FY 2019 Awarded GDUFA Science and Research Contracts and Grants

Batch-to-Batch Variability: Exploring Solutions for Generic BE Pathway

- Awarded to University of Maryland (75F40119C10068)
- This proposal aims to evaluate and develop methodologies that could facilitate approval of generics for products with very high batch-to-batch variability. The pharmacokinetic data from literature will form the basis for a population pharmacokinetic model. The model and its parameters (mean and variances) will be employed to perform computer simulations to assess the RLD versus RLD, and RLD versus generic comparisons under various scenarios. The probability of meeting BE for RLD versus RLD will provide an objective basis to evaluate the impact on the ability to meet BE.
- The outcome of this study will be to evaluate and develop methodologies that could facilitate approval of generics for products with high batch-to-batch variability.
- Supports FY2019 GDUFA Research Priority:
    - D. Tools and methodologies for BE and substitutability evaluation

Bioequivalence Considerations of Topical Rectal and Vaginal Suppositories

- Awarded to the University of Rhode Island (1U01FD006721)
- The award involves a combination of formulation manufacturing, quality and performance characterizations, and an evaluation of in vitro and ex vivo based approaches for evaluating the BE of rectal and vaginal products.
- This work will aid FDA in extending in vitro BE approaches for topical dermatological products to topical formulations that are applied using other topical mucosal routes of administration.
- Supports FY2019 GDUFA Research Priority:
    - B2. Expand characterization-based BE methods across all topical dermatological products

Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency

- Awarded to Drexel University (75F40119C10106)
- The purpose of this contract is to develop and implement a novel data tool based on text analysis and machine learning that will accelerate the development of product-specific guidances (PSGs). A novel neural abstractive summarization model integrated with a deep-learning based information retrieval system will be developed to aid the information collection and knowledge generation needed to develop a PSG and an open-source software package will be developed and delivered.
- The algorithm and software developed will save FDA staff a significant amount of time and effort in developing PSGs and provide industry even faster access to product specific guidance.
- Supports FY2019 GDUFA Research Priority:
    - D4. Develop methods 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

Development of model-informed bioequivalence evaluation strategies for long-acting injectable products

- Awarded to Uppsala University, Sweden (75F40119C10018)

- The proposed research will use PK modeling and simulation methodology to develop strategies and tools for bioequivalence (BE) evaluation of long-acting injectable products (LAI) based on multiple dose switch and single dose parallel studies.
- The outcome of this proposed research will help to develop new BE evaluation methods for LAI products to shorten BE study (multiple dose) and decrease number of subjects needed (parallel study). The methodology of optimal design will be also applied to shorten study duration and/or reduce the number of subjects.
- Supports FY2019 GDUFA Research Priority:
    - D. Tools and methodologies for BE and substitutability evaluation

Elucidating Sensorial and Functional Characteristics of Topical Formulations

- Awarded to the University of Queensland (1U01FD006700)
- The award involves formulation manufacturing, quality characterizations, and product performance characterizations in vitro as well as in vivo to understand how differences in product composition may impact functional properties that may be relevant to the clinical performance of a drug product or to patient perceptions of therapeutic efficacy and cosmetic elegance/acceptability.
- This work will aid FDA in extending in vitro BE approaches for topical dermatological products to formulations that are not qualitatively and quantitatively the same compared to each other. It will also aid generic developers in identifying limits for critical inactive ingredients, which may affect the overall performance of a topical products and provide data to correlate product quality parameters with product performance attributes, which may support the in silico modeling and simulation of topical product performance.
- Supports FY2019 GDUFA Research Priorities:
    - B1. Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
    - B2. Expand characterization-based BE methods across all topical dermatological products

Evaluating Innate Immune Response of Generic Peptide Drugs and Associated Impurities using In Vitro Assays

