FY 2015 Awarded GDUFA Regulatory Research Contracts and Grants

Bioequivalence Study of Lamotrigine Extended-Release Tablets in Healthy Subjects

- Awarded to Vince & Associates (#HHSF223201210030I).
- Modified release (MR) products are usually designed in a more complicated manner than their immediate release (IR) counterparts with regard to formulations, quality attribute profiles, and *in vivo* pharmacokinetic (PK) behaviors. The FDA is evaluating whether a fully replicated bioequivalence (BE) study design would provide important information regarding MR products with different formulation designs. The objective of this study is to conduct a single-dose, fully replicated, cross-over BE study comparing two generic lamotrigine extended-release tablets and the reference listed drug (RLD) in healthy volunteers.
- The study results will help the Agency determine whether fully replicated BE studies for MR products with different formulation designs are required to assess bioequivalence between the generic product and its RLD. The knowledge gained here will also help to address questions from the public regarding brand-to-generic or generic-to-brand substitutability of anti-epileptic MR drug products.

Pharmacokinetic Study of Opioid Drug Products Following Snorting of Milled Drug Products

- Awarded to Vince & Associates (#HHSF223201510138C).
- FDA encourages the development of abuse-deterrent formulations of prescription opioid drug products and is developing tools to evaluate properties relevant to abuse deterrence. The objective of this study is to examine factors that could affect bioavailability of opioid drug products following snorting of milled drug particles (i.e. a common method of abuse). These factors may include the milling procedure (e.g., tool and duration), amount of milled materials obtained from the drug product, particle size distribution, morphology, and in vitro dissolution of the milled products.
- The research will help the Agency determine critical parameters for in vitro and in vivo study designs to evaluate the relative performance regarding deterrence of nasal abuse between a generic opioid product and its RLD.

New Method for Evaluating *Ex Vivo* Release Profiles of a Long-Acting Biodegradable Form in a Canine Periodontal Disease Model

- Awarded to Intervivo Solutions Inc. (#HHSF223201510771P).
- This project aims to develop a method to measure the *ex vivo* release rate of a long-acting biodegradable periodontal dosage form in a canine periodontal disease model in beagle dogs. PerioChip (chlorhexidine gluconate dental tablets) will be used as a model drug in this study.
- The research will add new data on the *in vivo* release kinetics of periodontal dosage forms and support identification of critical attributes and development of equivalence recommendations for generic long-acting periodontal drug products.

Comparative Surveillance of Generic Drugs by Machine Learning

- Awarded to Marshfield Clinic (#HHSF223201510112C).
- The objective is to develop a postmarketing surveillance system based on machine learning, which utilizes algorithms that can learn from, and make predictions on, large data sources. This innovative approach will create an integrated system that compares generic- and brand-name

medication experience for early differential signal detection based on electronic health records (EHR).

- The new system will systematically sift through data captured in integrated EHR and claim databases with the purpose of detecting previously unknown substitution issues. This will provide a systematic assessment of population-level outcomes for generic drug substitution.

Wireless Analysis Device to Measure In Vivo Drug Dissolution in the Gastrointestinal Tract

- Awarded to the University of Michigan (#HHSF223201510146).
- The objective is to develop a wireless pharmaceutical analysis device (WPAD) that will acquire gastrointestinal (GI) fluids directly at multiple sites throughout the GI tract in order to determine the in vivo drug dissolution profiles. Initial efforts focus on developing a prototype WPAD that will be tested in in vitro dissolution vessels and an in vivo canine model.
- The ability to determine GI drug concentrations will aid in the development of in vitro dissolution conditions that are in vivo predictive. The project will provide an innovative technological solution over traditional means (intubation studies) to measure GI drug concentrations and in vivo drug dissolution and provide concentration data throughout the entire GI tract, including the colon.

In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence Regulation

- Awarded to the University of Michigan (#HHSF223201510157C).
- The objective is to incorporate the most recent advances in gastroenterology, imaging technology, computational mass transport analysis, and development of in vivo predictive dissolution (IPD) methodologies into a gastrointestinal (GI) motility dependent (i.e. under fasted or fed conditions) predictive absorption method (i.e., oral absorption PBPK) for oral drug products. This project includes the use of MRI studies to measure water content in the GI tract.
- The study results will help the FDA determine the underlying GI variables in order to develop adequate in vitro dissolution methodologies that accurately represent the in vivo conditions. In addition, PBPK modeling and simulation can be improved for evaluating the BE of generic drug products, especially locally-acting GI drugs.

