BsUFA Regulatory Research Pilot Program
New Research Awards

Under the commitments outlined in the third Biosimilar User Fee Act (BSUFA) commitment letter, FDA is exploring ways to enhance biosimilar and interchangeable biosimilar product development and regulatory science, specifically in the areas of **1) improving the efficiency of biosimilar product development** and **2) advancing the development of interchangeable products**. To this end, the following five new research grants were awarded from the funding opportunity - Biosimilar User Fee Act (BsUFA) Research Grant (U01) Clinical Trials Optional.

1. ***Improving the efficiency of biosimilar products development:*** Work in this area could be aimed at enhancing the identification and risk assessment of relevant product, excipient, and container closure attributes; better defining acceptable attribute differences; and advancing analytical tools to detect relevant differences and use of statistical methodologies that are demonstrated to facilitate the comparative analytical assessment.

Assessment of the performance of Multi-Attribute Method (MAM) vs conventional Quality Control (QC) methods for evaluation of Product Quality Attributes of adalimumab and etanercept

Principal Investigator: Diane McCarthy
Institute: U.S. Pharmacopeia
Selection from Abstract from Grant Application: Monoclonal antibodies and other biotherapeutics are subject to a variety of modifications that can impact activity and stability and therefore must be analyzed as part of QC and comparability. Mass spectrometry (MS) has become a workhorse for biopharmaceutical analytical laboratories due to its ability to detect protein modifications at a molecular level. Over the past few years, the Multi-Attribute Method (MAM)has gained traction throughout pharmaceutical development and QC labs, with several developers implementing some form of MAM in characterization or release. While replacing multiple QC tests provides an opportunity to streamline lab work and decrease development time and post-approval costs, several challenges remain. While some large biopharma companies are implementing MAM in QC, MAM is not as commonly used in biosimilar and small biopharma companies. This proposal addresses one of the key areas of consideration for implementation of MAM in QC as outlined in a 2019 publication from FDA staff: the performance of MAM vs conventional methods. Collecting data to support transitioning from conventional techniques to MAM is a significant investment that can prevent or delay development of biosimilars. The objective of this work is to assess the performance of the MS-based Mavers's conventional QC methods to identify changes in product quality attributes (PQAs) upon forced degradation and to correlate changes in those PQAs with bioactivity, binding affinity, and structure. Results of this study will help support transitioning from conventional techniques to MAM by creating a knowledge base that can lower the barrier to adoption of Marmande enable wider use of MAM by biosimilar manufacturers. The work proposed here will assess and compare PQAs of a monoclonal antibody (adalimumab) and Fc fusion protein (etanercept) acquired from three different sources using both conventional QC methods and MAM-based approaches.

Platform for reliable characterization and evaluation of comparability of biosimilar drug products in lyophilized and liquid formulations

Principal Investigator: Raj Suryanarayana
Institute: National Institute for Pharmaceutical Technology and Education (NIPTE)
Selection from Abstract from Grant Application: The standard for biosimilarity is the demonstration of analytical and functional similarity of a biosimilar product to the reference product, with no clinically meaningful differences between the two. Our objective is to develop a platform that allows for reliable characterization and evaluation of comparability of biosimilar drug products. A key challenge when performing these activities is that the excipients in the formulation interfere with the typical set of analytical and functional tools that are otherwise routinely used for the characterization and comparability of drug substances. As a result, biosimilar manufacturers resort to a variety of approaches

to isolate the biotherapeutic protein from the drug product formulation. However, this introduces an uncertainty brought about by the impact of this isolation on protein stability and function. We will first identify the root of challenges that impact the characterization of biotherapeutic drug products. Armed with this understanding, this project aims at creating an analytical platform that allows us to perform reliable analytical and functional characterization and evaluation of the comparability of biosimilar drug products. Comprehensive characterization of excipients, alone and in compositions simulating biosimilar products will be carried out. In addition, analytical and functional characterization of biosimilars and the reference product will be conducted. Finally, the container-closure systems will be evaluated.

