FY 2018 Awarded GDUFA Regulatory Research Contracts and Grants

In-silico and In-vitro Methods for Evaluating Generic Peptide Drug Immunogenicity

- Awarded to CUBRC & EpiVax, Inc. (HHSF223201810186C)
- This contract addresses the aspect of immunogenicity non-clinical assessment of certain peptide products, as mentioned in the recently published guidance on highly purified synthetic generic peptide drug products referencing the reference listed drug (RLD) of rDNA origin. An immunoinformatic suite software has been developed by EpiVax and is commercially available. Validation of the immunogenicity risk assessment using in silico tools will be obtained using orthogonal methods (in vitro assays such as HLC binding and T cell assays). The proposed model drugs to use for this work are salmon calcitonin and teriparatide. The proposed work also includes the development tools that may be useful when assessing other generic synthetic peptide products: an algorithm that will perform a scoring function for modeling risk associated with potential (unknown) product impurities, and in-silico modeling of unnatural amino acids.
- The proposed work will demonstrate how to use immunoinformatic-driven analysis and in vitro validation assays to perform an immunogenicity risk assessment, a workflow that is currently in use in the biologic drug industry, for synthetic peptide drug products submitted in ANDAs.
- Supports FY2018 GDUFA Research Priority:
    - Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products

Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres

- Awarded to the University of Michigan (HHSF223201810187C)
- The objective of this contract is to investigate influence of raw materials, manufacturing variables, and storage conditions on in vitro and in vivo performance of exenatide in PLGA microspheres. The contract identifies extended release exenatide as a model product for PLGA-peptide interactions and will develop test methodologies, prepare Q1/Q2 formulations using various raw materials and manufacturing variables, and evaluate product attributes, stability, and release performance of Q1/Q2 formulations in vitro and in vivo.
- The contract outcomes will provide critical information to both the Agency and to potential applicants developing Q1/Q2 PLGA based injectables containing large peptides.
- Supports FY2018 GDUFA Research Priority:
    - Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables

Impact of Polymer Source Variations on Parenteral Microsphere Drug Product Performance

- Awarded to the University of Connecticut (HHSF223201810115C)
- The goal of this contract is to provide a fundamental understanding of the impact of polymer (poly lactic-co-glycolic acid (PLGA)) source variation on the drug release characteristics and, hence, the in vivo performance of microsphere drug products.
- The experimental results from this contract will help product developers to determine if there are variations with respect to the PLGA polymer source, and if so, what the impacts are on the drug product properties, including drug release pattern and degradation duration. The results will also help FDA establish recommendations for PLGA (Q1) sameness.
- Supports FY2018 GDUFA Research Priority:
    - Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables

Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery

- Awarded to Princeton University (1U01FD006514) and the University of Sydney (1U01FD006525)
- The aim of these grants is to develop simulation platforms based on a computational fluid dynamics (CFD) - discrete element model (DEM) approach that can describe particle interactions in dry power inhaler (DPI) drug delivery. The emphasis is on simulating carrier-active pharmaceutical ingredient (API) particle agglomeration, breakup, and deposition that determine DPI performance. The two grants will explore different approaches to modeling both the interparticle forces and the particle interactions with the flow and the University of Sydney grant will include generation of new experimental data to validate the models.
- Outcomes of this research will aid the development of generic DPIs by providing a product development tool that can predict key interactions of carrier particles with the API. It is also a step toward improving the predictability of in vitro bioequivalence methods for DPIs with respect to in vivo performance.
- Supports FY2018 GDUFA Research Priorities:
    - Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Evaluating Batch to Batch Variability and its Origins in Dry Powder Inhalers

