018-09-01	On-going
	Development of computational models to predict delivery of Inhalation drug powders: from deagglomeration in devices to deposition in airways	University of Sydney	2018-09-01	On-going
	Three-dimensional approach for modeling nasal mucocilliary clearance via computational fluid dynamics (CFD)	North Carolina State University Raleigh	2018-09-01	On-going
	Physiologically-based model of the female reproductive tract: vaginal and intrauterine delivery components	University at Buffalo	2018-09-26	On-going
	Modifications and improvements to hybrid CFD-PBPK models for predication of nasal corticosteroid deposition, absorption and bioavailability	Applied Research Associates	2019-09-20	On-going
Post market analytics	Use of instrumental variable approaches to assess the safety and efficacy of brand-name and generic drugs used to treat hypothyroidism	Yale-Mayo CERSI	2018-07-20	On-going
	Characterizing safety and efficacy of brand and generic drugs used to treat hypothyroidism among patients who switch therapy formulation	Yale-Mayo CERSI	2019-05-28	On-going
	Research Proposal to better understand risk mitigation in the evaluation of relative bioavailability of pediatric generic products	University of Birmingham, UK	2018-09-21	On-going
Machine Learning	Developing tools based on text analysis and machine learning to enhance PSG review efficiency	Drexel University	2019-09-30	On-going

Modeling and Simulation Impact Various Regulatory Activities in the Office of Generic Drugs (Year 2019)

- PK metrics determination
- Alternative BE approach (reference scaling BE approach; Adaptive design)
- Clinical endpoint evaluation
- In vitro comparative dissolution study



- BE study design (e.g., Bayesian estimation)
- Develop a machine learning model
- Evaluation of Pharmacodynamic (PD) Endpoints
- Baseline Correction in BE Studies

- BE investigations
- Model-based BE assessment for PK and performance
- PBPK model development
- Post-market evaluation