Systematic Analytical Characterization of Innovator and Biosimilar Products with the Focus on Post-translational Modifications

Principal Investigator: Anna Schwendeman
Institute: University of Michigan – Ann Arbor
Selection from Abstract from Grant Application: Given the number of biosimilars in development, there is an urgent need for robust, established, and accessible methodologies for companies to implement when characterizing key attributes of biosimilars such as physicochemical properties, efficacy, immunogenicity, interchangeability. By applying for this BsUFA funded grant, we seek to aid in the development, implementation and standardization of methods that can be applied to multiple biosimilar types. As such, we are proposing five aims to conduct research on multiple biosimilar/innovator pairs in the following areas relevant to BsUFA: 1) structural features; 2) higher order structure; 3) aggregation and its effect on stability and immunogenicity; 4) glycosylation and its impact on functionality; 5) technical and regulatory hurdles for interchangeable approval. Our lab's extensive background in biosimilar analytical comparisons, in addition to our close collaborations with members from the FDA, industry, and the UM hospital system on several ongoing projects in this area, make us a strong candidate to perform the proposed aims in support of efficient biosimilar development.

2. ***Advancing the development of interchangeable products****:* Work in this area could be aimed at advancing use of in-vitro and in silico methods that predict immunogenicity risk associated with single or multiple switches; and Researching approaches other than switching studies to meet the interchangeability standard that leverage real world evidence.

ISPRI-HCP: CHO protein impurity immunogenicity risk prediction for improving biosimilar product development and assessing product interchangeability

Principal Investigator: Anne Searls Degroot
Institute: Epivax, Inc
Selection from Abstract from Grant Application: The identification and removal of host cell proteins (HCP) from biologic products is a critical step in biosimilar drug development. While the sequence of a biosimilar may be identical to the innovator, the process used to produce the biosimilar will be different, and as a result, new HCPs may be introduced into the product. Despite recent improvements to purification processes, biologics that are manufactured in different cell lines and purified using different processes contain variable HCP impurities, making it necessary to identify and quantify impurities for each product, be it a reference innovator product or a proposed biosimilar product. In this U01 program, we propose to develop a predictive model for HCP immunogenicity that can facilitate assessment of clinically meaningful immunogenicity risk for biologics and assess interchangeability risk between a biosimilar and an innovator product. We have developed a web-based tool called ISPRI-HCP (formerly called CHOPPI) that predicts the immunogenic potential of HCP sequences by evaluating T cell epitope count and density, and relative conservation with other epitopes in the human genome. Building on previous studies of monoclonal antibody and biologic protein immunogenicity using silico methods and our FDA generic peptide immunogenicity research experience, we hypothesize that ISPRI-HCP can accurately classify candidate HCP impurities according to their immunogenicity risk.

Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data (RWD)

Principal Investigator: Catherine Marie Lockhart

Institute: Academy of Managed Care Pharmacy, Inc

Selection from Abstract from Grant Application: The lack of evidence on the quality of RWD and on the relevance of real-world evidence (RWE) for regulatory decision-making about biosimilars is a major obstacle to using big-data analyses of RWD/RWE for these decisions. The study, "Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data to Produce Real-World Evidence," will provide the research community with analytical tools they can re-use for their own tests of interchangeability and other regulatory questions. In the proposed study, we will:

Aim 1: Determine the quality of RWD and the relevance of RWE for regulatory decision-making. We will conduct a literature review and convene an expert panel to establish the data needs for regulatory approvals of new biosimilars and designations of interchangeability. Then we will determine whether and where RWD/RWE could reasonably be used to address regulatory data needs.

Aim 2: Use RWD/RWE to emulate an FDA evaluation of interchangeability of a biosimilar drug. We will design and conduct a target trial emulation of a switching study and compare outcomes produced from the emulation to those obtained from the FDA's evaluations of interchangeability of the reference drug.