- Awarded to the University of Texas at Austin (HHSF223201810169C)
- The purpose of this contract is to develop relevant in vitro analytical and statistical approaches to assess the batch to batch variability of dry powder inhaler (DPI) products. The study will identify critical physiochemical properties of DPI formulations and devices that may contribute to batch-to-batch variability in these products.
- The ultimate result of this study will be the identification of the physicochemical properties of the DPI products that play the most substantial role in batch to batch variability. This information is critical to the development of generic inhalation products and will aid FDA in developing approaches to evaluate brand to generic equivalence in situations where the brand product batches differ from each other.
- Supports FY2018 GDUFA Research Priority:
    - Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids

A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs

- Awarded to CFD Research Corporation (CFDRC) (HHSF223201810182C)
- The purpose of this contract is to further enhance and validate the computational framework previously developed for grant 1U01FD005201 to simulate pharmacokinetics of orally inhaled drug products (OIDPs) and to develop model-based in vitro device protocols. The quasi-3D (Q3D) model was originally adapted to one lung geometry, and it will be expanded to other geometries. Respiratory airways will be added to the previous Q3D model, which only included conducting airways. In addition to Q3D model development, in silico models of drug dissolution in several in vitro apparatuses will be developed, where physicochemical parameters may be specified as inputs. Diffusion modeling will be included where necessary, and the modeling for volume-limited dissolution will be enhanced.

- Linking deposition models for inhalation delivery to PBPK models is a key step to more efficient bioequivalence methods for OIDPs. This type of model can help determine if bioequivalence for OIDPs can be evaluated by pharmacokinetic and in vitro studies without the need for comparative clinical endpoint studies.
- Supports FY2018 GDUFA Research Priorities:
    - Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Nasal Pharmacokinetic/Pharmacodynamic Studies of Oral Combination Products Containing Opioid Agonists and Antagonists

- Awarded to BioPharma (HHSF223201610004I-HHSF22301002T)
- The objective of this study is to investigate factors that affect pharmacokinetic and pharmacodynamic effects of opioid agonists and antagonists (i.e., human abuse potential) following snorting of physically manipulated oral combination products. Factors to be evaluated include, but are not limited to, physical manipulation (e.g., tool, duration, strength), amount of milled particles recovered from the drug product after physical manipulation, particle size distribution, morphology, and in vitro dissolution/release of opioid agonists and antagonists from the milled product.
- Outcomes of this study will help determine critical study design parameters when comparing abuse deterrence of a combination product in the nasal route between a generic product and its reference listed drug.
- Supports FY2018 GDUFA Research Priority:
    - Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

Nasal Mucociliary Clearance Affecting Local Drug-Absorption in Subject-Specific Geometries

- Awarded to North Carolina State University Raleigh (1U01FD006537)
- The goal of this grant is to develop a computational modeling approach to study the effects of mucociliary clearance on localized drug absorption in the nasal cavity. The modeling approach will include development and validation of transient 3-D mucociliary clearance and interactive particle transport/deposition models applied to different nasal geometries using computational fluid dynamics (CFD). It will use a representative configuration to simulate and analyze drug-aerosol transport, deposition, absorption and clearance, all subject to different inlet conditions, possible obstructed nasal geometry and different rheological conditions of the mucus layer. These models will help product developers and FDA reviewers understand how long nasally delivered particles remain in the nose.
- Outcomes of this research are the advancement of in vitro bioequivalence approaches for nasal sprays intended to deliver drug to the nose and a better understanding of abuse-deterrent formulations of opioids that are intended to provide barriers to nasal drug delivery.
- Supports FY2018 GDUFA Research Priorities:
    - Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies
    - Develop alternatives to clinical endpoint BE studies for locally-acting nasal products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition In Silico and In Vitro