Influence of Raw Materials Manufacturing Variables and Storage Conditions on Release Performance of Long-Acting Release (LAR) Microsphere Products

- Awarded to the University of Michigan (#HHSF223201510170C).
- The objective of this study is to develop a scientific approach that will bridge the knowledge gap for different types of LAR microspheres between in vitro dissolution and in vivo pharmacokinetics. The effects of storage conditions on product attributes, release performance, and release mechanisms will be investigated.
- Research outcomes will aid FDA in regulating generic LAR microspheres and developing relevant product-specific BE recommendations, and will help generic industries with material selection for generic long-acting microspheres.

Predictive In Vitro In Vivo Correlation of Parenteral Microspheres

- Awarded to Qrono Inc. (#HHSF223201510102C).
- The objective of this research is to develop a predictive mathematical model linking the dissolution and PK profiles of LAI products directly to critical quality attributes (e.g., microparticle size and drug distribution).

- This simulation-based approach will lay out a framework for assessing formulation performance of LAI products, particularly during critical periods such as the initial burst where carefully controlled drug delivery is essential to patient safety. The predictive simulations will also help FDA develop BE requirements of generic LAI products.

Evaluation of Formulation Effects of Metered Dose Inhalers on Pharmacokinetics

- Awarded to the University of Florida (#5U01FD004943-05).
- The objective is to establish an in vitro in vivo correlation for metered dose inhalers (MDI) through a systematic investigation of the effects of formulation changes on the pharmacokinetics.
- The research aims to offer an efficient tool to evaluate different MDI formulations and to contribute to the FDA's BE review process.

Dissolution Methods for Long-acting Levonorgestrel Intrauterine System

- Awarded to the University of Connecticut (1U01FD005443-01).
- The objective of this research is to develop dissolution methods, both real-time and under accelerated conditions, for the levonorgestrel intrauterine system (5-year application) and to analyze method capabilities with regard to robustness, detecting manufacturing differences, predicting *in vivo* performance.
- This research will help the FDA develop recommendations for determining the BE of generic intrauterine systems.

Dissolution Methods for Long-Acting Periodontal Drug Products

- Awarded to the University of Cincinnati (1U01FD005446-01) and Magee-Women's Research Institute and Foundation, Pittsburg (1U01FD005447-01).
- Compendial or bio-relevant in vitro drug release assays are needed for long-acting periodontal dosage forms, including biodegradable microspheres, *in situ* forming implants, and matrix tablets. The study purpose is to develop a bio-relevant dissolution method for a long-acting periodontal dosage form and to identify the drug product's key physicochemical attributes that affect drug dissolution behavior and bioavailability.
- The University of Cincinnati will use computer model simulations to evaluate the drug concentration profiles in the periodontal packet in order to design dissolution apparatus prototypes using 3D printing technology. Magee-Women's Research Institute and Foundation will focus on a biologically relevant dissolution testing method that mimics the physiological conditions in the periodontal pocket environment (e.g., pH, osmolarity, viscosity).
- Project results will aid the FDA in developing BE recommendations for generic long-acting periodontal drug products.

Pharmacometric Modeling and Simulation for Long-Acting Injectable (LAI) Products

Topic 1: Physiologically-Based Pharmacokinetic (PBPK) Modeling of LAI Products

- Awarded to Simulations Plus Inc. (1U01FD005463-01).
- The purpose is to develop and validate general PBPK models for long-acting injectable (LAI) products, including both microspheres and active pharmaceutical ingredients, to relate critical quality attributes (CQAs) to *in vitro* and *in vivo* performance and to evaluate bioequivalence criteria for LAI products. This will be accomplished by expanding the current knowledge of PBPK

modeling and enhancing the existing GastroPlus software to more accurately reflect the physiology of human and animal tissues.

- Models that embody mechanistic absorption modeling and PBPK can be useful tools for both industry scientists and regulators to determine whether a new formulation will be bioequivalent to an approved LAI product.

Topic 2: Pharmacometric Modeling and Simulation and Statistical Analysis for LAI Microsphere Products

- Awarded to the University of Utah (1U01FD005442-01) and the University of Massachusetts, Lowell (1U01FD005444-01).
- The purpose of this research grant is to conduct pharmacokinetic-pharmacodynamic (PK-PD) modeling and statistical analysis for LAI products to identify appropriate PK metrics and ways to reduce residual variability. This allows for BE assessment in parallel BE studies with acceptable sample size. The University of Utah will simultaneously collect PK and PD data from patients who are being treated with Lupron Depot for population PK-PD modeling and statistical analysis. On the other hand, researchers from the University of Massachusetts at Lowell propose a data-fusion platform: mechanistic and data-driven models will be developed for BE evaluation and covariate assessment of generic LAI products.
- Findings will help establish scientific and regulatory standards for assuring BE of future generic LAI products.

