**FY 2014 Awarded GDUFA Regulatory Research Contracts and Grants**

**Characterization of Epilepsy Patients at Risk for Adverse Outcomes Related to Switching Antiepileptic Drug Products**

- Awarded to the University of Maryland (#HHSF223201400188C).
- The project objective is to evaluate the physiologic, psychological, and pharmacogenetic factors that can cause generic brittleness (GB), i.e. patient sensitivity to antiepileptic drug formulation changes, in epilepsy patients.
- This exploratory research will uncover potential factors causing patients to be GB and assess whether those factors result in pharmacokinetic differences between brand and generic drugs in GB individuals.

**Bioequivalence and Characterization of Generic Drugs**

- Awarded to Vince & Associates Clinical Research, Inc. (#HHSF223201210030I).
- As part of the continuous monitoring of approved generics, this contract will support bioequivalence studies of approved generic drugs including bioequivalence between: (1) generic and brand methylphenidate hydrochloride extended release (ER) tablets and (2) a reference listed drug and generic warfarin sodium products from different suppliers and stored under different conditions, including real world use conditions.
- Research outcomes will include evaluating the use of replicate design bioequivalence studies for generic methylphenidate hydrochloride ER products and developing clinically relevant quality standards for warfarin sodium products.

**Pharmacometric Modeling and Simulation for Generic Drug Evaluation**

**Topic 1: Population pharmacokinetic and pharmacodynamic dose-toxicity modeling and simulation for narrow therapeutic index drugs**

- Awarded to the University of Maryland, Baltimore (1 U01 FD0005188-01).
- This project will use principles of pharmacokinetics (PK), pharmacodynamics (PD), and steepness of the pharmacokinetic and pharmacodynamic (PK/PD) relationship to propose quantitative metrics for identifying narrow therapeutic index drugs and propose bioequivalence criteria to better understand the difference between brand and generic drugs.
- Project results will assist FDA in developing models and modeling approaches that classify drugs as having a narrow therapeutic index and identifying those products that have a clinical use profile that requires tighter control of product quality and equivalence attributes.

**Topic 2: Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post-marketing risk assessment**

- Multiple awards to the University of Maryland, Baltimore (1 U01 FD0005192-01) and the University of Florida (1 U01 FD0005210-01).
- The University of Maryland project will use advanced pharmacometric analysis to devise a novel signal-to-noise ratio classification system that rank orders therapeutic areas to further probe in post marketing. The University of Florida project will investigate a risk-based systems pharmacology approach to address issues of post-marketing risk of generic drugs and to interpret post-marketing adverse event reports or product substitution complaints.

- Project results include developing pharmacometrics approaches that will assist the Office of Generic Drugs in evaluating risks associated with post-market product substitution complaints and interpreting post-market adverse event reports for generic drugs.

**Topic 3: Pharmacometric modeling and simulation for pAUC**

- Awarded to the University of Utah (1 U01 FD0005191-01).
- The goal of this grant is to develop quantitative PK/PD models for cyclosporine, tacrolimus, sirolimus, and mofetil mycophenolate in patient populations across all age ranges and use the models to evaluate potential bioequivalence criteria, including partial area under the curve (pAUC).
- Project results will aid FDA in developing modeling and simulation tools that will identify which generic drug products require a greater degree of pharmacokinetic profile similarity to assure therapeutic equivalence.

**Physiologically-Based Absorption and Pharmacokinetic Modeling and Simulation for Non-Gastrointestinally-Absorbed Drug Products in Humans**

- Planned project outcomes are simulation tools that capture the current understanding of the complex interplay between product attributes and human physiology and that help to develop new bioequivalence approaches for locally-acting drugs. Models that embody mechanistic absorption modeling and physiologically-based pharmacokinetics (PBPK) can be useful tools for both industry scientists and regulators to reduce the time and expense involved in determining whether a new formulation will be bioequivalent to an approved dosage form.

**Topic 1: Dermal absorption**

- Awarded to the University of South Australia (1 U01 FD005232-01) and Simcyp, Ltd. (1 U01 FD005225-01).
- The University of South Australia project aims to develop a framework of physiologically-based absorption and pharmacokinetic models that define the interactions between the product and the skin and seek to predict drug and drug plasma/blood concentrations at the site of action. The Simcyp, Ltd. project goal is to develop a physiologically-based dermal absorption and disposition model supported by a clinical trials simulator platform model that accounts for variability and gender effects in healthy Caucasian volunteers. This model will be mechanistically enhanced and validated with reference to other races and special populations including pediatric, geriatric, and those populations with diseases, such as rheumatoid arthritis. The performance of the PBPK model and associated databases will be validated against clinical pharmacokinetics data for dermal products.