- Awarded to NCL/NCI/NIH (224-19-3008S)
- This contract will examine a collection of in vitro assays that can evaluate the risk of immunogenicity due to innate immune responses and reveal potential differences between a proposed generic product and the corresponding reference listed drug (RLD) product. Differences in immunogenicity may be due to process-related impurities, aggregation, and other physicochemical attributes of peptide drug products as well as innate immune modulating impurities (IIMIs, such as endotoxin and beta-glucans). A correlation (or a lack thereof) between the innate immune responses, IIMIs and physicochemical attributes of generic drug products and their corresponding RLDs will be evaluated in vitro.
- This contract work will establish the best practices and protocols for in vitro evaluation of innate immune responses in peptide drug products that will support the development and evaluation of data and information submitted consistent with the recommendations in the draft guidance on *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*. It will help generic applicants provide supporting data to demonstrate that their proposed synthetic peptide drug product does not contain impurities or contaminants that

produce a greater or distinct stimulation of the innate immune response as compared to the RLD product.

- Supports FY2019 GDUFA Research Priority:
    - A3. Establish predictive in silico, in vitro and animal models to evaluate immunogenicity risk of formulation or impurity differences in generic products.

Evaluation of Model-Based Bioequivalence (MBBE) statistical approaches for sparse designs PK studies

- Awarded to Inst Nat Sante Et La Recherche Medicale, France (75F40119C10111)
- The objective of this contract is to develop, evaluate and compare model-based methods to analyze BE studies with sparse PK designs with the aim to find adequate statistical approaches to control type I errors and to achieve enough power to conclude BE using nonlinear mixed-effects models.
- The outcome of this study will be to develop and evaluate new approaches for assessment of BE in sparse PK designs.
- Supports FY2019 GDUFA Research Priority:
    - D. Tools and methodologies for BE and substitutability evaluation

Expanding BCS class 3 waivers for generic drugs to non-Q1/Q2

- Awarded to Absorption Systems LP (75F40119C10127)
- This contract will 1) evaluate of the suitability of in vitro dissolution absorption system (IDAS) to assess the effects of selected excipients on Biopharmaceutics Classification System (BCS) Class 3 drug substances and 2) study the impact of combinations of excipients in solid oral drug products on drug dissolution and permeation. The IDAS is able to evaluate dissolution and permeation simultaneously, which has more advantages when compared to separate testing. The data generated by the IDAS system will be an input to PBPK models that will predict the impact of changes in formulation composition on drug absorption.
- This work will potentially promote the use of BCS Class 3 biowaiver pathway and provide data that could be used to evaluate expanding BCS Class 3 waivers to non-qualitatively and quantitatively equivalent (Q1/Q2) formulations.
- Supports FY2019 GDUFA Research Priority:
    - D3. Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of BCS of Class 3 biowaivers to non-Q2 (quantitatively inequivalent) formulations

Formulation development of hydrocodone bitartrate opioid test drug product for use in chewing pharmacokinetic studies

- Awarded to NIPTE (3U01FD004275-07S1)
- The objective of this study is to develop a hydrocodone bitartrate abuse deterrent formulation with a higher rate of hydrocodone release upon chewing. The product will be used in a chewing pharmacokinetic (PK) study under a separate contract (HHSF223201610004I-75F40119F19004).
- The outcome of this study in conjunction with chewing PK study will be used to determine critical study design parameters when comparing abuse deterrence of an opioid product in the oral route between a generic product and its reference labeled drug when chewed.
- Supports FY2019 GDUFA Research Priority:
    - A. Complex active ingredients, formulations, or dosage forms

In Vitro and Non-Clinical Evaluation of Locally-Acting Topical Dermal and Ophthalmic Formulation Properties

