

FY 2017 Awarded GDUFA Regulatory Research Contracts

(No grants were awarded in FY 2017)

Phase Behavior and Transformation Kinetics of a Poorly Water Soluble Weakly Basic Drug upon Transit from Low to High pH Conditions

- Awarded to Purdue University (#HHSF223201710137C).
- The project aims to understand the supersaturation and precipitation behaviors of weakly basic drugs that are poorly soluble in water. Weakly basic drugs have pH-dependent solubility and inherent tendencies to undergo supersaturation in vivo. Supersaturation may cause drug precipitation and decrease bioavailability; leading to slower absorption. Physiologically-based pharmacokinetics (PBPK) modeling would provide helpful insights into understand and probe in vivo variability of supersaturating systems. However, the model would need experimental data inputs such as physical properties and phase behaviors of these compounds to successfully run PBPK simulations. To acquire these inputs, the researchers propose to:
 - Characterize the solution phase behavior of posaconazole—a model drug that is weakly basic and poorly soluble—by investigating the phase transformations of amorphous and crystalline posaconazole as a function of pH, and define a phase diagram
 - Demonstrate that nucleation induction time is a function that depends on three independent variables:
 - Degree of supersaturation
 - Amount of colloidal amorphous drug present in the supersaturated solution
 - Presence of undissolved free base in the supersaturated solution
 - Evaluate specific media components for their impact on phase boundaries and nucleation induction time, specifically bile salts and commercial vehicle compounds
 - Demonstrate that the colloidal phase changes size with time in a manner that is dependent on the medium used
- The experimental results from this project will yield a range of input values for PBPK modeling and simulations currently being conducted by Simcyp Limited (a Certara Company) in collaboration with FDA under another GDUFA funded grant, “Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug” (FDA grant: 1U01FD005865).

In vitro In vivo Correlation of the Long-acting Injectable Suspensions Improve Scientific Approaches to Evaluate Generic Drugs

- Awarded to the University of Connecticut (#HHSF223201710135C).
- The project aims to develop appropriate in vitro performance testing methods for long-acting injectable (LAI) suspension drug products that will allow correlation of in vitro and in vivo release data. The researchers propose to use medroxyprogesterone acetate (MPA) as the LAI suspension drug model and conduct the following studies:
 - Prepare and characterize qualitative and quantitative (Q1/Q2) equivalent MPA suspensions with manufacturing differences

- Develop robust in vitro release testing methods (both real-time and accelerated) for Q1/Q2 equivalent MPA suspensions
- Study in vivo drug release of the Q1/Q2 equivalent LAI suspensions in animal models based on different routes of administration
- Establish in vitro-in vivo correlation (IVIVC) for Q1/Q2 equivalent MPA suspensions
- The primary objective of this research project is the establishment and validation of IVIVCs for LAI suspensions. This will help minimize the number of human studies needed without compromising the quality of drug products, and enable the development of cost-effective generic drugs. This study will also support FDA's understanding of critical process parameters during manufacturing and will advance formulation development of LAI suspensions.

Development of Analysis Technique for Structural Characterization of Star-shaped Polyesters Used for Drug Delivery

- Awarded to Akina Inc (#HHSF223201710123C).
- The majority of the injectable long-term depot formulations utilize linear poly(lactide-co-glycolide) (PLGA) polymers. Currently, there is only one product that contains glucose-based star-shaped PLGA (Glu-PLGA). While a protocol for identifying the type of linear PLGA in a finished drug product has been published, no protocols or studies are available for characterizing and describing Glu-PLGA. The primary objective of this research project is to establish and validate an assay method protocol for Glu-PLGA used in parenteral depot formulations. To accomplish this goal, researchers at Akina Inc will:
 - Develop star-shaped PLGA standards that will be used in quantifying the number of branches, as well as characterizing their structures
 - Quantitatively characterize Glu-PLGA in commercially available products
 - Establish an assay protocol and validate the method against the reference materials
- The lack of structural information on Glu-PLGA and its assay protocol makes it difficult to establish guidance for evaluating Q1/Q2 status of generics as well as batch-to-batch reproducibility of clinical products. The assay protocol developed from this project will facilitate such guidance efforts and support FDA in regulating future Glu-PLGA or star-shaped PLGA generic products.

Investigating the Microstructure of Dry Powder Inhalers using Orthogonal Analytical Approaches

- Awarded to the University of Bath (#HHSF223201710116C).
- The overall objective of this research project is to evaluate a range of orthogonal analytical techniques and utilize a combination of them to support the development and validation of methods in characterizing microstructures of an array of reference listed drug (RLD) dry powder inhaler (DPI) formulations. Specifically, the study aims to:
 - Present a set of different characterization pathways depending on the physico-chemical active pharmaceutical ingredient (API) properties and device characteristics
 - Demonstrate the use of chemometric-based analysis—this includes particle analysis on size and morphology, chemical identification using Raman Spectroscopy, surface distribution of formulation components, as well as measurements of product

functionality—on the similarity of microstructures (Q3) between test and RLD DPI formulations.

- For DPI formulations, the formulation microstructure is dominated by the relative magnitude of cohesive and adhesive interactions between the constituent materials (of the formulation) and the processing conditions. Thus, to properly support Q3-equivalence of DPI formulations, a range of analytical tools may be required to fully understand the relationship between the microscopic and macroscopic properties of the formulated and aerosolized forms of a DPI product. The results of this project will provide FDA with a range of validated methods to assess Q3-equivalence of DPI formulations and insight into the nature of surface interfacial properties that govern the formulation microstructure.