- Awarded to Virginia Commonwealth University (HHSF223201810144C)
- The goal of this contract is to develop three anatomical nasal airways that cover the range of intranasal deposition of sprays for standardized testing of new and generic nasal products to confirm the sameness in regional deposition in comparison to seven reference products. These three models will be developed based on the data resulting from a hybrid strategy using realistic in vitro testing with multiple nasal airways in combination with advanced computational modeling. In addition, these three models will provide a platform to evaluate the effect of various device- and patient-related parameters on regional nasal deposition. The work includes generating anatomical parameters from 20 adult nasal cavities and using computational fluid dynamics (CFD) models to refine the parameters into three representative in vitro models.
- Results from this contract will aid in the development and refinement of in vitro bioequivalence tests for nasal sprays. Based on improved nasal deposition models it may be possible to reduce the number of in vitro tests bioequivalence tests recommended for nasal sprays.
- Supports FY2018 GDUFA Research Priorities:
    - Develop alternatives to clinical endpoint BE studies for locally-acting nasal products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations

- Awarded to the University of South Australia (1U01FD006496) and the University of Mississippi (1U01FD006507)
- These two grants aim to develop an understanding of fundamental processes governing the comparative performance of topical dosage forms that have Q1/Q2 differences relative to each other. Work will include the measurement of physical, structural and functional properties for a range of formulations (with systematically varied components and/or compositions) to understand how differences in the physicochemical properties and the metamorphosis of these formulations on the skin alter such properties as the solubility and thermodynamic activity profiles of the active ingredient in the formulation as it dries on and permeates into the skin. The two awards involve distinct but complementary approaches to the work, including a combination of formulation manufacturing, quality and performance characterizations, as well as mathematical modeling and simulations based upon computational fluid dynamics, thermodynamics, and potentially other approaches.
- This work will aid FDA in extending in vitro bioequivalence approaches for topical dermatological products to formulations that are not Q1 and Q2 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.
- Supports FY2018 GDUFA Research Priorities:
    - Expand characterization-based bioequivalence (BE) methods across all topical dermatological products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems

- Awarded to Simulations Plus, Inc. (1U01FD006526) and the University of Queensland (1U01FD006522)
- These two grants are awarded to advance the incorporation of formulation drug product quality attributes into dermal PBPK models. The grant to Simulations Plus will expand the capabilities of the GastroPlus™ Transdermal Compartmental Absorption and Transit (TCAT)™ model to include the ability to identify and quantify drug-product-specific critical quality and performance attributes and to perform virtual bioequivalence assessments comparing brand name and generic topical and transdermal drug products. Published data on the quality and performance attributes of topical and transdermal formulations will be used to develop and validate mechanistic equations describing the in vitro release/permeability assays for a variety of formulations. The grant to the University of Queensland will use the MechDermA PBPK model, developed by the industry partner, Simcyp®, as the core PBPK model. Pertinent literature and in-house studies to define necessary drug product quality attributes from a wide range of formulations will be used and included in the developed models. Further development of models to account for active pharmaceutical ingredient (API) – product – skin interactions during the metamorphosis of various products applied to human skin will take place.
- The intended outcomes of these grants are the development of modeling and simulation tools that can be used to perform virtual bioequivalence studies of topical products that allows the evaluation of the impact of formulation differences (especially Q3 differences) on the in vivo performance of dermatological drug products. These tools can inform regulatory decisions and guide generic product developers in the design of bioequivalent dermal and transdermal drug products.
- Supports FY2018 GDUFA Research Priorities:
    - Expand characterization-based bioequivalence (BE) methods across all topical dermatological products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Characterize Skin Physiology Parameters Utilized in Dermal Physiologically-Based Pharmacokinetic Model Development Across Different Skin Disease States

- Awarded to Simcyp®, Ltd. (1U01FD006521)
- This grant aims to further enhance the currently available PBPK Multi Phase Multi Layer (MPML) MechDermA skin model with the quantitative description of the disease triggered histological and functional modifications of the skin. Information on thickness of various skin layers, presence of cracks, dryness, modification of the blood flow and skin temperature, sebaceous glands infection and inflammation, flaking, presence of pustules, comedones, vacuoles, cysts, and pseudocysts will be taken into consideration during model building. Histopathological modifications of the healthy skin will be used as the building blocks allowing for ad hoc development of the disease of interest. An important element of the project will be a quantitative verification of the developed models together with the pre-defined diseases versus the literature derived clinical reports data.
- The inclusion of skin disease states into PBPK models will help the generic industry develop non-Q1/Q2/Q3 formulations and simulate their in vivo performance in patient population to further support their substitutability in diseased skin.