- Awarded to Absorption Systems LP (75F40119D10024)
- This award is an indefinite delivery/indefinite quantity (IDIQ) contract. The purpose of the contract is to conduct in vitro release testing (IVRT), in vitro permeation testing (IVPT), and in vivo animal studies of locally-acting topical dermal and ophthalmic drug formulations. Studies will assess how formulation properties, known as the critical quality attributes (CQAs), effect local and systemic PK, and pharmacodynamics (PD) will be used to establish in vitro-in vivo correlation (IVIVC) or in vitro-in vivo relationship (IVIVR) models.
- Development of IVRT and IVPT testing methods as well as IVIVC and IVIVR models that are sensitive and discriminatory of CQA differences will support the regulatory review and development of bioequivalence testing recommendations for these complex drug products.
- Supports FY2019 GDUFA Research Priorities:
    - B1. Improve PBPK models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
    - B2. Expand characterization-based BE methods across all topical dermatological products
    - B3. Expand characterization-based BE methods across all ophthalmic products

Microstructure characterization with micro-imaging and image-based analytics: a new tool to characterize complex polymer-based long acting drug products

- Awarded to DigiM Solution LLC (75F40119C10157)
- This contract seeks to provide a fundamental understanding of in vitro release characteristics of long-acting controlled release drug products for local use and develop a quantitative microstructure image-based release prediction tool. Three-dimensional structural imaging of selected long-acting drug products will be obtained using advanced micro-imaging technologies and image-based analytics and the image-based microstructure will be correlated with the in vitro release characteristics. Locally acting microspheres and long-acting levonorgestrel intrauterine systems will be the model products.
- A successful correlation between the quantitative image-based microstructure and in vitro release characteristics of such complex dosage forms is a potential new type of in vitro studies for evaluating bioequivalence of long-acting microspheres.
- Supports FY2019 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectables including the identification of the CQAs for these products

MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products

- Awarded to Institute of Quantitative Systems Pharmacology (75F40119C10139)
- This contract will utilize a model-informed drug development approach to identify cost-effective tools for evaluating target site bioequivalence of drug products that incorporate nanomaterials (e.g., liposomal drug products). An in silico systems-based multiscale model can capture the various biological and physicochemical events that affects the transport and residence of nanoparticles (NP) and its cargo active pharmaceutical ingredient (API). The contract will improve these models by measuring the NP/API specific model parameters and the release characteristics of API from NP via in vitro studies and in vivo (in mice) experiments.

- Development of IVIVC and IVIVR models for nanotechnology products that are sensitive and discriminatory will support the regulatory review and development of bioequivalence testing recommendations for these complex drug products.
- Supports FY2019 GDUFA Research Priorities:
    - A2. Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products
    - B1. Improve PBPK models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Modifications and Improvements to hybrid CFD-PBPK models for predication of nasal corticosteroid deposition, absorption and bioavailability

- Awarded to Applied Research Associates, Inc. (75F40119C10079)
- The purpose of this contract is to modify and improve a hybrid computational fluid dynamics (CFD) and PBPK model of nasal drug delivery that was previously developed for grant 1U01FD05201. To validate the CFD model, gamma scintigraphy data will be collected in three healthy and three rhinitic in vitro nasal models. A coupled air-particle approach will be tested in the CFD model and the PBPK model will now include the ability to specify a polydisperse particle size distribution. The hybrid CFD-PBPK model will be tested using fluticasone furoate and triamcinolone acetonide.
- Improvements in model validation and particle size distribution input will allow FDA to evaluate the sensitivity of local and systemic pharmacokinetics to differences in various in vitro parameters that are often recommended for establishing bioequivalence of generic nasal suspension spray products. This can lead to more efficient BE approaches for nasal sprays.
- Supports FY2019 GDUFA Research Priorities:
    - B1. Improve PBPK models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
    - B5. Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products that are more predictive of and sensitive to differences in local delivery

New analytical methods for complex sameness of injectable, long-acting PLGA formulations

- Awarded to Akina Inc., (75F40119C10096)
- The objective of this contract is to develop and validate poly lactic-co-glycolic acid (PLGA) analytical tools for determining the qualitative, quantitative, and microstructural properties of PLGA-based depot formulations. The project will determine the limit of semi-solvent effect by creating new solvent systems for separating PLGAs based on the monomer (L:G) ratio. A Molecular Topology Fractionation method will be developed to separate PLGAs based on molecular structures from mixtures of linear and branches PLGAs. In addition, 3-dimensional (3D) microstructures of PLGA microparticles will be quantitatively characterized.
- The outcomes of this project will further advance our understanding of evaluating microstructures of PLGA microparticles, as well as solid implants, and enable quantitative comparisons between proposed generics and RLD products.
- Supports FY2019 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectables including the identification of the CQAs for these products