**Topic 2: Ocular delivery**

- Awarded to Simulations Plus, Inc. (1U01FD005211-01) and CFD Research Corporation (1U01FD005219-01).
- The Simulations Plus award will advance the state of the art for ocular PBPK and mechanistic absorption modeling (MAM) software through a combination of expanding the existing knowledge base for ocular drug absorption and pharmacokinetics and implementing enhanced physiological models for human and animal eyes in the well-established Ocular Compartmental Absorption and Transit™ (OCAT™) MAM/PBPK model within the GastroPlus™ software program.
- The CFD Research grant will support high-fidelity models in the form of a parametric 2D/3D eye mesh model (human and animal), enabling simulation of various modes of delivery. The novel

computational tool will simulate ocular drug delivery and its interaction locally and systemically within the whole body, thereby providing an accurate and efficient computational platform to virtually test, design, and develop generic ocular drug products.

**Topic 3: Complex Drug Products**

- Awarded to the State University of New York at Buffalo (1U01FD005206-01).
- The goal of this grant is to develop a specialized PBPK model platform to address challenges in the development of liposomal formulations. This specialized PBPK model is expected to enable effective translations from drug product critical quality attributes to their in vivo performance, allowing early interactions between developers and regulators, ultimately expediting liposomal drug development.

**Topic 4: Nasal Delivery**

- Awarded to Applied Research Associates, Inc. (1 U01 FD005201-01).
- In this proposal, PBPK absorption models will be linked to computational fluid dynamics models to simulate the delivery of sprayed droplets to the nose, the absorption of the drug through the nasal mucosa, and the systemic bioavailability of intranasal corticosteroids. Model simulations will improve our understanding of the absorption of intranasal corticosteroids under different dosing scenarios and will support and facilitate generic drug guidance and product development for nasal suspensions.

**Topic 5: Pulmonary Delivery**

- Awarded to CFD Research Corporation (1U01FD005214-01).
- A hybrid CFD model will be developed to predict particle deposition throughout the human airway. The hybrid model will be linked to PBPK and PD models to predict in vivo performance for orally-inhaled drug products. This computational tool will serve as a virtual platform to simulate drug PK/PD, optimize pulmonary drug delivery, and facilitate generic pulmonary drug development.

**Development of a Clinically Relevant In Vitro Performance Test for Generic Orally-Inhaled Drug Products**

- Awarded to the Virginia Commonwealth University (1U01FDD005231).
- The project goal is to determine whether realistic physical mouth-throat models provide better in vivo predictability than pharmaceutical induction port assembly in order to characterize aerodynamic particle size distribution of orally-inhaled drug products.
- This research will provide a more realistic aerodynamic particle size distribution characterization method that can be used as a pharmaceutical development tool in the early stages of orally-inhaled drug product development.

**Dissolution Methods for Suspension and Emulsion Ocular Drug Products**

- Awarded to the University of Eastern Finland (1U01 FD005180-01) and Texas A&M University (1U01 FD005184-01).
- Study goals are to investigate dissolution methods for an ocular suspension or emulsion and to evaluate their capabilities to detect manufacturing differences, predict in vivo performance, and assess method robustness. The Texas A&M project will investigate drug release methods for Difluprednate microemulations. The University of Eastern Finland will develop dissolution methods in simulated lacrimal fluid for ocular suspension drug products.

- Study outcomes will help FDA develop recommendations that determine bioequivalence of generic ocular suspension and emulsion drug products.

**Dissolution Methods for Semisolid Ocular Drug Products**

- Awarded to the University of Connecticut (1 U01 FD005177-01) and (1U01FD005174-01).
- Project goals are to develop dissolution methods for semisolid ocular drug products that predict in vivo performance and are sensitive and robust in detecting manufacturing differences. The first University of Connecticut project will manufacture, characterize, and evaluate drug release from loteprednol ointment formulations using several dissolution methods. The second University of Connecticut project will investigate the use of artificial corneas as a biorelevant release method for tobramycin ointment formulations manufactured and characterized in the laboratory.
- Study outcomes will help FDA develop recommendations for assessing bioequivalence of generic ocular semisolid drug products.

