FY2020 Awarded GDUFA Science and Research Contracts and Grants

Impact of Polymer Attributes on the Performance of In Situ Forming Implants: Improve Scientific Approaches to Evaluate Generic Drugs

- Awarded to University of Connecticut (75F40120C00021)
- This research will characterize in situ forming implants with a model drug, determine the physicochemical properties of a series of customized poly[lactic-co-glycolic acid] (PLGA) polymers with different properties, study the impact of PLGA attributes on the in situ forming implants' performance, develop in vitro release testing methods, and determine the impact of PLGA attributes on drug release from the in situ forming implants.
- Research outcomes from this contract will facilitate the development of in vitro (only) approaches to support a demonstration of bioequivalence (BE) for generic in situ forming implants.
- Supports FY2020 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectable drug products including the identification of the critical quality attributes (CQA) for these products

Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations

- Awarded to Nanopharm Ltd. (75F40120C00036)
- This research aims to develop and validate a morphology-directed Raman spectroscopy (MDRS) method to characterize the drug particle size distribution (PSD) of mometasone furoate containing nasal suspensions that have been used in a clinical pharmacokinetic study with healthy subjects, which was conducted as part of a previously awarded research contract to the University of Florida. In addition, the mometasone furoate PSD from these nasal suspensions will be measured across different storage times (e.g., 1, 3, 6, and 12 months) and under different conditions to evaluate the stability characteristics of the nasal suspensions.
- The outcomes of this research will support FDA's efforts to develop new in vitro methods to support a demonstration of BE by evaluating the relationship between the mometasone furoate PSD of these nasal suspensions and the systemic exposure measured using a pharmacokinetic (PK) study in healthy subjects.
- Supports FY2020 GDUFA Research Priority:
    - 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

Evaluation of Critical Process Parameters for the Preparation of Amphotericin B that Influence Toxicity

- Awarded to Landrau Scientific Innovations (75F40120C00055)
- This research will examine how the critical process parameters (CPPs) of heat treatment and lyophilization conditions impact the critical quality attributes (CQA) of amphotericin B liposomes. The work will focus on developing analytical methods to characterize how differences in the CQAs correlate to product toxicity through in vitro and in vivo animal toxicity studies. This award is an extension to a previous contract (HHSF223201610093C) that identified CPPs and a correlating CQA design space.
- Outcomes from this research will support the development of in vitro tests and the identification of specific CQAs (and associate ranges) that correlate to changes in product safety. These are essential to developing and evaluating high-quality generic amphotericin B liposome products. Moreover, outcomes from this project will help develop appropriate in vitro tests and facilitate a

better understanding of the factors impacting product quality and performance for all liposomal products.

- Supports FY2020 GDUFA Research Priority:
    - A2. Improve particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

Characterization of Exparel®: Understanding of Critical Manufacturing Process Parameters and Characterization of Drug Release Mechanisms In Vitro and In Vivo

- Awarded to University of Michigan (75F40120C00127)
- The research will develop appropriate analytical methods for the physicochemical characterization of multivesicular liposome (MVL) products and evaluate the in vitro and in vivo drug release behavior of these systems.
- This research will provide: 1) Analytical methods and data to facilitating the reverse engineering of the reference listed drug, Exparel®; 2) Guidance on developing in vitro drug release testing methods for MVLs; and 3) An improved understanding on potential drug release mechanisms of MVLs.
- Supports FY2020 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectable drug products including the identification of the critical quality attributes (CQA) for these products

Assessing Long-Acting Injectable Formulations Using In Vivo Imaging

- Awarded to University of Connecticut (75F40120C00136)
- This research aims to provide an improved understanding of the phase inversion process occurring in vivo, and the drug release kinetics, of in situ forming gels through non-invasive imaging techniques and complementary in vitro and in vivo studies. This research will assess polymeric depot formation and erosion as well as the impact of these processes on drug release from in situ forming implant products. This research will also determine the impact of polymer microstructure and molecular weight on depot formation in subcutaneous tissue and assess if a correlation exists between in vitro and in vivo drug release, depot erosion, or the pharmacokinetics of an active agent or a surrogate.
- Outcomes from this research will facilitate the development of in vitro (only) approaches by which to support a demonstration of BE for generic in situ forming implants.
- Supports FY2020 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectable drug products including the identification of the critical quality attributes (CQA) for these products

Robust In Vitro/In Silico Model to Accelerate Generic Drug Product Development for the Oral Cavity Route of Administration

- Awarded to Simulations Plus (75F40120C00150)
- This research aims to develop a predictive in silico modeling and simulation platform informed by dynamic in vitro dissolution and absorption model (DIVDAM)-estimated oral cavity permeability of FDA approved drug products and to expand the current in vitro - in vivo correlation (IVIVC) model with the derivation of new equations to extend the IVIVC capacity of the GastroPlus® modeling platform to include drug products administered in the oral cavity. The research will further assess the sensitivity of the predictive in silico modeling and simulation platform to formulation excipients that can alter an active pharmaceutical ingredient's (API's) dissolution and absorption behavior across the oral cavity mucosal barriers.