Pharmacokinetic study of opioid drug products following oral ingestion of chewed products

- Awarded to Biopharma Services USA Inc. (HHSF223201610004I-75F40119F19004)

- The objective of this study is to develop and validate an in vitro chewing method that can predict in vivo opioid availability after chewing of opioid drug products.
- The outcome of this study will help to determine critical study design parameters when comparing abuse deterrence of an opioid product in the oral route between a generic product and its reference labeled drug when chewed.
- Supports FY2019 GDUFA Research Priority:
    - A. Complex active ingredients, formulations, or dosage forms

Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence

- Awarded to Massachusetts General Hospital/Harvard Medical School (1U01FD006698)
- The award involves research to develop pharmacokinetic tomography imaging tools to measure the concentration of the drug at selected depths in the skin (e.g., in the epidermis and dermis) by non-invasive methods.
- This work will aid FDA in extending in vitro BE approaches for topical dermatological products to formulations that are not qualitatively and quantitatively the same compared to each other, and provide data characterizing how components of a formulation (both active and inactive ingredients) permeate into and through the skin; this information may support the development of in silico models of topical drug delivery.
- Supports FY2019 GDUFA Research Priorities:
    - B1. Improve PBPK models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
    - B2. Expand characterization-based BE methods across all topical dermatological products

Systematic evaluation of the ex-throat plume properties of metered dose inhaler (MDI) formulations

- Awarded to University of Florida, USA (75F40119C10154)
- This contract will investigate how plume characteristics (in terms of droplet size distribution and aerodynamic particle size distribution) from commercial MDI drug products are changed when passing through different anatomical mouth throat models made with different materials. These studies will also investigate the potential effects of different flow rates, device insertion angle, and coating, on the MDI plume characteristics.
- Improvement in the Agency's understanding of how a patient's anatomical physiology can influence drug delivery from MDI drug products and can lead to more efficient in vitro based BE approaches for MDI products.
- Supports FY2019 GDUFA Research Priority:
    - B4. Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids

Tear Film Thickness and Menisci Measurements on Rabbit Ocular Surface After Instillation of Cyclosporine Ophthalmic Emulsion

- Task order awarded to Absorption Systems LP (75F40119D10024-75F40119F19001)
- This is a non-clinical rabbit study examining ocular tear film thickness and menisci changes when ophthalmic formulations with different physicochemical properties are administered. Data from the study will be used to validate a PBPK model that uses a combination of physics-based and compartmental approaches to predict bioavailability at the ocular site(s) of action.
- This will help FDA improve in vitro bioequivalence approaches for ophthalmic formulations through a deeper understanding about how generic formulation physicochemical properties

impact tear film thickness. FDA could use this knowledge to determine more clinically significant equivalence limits for generic formulation physicochemical properties.

- Supports FY2019 GDUFA Research Priorities:
    - B1. Improve PBPK models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
    - B3. Expand characterization-based BE methods across all ophthalmic products

Use of instrumental variable approaches to assess the safety and efficacy of brand-name and generic drugs used to treat hypothyroidism

- Awarded to Yale-Mayo Clinic, FDA Center of Excellence in Regulatory Science and Innovation (CERSI) (3U01FD005938-03S1)
- This project will explore the opportunity to utilize more advanced methodology (instrumental variable) to adjust for unobservable confounding in observational studies that are intended to compare brand and generic products. This method will be compared with propensity score matching.
- The methods evaluated in this study may help FDA to accurately evaluate the therapeutic equivalence of generic products.
- Supports FY2019 GDUFA Research Priority:
    - D4. Develop methods 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

GDUFA Regulatory Science Priorities for Fiscal Year 2019