**Dissolution Methods for Microsphere and Implant Drug Products**

- Awarded to the University of Connecticut (1U01FD005169-01), Akina, Inc. (1 U01 FD005168-01), and the University of California, San Diego (1U01 FD005173-01).
- The University of Connecticut project will standardize dissolution methods for sustained release of in situ-forming gels and analyze their capability to detect manufacturing differences and to evaluate method robustness. The UC San Diego grant will design, develop, and validate vitreous models for the dissolution of ophthalmic formulations and implants. Various gels and tear fluids for mimicking the vitreous environment will be investigated. The Akina project will design and develop new in vitro dissolution apparatus for testing parenteral sustained release products. A hydrogel-based system will be incorporated into the current USP 4 apparatus to mimic the subcutaneous and muscular tissue environment with the goal of developing an in vitro in vivo correlation of parenteral sustained release injectable microspheres.
- Outcomes will advance the Agency's understanding of the impact of different manufacturing processes on the physicochemical properties of long-acting sustained release products; develop and evaluate generic ophthalmic formulations and implants that will be injected into vitreous humor; and improve the capability to predict in vivo performance of sustained release products through in vitro methods.

**Characterization of Critical Quality Attributes for Semisolid Topical Drug Products**

- Awarded to the University of Mississippi (1 U01 FD005233-01) and the University of South Australia (1 U01 FD005226-01).
- Study goals are to characterize measurable physical/chemical qualities of different dosage forms of semisolid topical drug products; identify appropriate methodologies for measuring each of these quality attributes; characterize formulation and manufacturing parameters that alter the arrangement of matter in the dosage form as measured by specific quality attributes; and use in vitro or in vivo measures of product performance to correlate variations in critical quality attributes with a failure mode for a drug product. The University of Mississippi project will evaluate product performance by relevant in vitro methodologies and characterize the links between manufacturing process variables, the physical microstructure of the drug product, and product performance failure modes. The University of South Australia project characterizes additional product failure modes associated with patient acceptability and compliance.

- The outcome will be a substantially advanced understanding of the influence of varying aspects of product manufacturing and process controls on the physical microstructure and associated quality and performance of topical semisolid dosage forms. Sophisticated knowledge of the relationship between the qualities of a semisolid dosage form and its performance as a topical drug product will support the development and control of high quality generic topical drug products.

**Evaluation of Plasma NTBI levels in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate**

- Awarded to the University of Maryland, Baltimore (1 U01FD005266).
- Study goals are to conduct in vivo research comparing plasma total iron (TI), transferrin bound iron (TBI), non-transferrin bound iron (NTBI), and oxidative stress levels after intravenous administration in healthy subjects of generic and reference sodium ferric gluconate. This study is part of post-market surveillance on approved generic products (e.g., NulecitTM) that can help support the Agency's review standards and address potential concerns regarding the substitution of generic iron complex products.
- The predicted outcome will confirm the in vivo equivalence of generic and reference iron complex products and help to revise the current bioequivalence guidance to recommend a crossover study design.

**Effect of Therapeutic Class on Generic Drug Substitutions**

- Awarded to Johns Hopkins University (1U01FD005267-01).
- The study goal is to rank order generic drugs based on therapeutic class and generic substitution rate and to analyze patient, prescriber, and health system level factors affecting generic substitution in each therapeutic class.
- This study will identify incentives and barriers to using generic drugs and align FDA's regulatory science efforts to monitor and ensure successful generic substitution.

**Post-market Surveillance Evaluation of Authorized Generic Drug Products**

- Awarded to Brigham and Women's Hospital (1U01FD005279-1) and Auburn University (1U01FD005272-1).
- The project goal is to compare authorized generics (products nearly identical to the brand product, but marketed under a different label) to brand name and other generic drugs to evaluate existing tools and to develop new methods to monitor the safety, efficacy, usage, and substitution patterns of generic drugs in different therapeutic categories. The Brigham and Women's Hospital project focuses on whether negative perceptions of generics affect acceptance, use, and patient outcomes. The Auburn University study evaluates novel generic drug surveillance methods using electronic health records.
- Study results will ascertain the extent to which bias against generic drugs affects generic substitution.

**Pharmacokinetic/Pharmacodynamic Studies of Generic Cardiovascular Drugs in Hypertensive Patients**

- Awarded to the University of Florida (1U01FD005235-01).
- The project goal is to conduct a PK/PD study to identify the key product attributes and patient factors (including gastric pH and motility as well as genomic factors for CYP2D6) that may impact the PK/PD and therapeutic equivalence of metoprolol products.

- Results from the PK/PD study will help to establish scientific and regulatory standards for assuring therapeutic equivalence of generic metoprolol products.