- Outcomes from this research will support generic drug development for drug products administered through oral cavity route. A better understanding of excipient effects will assist the design and development of formulations for oral cavity drug products including abuse-deterrent opioid formulations. The improved models may be used to extend Biopharmaceutical Classification System (BCS)-based biowaivers to products delivered via the oral cavity.
- Supports FY2020 GDUFA Research Priority:
    - D2. Integrate predictive dissolution, PBPK and Pharmacokinetic/Pharmacodynamic (PK/PD) models establishing generic drug bioequivalence standards

Immunogenicity Risk of Peptide Generic Drug Products and Their Impurities: In Silico and In Vitro Assessment and Validation Methods

- Awarded to EpicVax/CUBRC (75F40120C00157)
- The objective of this research is to develop and validate an in silico assessment tool for predicting the immunogenicity risk of synthetic peptide drug products. The in silico assessment tool or algorithm will generate a list of potential manufacturing-related impurities for synthetic peptide generic drug products and evaluate peptide-related impurities for T cell immunogenicity using immuno-informatics. This research will test the model predictions by synthesizing the drug substance and selected impurities for in vitro validation by human leukocyte antigen binding.
- Outcomes from this research will include comprehensive reports evaluating the immunogenicity for teriparatide and semaglutide impurities. When validated, an in silico algorithm for assessing the immunogenicity risk of potential impurities can be used to assess a product's immunogenicity risk based on the impurity profiles.
- Supports FY2020 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 Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children

- Awarded to Virginia Commonwealth University (75F40120C00172)
- This research aims to develop a hybrid in vitro – in silico drug deposition testing platform for nasal suspension sprays in children through the creation of anatomical nasal airway models for children. Three pediatric nasal cavity models will be selected and manufactured to measure the range of drug delivery to different nasal regions using different reference nasal suspension drug products. Once the optimal nasal models are identified, three models will be selected to represent low, medium, and high deposition and will be used along with three previously developed adult models for in vitro BE testing using generic and brand-name nasal suspension spray drug products. The in vitro results will also be used as inputs to a newly developed computational fluid dynamics – PK model.
- The outcomes of this research will support FDA's efforts to develop new in vitro and in silico BE methods by identifying anatomical nasal models for children that may be more predictive of regional drug deposition to the nose, as well as computational tools that maybe useful for predicting how formulation changes can impact performance and BE.
- Supports FY2020 GDUFA Research Priority:
    - B5. Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products that are more predictive and sensitive to differences in local delivery

Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants

- Awarded to University of Texas at Austin (75F40120C00198)
- This research aims to develop methods to characterize the blockiness of poly[lactide-co-glycolide] (PLGA), to control blockiness through model PLGA synthesis, and to determine the effect of PLGA blockiness on polymer properties and melt-extruded implants.
- Outcomes from this research will facilitate the development or revision of BE recommendations for PLGA-based long-acting injectable products to provide more specific advice on PLGA characterization. This research will also provide knowledge related to key characteristics used to demonstrate the qualitative (Q1) sameness of PLGA polymers.
- Supports FY2020 GDUFA Research Priority:
    - A4. Develop predictive in vitro BE methods for long-acting injectable drug products including the identification of the critical quality attributes (CQA) for these products

Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive In Vitro Dissolution Models

- Awarded to University of Michigan (75F40120C00200)
- This research aims to develop biopredictive methods that will be instrumental for setting PCQS in in vitro-in vivo correlation (IVIVC) models for modified release (MR) oral drug products. The research will generate gastrointestinal tract (GIT) physiology, in vivo drug dissolution and in vivo pharmacokinetic data that can inform predictive in vitro dissolution models which can be used to define PCQS in IVIVC. Data generated will include release and dissolution data from two MR drug formulations in different human GIT regions and a radiolabeled oral solution of the same API.
- The outcomes of this research will establish a unique reference data source to advance bioperformance risk assessments not achievable with current IVIVC methods and will help establish more biorelevant in vitro dissolution testing conditions for MR products.
- Supports FY2020 GDUFA Research Priority:
    - D2. Integrate predictive dissolution, PBPK and Pharmacokinetic/Pharmacodynamic (PK/PD) models establishing generic drug bioequivalence standards

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

- Awarded to Absorption Systems (75F40119D10024-75F40120F19002)
- This research will examine how the physicochemical properties of topical ocular drug products correlate to the ocular tissue distribution pharmacokinetics (PK) and pharmacodynamics (PD) properties. The study will utilize a rabbit animal model and will provide PK/PD information for both single and multiple dose states that can be used to better understand the impact of formulation properties on in vivo performance, thereby establishing critical in vitro-in vivo relationships (IVIVR) for intraocular pressure (IOP) lowering products.
- This research will help develop IVIVRs that may reduce the need for in vivo studies to demonstrate BE and may ultimately lead to in vitro (only) approaches to support a demonstration of BE for these complex locally-acting ophthalmic products.
- Supports FY20 research priorities:
    - B3. Expand characterization-based BE methods across all non-solution ophthalmic products