Evaluation and Development of Model-based Bioequivalence Analysis Strategies

- Awarded to Uppsala University (#HHSF223201710015C).
- The objective of this research project is to develop new population model-based—nonlinear mixed effects models—bioequivalence (BE) analysis strategies applicable in both rich and sparse pharmacokinetics (PK) study settings. Optimal design methodologies will be used to inform the study design of these model-based strategies and compare them with existing model-based strategies such as bootstrap-based non-compartmental analysis (NCA) and standard NCA methods. These comparisons will be made with a wide range of simulations in addition to in-house FDA BE study data. Finally, researchers will develop an open source software package (R-based) to support others using the appropriate model-based strategies for BE analysis.
- Standard BE analysis compare the area under the concentration-time curve and the maximal concentration between formulations using standard NCA calculations. This method is adequate for drug studies where dense PK sampling is possible, however, dense sampling is not always possible – for example in ophthalmic studies or studies involving children or cancer patients. Furthermore, standard BE analysis also suffers from a number of drawbacks including assumptions about equal weights of all observations, sensitivity to missing data and data below the limit of quantification, and interpolation problems. The results of this new analysis strategy will try to address the above issues and provide FDA with another tool to utilize when assessing the BE of a generic drug application with sparse PK data.

Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations

- Awarded to the University of Bath (#HHSF223201710163C).
- The objective of this project is to utilize a combination of orthogonal analytical techniques to analyze both test and reference nasal spray formulations and use these approaches to support in vitro BE studies for nasal suspension drug products. These techniques are:
 - Morphology directed Raman spectroscopy—chemically identify API in situ, and characterize the size, shape, and distribution of these API particles in complex nasal suspensions
 - Rheological measurements—ascertain characteristics such as shear thinning properties and gel-like consistencies between test and reference formulations are similar

- UniDose-enabled dissolution testing—measure force displacements of API particles and determine the rate of dissolution as well as permeability at site of deposition
- The scarcity of validated methods for characterizing API-specific drug particle size and particle size distribution (PSD) in nasal formulations has resulted in limited understanding of the relationship between API PSD, regional deposition in the nasal cavity, dissolution, and absorption of the API from the nose. Although PSD can be readily determined by a number of methods prior to formulation into a finished product, determination of PSD of a drug substance in the finished nasal aqueous suspension in the presence of undissolved excipients has been a challenge. For nasal sprays, excipients such as microcrystalline cellulose and carboxymethyl cellulose tend to undergo cross-linking and the formation of gel-like suspensions. Such formation complicates particle size determination as these excipients have a median particle size larger than the API. Variation in particle sizes also leads to a broader PSD spectrum.

This study aims to develop a systematic approach to quantify and compare the microstructure of nasal suspension formulation systems. The results of the project will provide FDA with information to assess the approach as a means of allowing demonstration of Q3-equivalence of nasal suspension formulations and help FDA direct industry to define quality and functionality of nasal suspension drug products.

Patient's Perception of Dry Powder Inhaler Airflow Resistance

- Awarded to Imperial College of Science and Technology (#HHSF223201710072C).
- The goal of this project is to:
 - Develop a systematic way to evaluate patient's perception of DPI airflow resistance
 - Evaluate patient preference for a particular airflow resistance range
 - Determine if patient preference for airflow resistance range varies with disease condition and/or severity and patient's response to changes in device resistance for a specific class of products
 - To achieve this goal, the researchers of this project propose to:
 - Engineer and optimize a device and methodology for the collection of inspiratory flow profiles through passive DPIs
 - Develop a questionnaire and a scoring method for the qualitative and quantitative evaluation of the patient's perception of DPI airflow resistance
 - Record inspiratory flow profiles in conjunction with the perception of airflow resistance of various patient populations – such as asthma or chronic obstructive pulmonary disease patients – inhaling through varied airflow resistances in a drug-free clinical study using the methods developed in above items 1 and 2
 - Produce a standardized method for the collection of patient inspiratory flow profiles through DPIs and a standardized questionnaire for the assessment of patient perception of DPI airflow resistance
- The outcome of this research will produce a standardized method for the collection of inspiratory flow profiles through DPIs and a standardized questionnaire for the assessment of patient perception of DPI airflow resistance. The questionnaire and method for inspiratory flow measurement will provide FDA with a reliable regulatory path for the assessment of the patient

perception of new DPI products and a comparative matrix for the assessment of patient's perception of generic DPIs that have different airflow resistances to the reference products. For patients, this means improved access to safe, high-quality, and effective generic DPIs.

Clinical Site Monitoring

- Awarded to the Emmes Corporation (#HHSF223201710031I).
- FDA requires scientific and clinical support for monitoring the conduct and progress of extramural FDA-funded research in human subjects. The clinical site monitoring of these clinical research projects ensures adequate protection of the rights, welfare, and safety of human subjects. It also ensures that the data resulting from the clinical research projects are of the highest quality. This contract will be used to assign some monitoring visits to a third-party contractor to reduce the burden on FDA staff.
- The contractor will conduct both routine and specialized visits to FDA-funded domestic and foreign clinical sites.
- This contract was awarded as an indefinite delivery/indefinite quantity contract where the monitoring of each clinical site will be awarded as a separate task order.