**Pharmacokinetic/Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder Patients**

- Awarded to the Massachusetts General Hospital (1U01FD005240-01).
- The purpose of this project is to conduct a PK/PD study in pediatric attention deficit hyperactivity disorder patients (6-12 years of age) to link the PK profiles to the time-course of PD activity of methylphenidate ER products. The link may identify additional PK metrics that impact the therapeutic equivalence of these products. A study simultaneously collecting individual PK and PD data in pediatrics has not yet been performed for methylphenidate ER products, and these data can improve existing PK/PD models for these products.
- The PK/PD study will help to establish scientific and regulatory standards for assuring therapeutic equivalence of generic methylphenidate extended release products.

**Effect of Different Preparation Methods on the In Vitro and In Vivo Performance of Solid Dispersion Formulations**

- Awarded to Purdue University, West Lafayette (1U01FD005259-01).
- The study goal is to investigate the in vitro and in vivo performance of solid dispersion drug products originating from different manufacturing processes or polymer carriers and to assess performance consistency among batches and during storage.
- Study outcomes will identify critical process parameters and critical quality attributes for solid dispersion drug products originating from various preparation methods and will develop discriminating analytical methods for these drug products.

**Prospective Studies on the Impact of Generic Immunosuppressants on Acute Rejection and Long-Term Graft Survivals**

- Awarded to the University of California, Los Angeles (1 U01 FD005271-01).
- The project goal is to conduct prospective clinical studies for determining the impact of generic immunosuppressants on short-term acute rejection and long-term patient graft survival. The study will measure patients' immune responses, evaluate differences in transplant recipients' acute rejection rate and 3-year graft and patient survival rate, and analyze successful clinical outcomes and behavior to determine how generic substitution impacts patient adherence to prescribed drug regimens.
- Study results will address public concern regarding the interchangeability of generic immunosuppressants and improve generic immunosuppressant review practices, if necessary.

**Retrospective Analysis on the Impact of Generic Immunosuppressants on Acute Rejection and Long-Term Graft Survivals**

- Awarded to Arbor Research Collaborative for Health (1 U01FD005274-1 ).
- The goal of this study is to conduct a retrospective analysis on the impact of generic immunosuppressants on short-term acute rejection and long-term patient and graft survival since the introduction of generic immunosuppressants.
- Study outcomes will address public concern regarding the interchangeability of generic immunosuppressants and improve review practices for generic immunosuppressants.

**Evaluation of In Vitro Release Methods for Liposomal Drug Products**

- Awarded to ZoneOne Pharma, Inc. (U01FD005249-1).
- The study goal is to evaluate different in vitro release assays for amphotericin B liposome in order to assess method capacities for detecting formulation differences and for predicting in vivo release of the liposomal formulation.
- The result will be improved in vitro release method(s) for amphotericin B liposome. This outcome will advance the regulatory review process and ultimately improve public access to quality generic liposomal drug products.

**Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules**

- Awarded to the Massachusetts Institute of Technology (U01FD005291-1)
- The study goal is to construct a robust set of integrated algorithms to determine how much characterization is required to establish equivalence of complex mixtures. The project will use pentosan polysulfate as a case study for methodology development and will include high-resolution analytical methods and computational tools to integrate data from multiple high-resolution methods into a decision framework for product equivalence.
- The results will be improved tools for evaluating equivalence of complex drug products.

**Development of Process Simulation and Modeling Tools for Integrated Pharmaceutical Manufacturing Processes**

- Awarded to University of Massachusetts Lowell (U01FD005294-01) and Rutgers (U01FD005295-01)
- The goal of these projects is to develop a process simulation and modeling platform for integrated pharmaceutical manufacturing processes. Specifically, they will focus on manufacturing processes for solid based drug products which comprise the majority of pharmaceutical products. The tools developed will be used to facilitate the risk assessment of manufacturing processes and control strategies and to identify critical material and process attributes through sensitivity analysis.
- The results will advance the understanding of how raw material attributes and process parameters affect quality of the final drug product.

**Establishing Specifications to Assure the Quality of the Heparin Supply Chain**

- Awarded to G Ronzoni Institute for Chemical and Biochemical Research (HHSF223201400578P)
- The objective of this contract is to establish specifications for a key intermediate in teh heparin supply chain that currently has no defined properties. The impact of this work will be to establish crude heparin as an intermediate which can be monitored for quality.
- The outcome will allow FDA to check heparin quality earlier in the supply chain thereby preventing contaminated material from reaching the active pharmaceutical ingredient purification process and thus help ensure the quality of generic heparin products