Center for Research on Complex Generics

- Awarded to University of Maryland and University of Michigan (U18FD007054)
- The purpose of this award is to create a Center for Research on Complex Generics which will support FDA's efforts to enhance research collaborations with the generic industry.
- The Center for Research on Complex Generics aims to aid the generic drug industry and other stakeholders by offering collaborative research and training through webinars, workshops, laboratory projects, and a Complex Generics Scholars program, among other initiatives to meet generic drug development needs. This first of its kind, cutting-edge center will stimulate innovative thoughts, disseminate an understanding of complex drug products and practices, and generate new knowledge in support of FDA's mission to promote and protect the public health.
- Supports FY2020 GDUFA Research Priorities:
    - A. Complex active ingredients, formulations, or dosage forms
    - B. Complex routes of delivery
    - C. Complex drug-device combinations
    - D. Tools and methodologies for BE and substitutability evaluation

The Effect of Excipients on the Oral Absorption of Fexofenadine in Humans

- Awarded to University of California, San Francisco (3U01FD005978-04S3)
- This research will evaluate whether the pharmaceutical excipient, sodium lauryl sulfate (SLS), which interferes with the in vitro activity of the uptake transporter OATP2B1 in the gut, has the potential to clinically impact the oral bioavailability of fexofenadine, a OATP2B1 substrate, and a Biopharmaceutics Classification System (BCS) class 3 drug. Fexofenadine was chosen as a model drug because its absorption in the gut has been reported to be primarily dependent on OATP2B1-mediated uptake.
- Research outcomes will support guidance on what range of SLS may be used without likely inhibition of OATP2B1-mediated absorption of BCS class 3 drugs.
- Supports FY2020 GDUFA Research Priority:
    - D3. Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System (BCS) of Class 3 biowaivers to drug products with differences in formulations larger than currently recommended in FDA guidance

Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics

- Awarded to University of Maryland (U01FD005946)
- This research aims to develop a new method, hyperspectral interferometric scattering microscopy, to characterize nanoparticle-based drugs
- Research outcomes will provide a new orthogonal analytical technique to characterize the particle size and shape of nanoparticle-based drugs
- Supports FY2020 GDUFA Research Priority:
    - A2. Improve particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

Evaluation of the Fundamental Principles of Cutaneous Pharmacokinetic Studies to Support a Demonstration of Bioequivalence

- Awarded to Long Island University (U01FD006930)
- This research will elucidate how pharmacokinetic principles and concepts (e.g., dose, fraction of drug absorbed, apparent volume of distribution, C_{max}, $AUC_{infinity}$, etc.) should be applied or adapted

when evaluating the rate and extent to which a topically applied compound becomes available in the dermis, and to evaluate the relative sensitivity of in vivo dermal PK methods to discriminate differences in drug concentrations in the skin.

- Research outcomes will establish appropriate designs and analyses for in vivo dermal microdialysis (dMD) or dermal open flow microperfusion (dOFM) studies to evaluate topical bioavailability and BE based upon appropriate dermal PK endpoints.
- Supports FY2020 GDUFA Research Priority:
    - D1. Improve quantitative pharmacology and BE trial simulation to optimize design of BE studies for complex generic drug products

Development and Validation of a PBPK/PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human

- Awarded to Simulations Plus (U01FD006927)
- This research aims to determine likely changes in ocular physiology between preclinical species and humans, and then understand which aspects of the physiology will critically impact the extrapolation to humans of predictions from a model calibrated on preclinical PK/PD models.
- The research will further improve the human physiology model by including the most up-to-date measurements available for the healthy human eyes as well as quantifying changes in eye tissue properties with age and common eye diseases. The inter-subject variability of physiology parameters will be investigated in order to perform virtual BE studies.
- Research outcomes will improve current ocular models to provide a better tool for ocular drug development by enhancing their capacity to perform human extrapolation using preclinical PK and PD data. New ophthalmic formulations such as gels and emulsions will be incorporated in the model.
- Supports FY2020 GDUFA Research Priority:
    - B1: Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

Computational Biology (Cobi) Tools as a Framework for Physiologically-Based Pharmacokinetic/Pharmacodynamic Model Extrapolation from Rabbit to Human for Ophthalmic Drug Products

- Awarded to CFD Research Corporation (U01FD006929)
- This research aims to develop a computational platform for interspecies extrapolation of ophthalmic PK and PD via physiologically-based modeling and to identify translational knowledge gaps during interspecies extrapolation. This research will extrapolate existing rabbit models to human models using physiologically-based modeling and compare the human models to collected human PK and PD models.
- Outcomes from this research are expected to be the development of computational tools to translate preclinical testing results from animals to humans for ophthalmic drug products, which will provide researchers with a better understanding of the species differences between animal and human eyes that result in differences in ocular drug distribution.
- Supports FY2020 GDUFA Research Priority:
    - B1: Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

For reference: link to FY2020 posted document (https://www.fda.gov/media/132370/download)