Educating Groups that Influence Generic Drug Use

- Awarded to the University of Auburn (1U01FD005486-01) and the University of Chicago (1U01FD005485-01).
- The objectives of this study include identifying the key groups influencing the use of generic drugs, determining the informational needs of these groups regarding generic drugs, and testing and revising draft messages designed to address those needs. The University of Auburn (Auburn) will identify the key groups and the extent of their influence and evaluate their educational needs pertaining to generic drugs (overall and by specific therapeutic class). Auburn will develop educational materials through approaches that include systematic reviews of clinical and observational studies, robust empirical analysis of publicly available datasets and surveys, and qualitative key informant interviews. The University of Chicago will focus on anti-depressants, oral contraceptives, and cholesterol lowering agents, developing messaging and interventions to promote generic prescribing of these products for primary healthcare providers, including primary care clinicians, nurse practitioners, and primary care physicians.
- The two research groups will employ complementary approaches to effectively design and deliver educational materials about generic drugs to the key groups influencing consumer acceptance and usage of generic drugs.

Development and Application of Case-Control Analysis for Generic Drugs

- Awarded to Brigham and Women's Hospital (1U01FD005555-01) and Johns Hopkins University (1U01FD005556-01).
- The objectives of this research grant include identifying data sets that could be used for postmarketing generic drug surveillance, establishing novel analysis methods specific to comparative observational studies of generic drugs, and validating these approaches via application to case examples. Brigham and Women's Hospital aims to identify optimal strategies for confounder selection and to evaluate the performance of different methods for confounding

control in comparative studies of generic drugs. Novel data sources will be identified and linked to augment the validity of observational studies. Applicable confounders will be assessed, and the performance of various methods for confounding control will be compared by applying these methods to several drug examples. Johns Hopkins University aims to develop and apply innovative methods using healthcare utilization databases and electronic medical records to enhance the FDA's ability to monitor the post-approval safety and effectiveness of generic drugs. Investigators will develop a novel causal inference approach to compare the toxicity and efficacy of generic- and brand-name drugs by using structural nested models. These models address challenges using secondary data sources, which include treatment selection bias, dynamic treatment patterns, potential misclassification of outcomes, and missing data.

- Both projects will advance methodological research in postmarketing surveillance studies of generic drugs by improving the validity of observational comparative effectiveness and safety studies for generics and their brand-name equivalents.

Pharmacometric Modeling and Simulation for Generic Drugs Evaluation

- Awarded to the University of Florida (3U01FD005210-02S1).
- The primary objective is to develop pharmacometric modeling and simulation tools for generic drug substitutability and postmarket risk assessment. Researchers will develop pharmacometric approaches that will aid the FDA in evaluating postmarket risk and interpreting postmarket adverse event reports or product substitution complaints. The risk-based methodology will be applied to predict which generic drug products are most likely to encounter switching issues.
- This new award focuses specifically on Novel Oral Anti-coagulants. The research will aid in the development of BE evaluation for this product class and will support the development of postmarket monitoring of future generic products in this class.

UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI)

Topic 1: Prediction and Testing of Excipient Molecular Targets

- Awarded to the University of California, San Francisco (3U01FD004979-02S3).
- A longstanding, if rarely tested, belief is that excipients are safe, inert and do not interact with pharmacologic targets. The objective of this project is to examine potential interactions with pharmacologic targets of commonly used FDA-approved excipients. A state-of-the-art *in silico* methodology will be applied to predict the molecular targets for all the FDA-approved excipients. Based on the predictions, functional excipients will be tested against their predicted molecular targets in functional assays.
- The goal is to provide additional tools to help FDA and industry establish safe levels of excipients in generic drug formulations.

Topic 2: Interactions of Excipients with Intestinal Transporters

- Awarded to the University of California, San Francisco (3U01FD004979-02S3).
- Oral generic drug products may fail to demonstrate BE to the brand-name product if inactive ingredients in the generic product formulation affect the rate and extent of absorption of the drug differently from those in the RLD. The objective of this project is to characterize the interaction of intestinal absorptive transporters with excipients using high-throughput methodologies. Enhanced understanding of how excipients in generic drugs may alter absorption of oral dosage forms via excipient-transporter interactions will aid future generic drug development.