- Supports FY2018 GDUFA Research Priorities:
    - Expand characterization-based bioequivalence (BE) methods across all topical dermatological products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products using Non-Invasive Techniques

- Awarded to the University of Bath (1U01FD006533)
- This grant will evaluate whether spectroscopic - and, in particular, Raman - imaging is able to provide a non-invasive, accurate, sensitive, and reproducible determination of the rate and extent to which a topically administered drug becomes available at its site of action in the skin (and, specifically, the viable epidermis). The initial goal is to establish experimental methods, combining Raman and mass spectrometry imaging, to prove this hypothesis ex vivo. Then the approach will be calibrated using complementary techniques, including stratum corneum sampling and reverse iontophoresis, an additional, alternative, non-invasive method.
- If this grant is successful it will lead to a non-invasive bioequivalence method for topical dermatological products that directly measures drug at the site of action. This will reduce the need to use comparative clinical endpoint bioequivalence studies for topical products.
- Supports FY2018 GDUFA Research Priority:
    - Expand characterization-based bioequivalence (BE) methods across all topical dermatological products

Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations

- Awarded to RTI International (HHSF223201810113C)
- The purpose of this study is to conduct a qualitative, enhanced focus group study to advance FDA's understanding of patient and caregiver attitudes toward generic drug-device combination product substitution and build an evidence base to inform policy. Specifically, the focus group data will utilize participatory research design methods to ascertain in-depth reactions and perceptions of differences of quality, use, and efficacy between a generic drug-device and its RLD or "brand" drug-device.
- The results of this research will help FDA and the generic industry identify what user interface differences may have an impact on patient substitution.
- Supports FY2018 GDUFA Research Priority:
    - Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products

Development of a Virtual Bioequivalence Trial Simulation Platform that Integrates Population Pharmacokinetic Modeling Algorithms into Physiologically-Based Pharmacokinetic Models

- Awarded to the Children's Hospital of Los Angeles (1U01FD006549)
- The goal of this grant is to develop a comprehensive, freely available, open-source software platform for bioequivalence (BE) study design. Components of the platform will implement a framework for population modeling based on physiologically-based pharmacokinetic (PBPK) models integrated with a trial simulator. Appropriate model structures for a wide range of compounds and routes of administration will be combined with diverse and robust methods for population modeling to allow simulating a variety of BE trial designs with standard and novel

optimal sampling strategies. A BE trial simulator will be created to simulate output for a wide range of BE trial designs.

- The ability to perform virtual bioequivalence studies will decrease the risk in generic drug development by allowing product developers to assess the probability of BE for a given generic drug product by using modeling and simulation tools. Success in this area may support the future use of virtual bioequivalence studies in regulatory submissions.
- Supports FY2018 GDUFA Research Priorities:
    - 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

To Better Understand Risk Mitigation in The Evaluation of Relative Bioavailability of Pediatric Generic Products

- Awarded to the University of Birmingham, UK (HHSF223201810112C)
- This contract aims to identify product- and population-related risk factors associated with evaluation of bioequivalence/relative bioavailability of pediatric drug products in adult subjects. Generic pediatric products are generally not required to be tested in pediatric populations. The contract will involve data mining to bring together all available information on the bioequivalence/relative bioavailability of pediatric formulations and determine risk factors for differences in adult and pediatric relative bioavailability and the development of specific in vitro and in silico tools to generate greater understanding.
- The research findings will help develop in vitro tests and in silico simulation tools to evaluate risk factors of pediatric products. These tools will help ensure the bioequivalence of pediatric generic products in pediatric population without additional in vivo studies.
- Supports FY2018 GDUFA Research Priority:
    - Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards

GastroPlus Ocular Compartmental Absorption and Transit (OCAT) Model Extension and Validation

- Awarded to Simulations Plus (HHSF223201810255P)
- The overall goal of this contract is to further develop an existing ophthalmic physiologically based pharmacokinetic (PBPK) model – the OCAT model - previously worked on by Simulations Plus under grant 1U01FD005211. That work previously focused on ophthalmic suspension formulations. This new effort will focus on three tasks: 1) incorporation of protein binding kinetics into eye tissue compartments; 2) application of a simplified macroscale pH calculation engine into precorneal compartment to more accurately estimate local solubility/precipitation parameters; and 3) development of options for ointment formulations which allow for input of in vitro data to characterize physiochemical property data.
- The outcomes of this contract will help advance further understanding of the mechanistic impact of physiochemical properties of ophthalmic formulations on in vivo ocular pharmacokinetic performance and support the use of in vitro BE approaches for ophthalmic products.
- Supports FY2018 GDUFA Research Priority:
    - Expand characterization-based BE methods across all ophthalmic products

In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence

- Awarded to the University of Connecticut (HHSF223201810114C)
- This contract is aimed at establishing versatile in vitro approaches based on microstructure characterization to assesses bioequivalence of Q1/Q2 equivalent ophthalmic ointments and to validate in vitro assessments through ex vivo and in vivo pharmacokinetic studies in rabbit eye comportments. The contract involves defining optimal dissolution conditions and comparing release profiles of APIs from Q1/Q2 equivalent ointments followed by evaluation of the correlation between in vitro, ex vivo, and in vivo studies.
- The study results will aid the development and revision of product-specific guidances for ophthalmic ointment products.
- Supports FY2018 GDUFA Research Priorities:
    - Expand characterization-based BE methods across all ophthalmic products
    - Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products

- Awarded to CFD Research Corporation (HHSF223201810151C)
- The overall goal of this contract is to further develop an existing ophthalmic physiologically based pharmacokinetic (PBPK) model previously created for grant 1U01FD005219. The new model will include several enhancements, where accuracy of physiology characterization will be improved and a system for developing in vitro-in vivo extrapolations or correlations (IVIVEs or IVIVCs) will be developed. The project will enhance the tear-film model by including considerations for tear film salt concentrations, which will allow for tracking tear film osmolarity and pH. The new model will also include improved posterior eye physiology, consideration of disease states, and whole-body physiologically-based pharmacokinetic (PBPK) modeling. The dissolution model will be developed using a computational fluid dynamics (CFD) Eulerian approach, which will allow for greater precision of these predictions.
- The outcomes of this contract will help advance further understanding of the mechanistic impact of physiochemical properties of ophthalmic formulations on in vivo ocular pharmacokinetic performance and support the use of in vitro BE approaches for ophthalmic products.
- Supports FY2018 GDUFA Research Priorities:
    - Expand characterization-based BE methods across all ophthalmic products
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Physiologically-Based Model of The Female Reproductive Tract: Vaginal and Intrauterine Delivery Components

- Awarded to the University of Buffalo (HHSF223201810188C)
- The objective of this grant is to develop a generalized PBPK model of the female reproductive track. Currently, there is limited information available for the development of a PBPK modeling platform for these complex products and there is no available PBPK module of the female reproductive track. This grant will collect physiological, pharmacokinetic, and drug physicochemical data not currently available in the literature through a series of in vitro, ex vivo, and in vivo studies. These data will be used to fill critical gaps needed to develop and validate a generalized PBPK modeling platform for complex products delivered through the female reproductive tract

- The outcomes of this grant will help FDA develop alternate bioequivalence approaches for products that use this route of delivery.
- Supports FY2018 GDUFA Research Priorities:
    - Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables
    - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

GDUFA Regulatory Science Priorities for Fiscal Year 2018