BsUFA Regulatory Research Pilot Program
FDA 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 through 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 research projects were awarded support as part of the BsUFA III Regulatory Science Pilot Program (in order of the research priority[1] the project addresses). The total amount awarded for all 18 projects is $18,395,602 USD. The total amount awarded per research priority is detailed under each research priority section.

Research Priority A: Characterize relationships between product quality attributes with clinical performance

Total Amount Awarded for Research Priority A: $800,000 USD.

1. **Landscape Assessment of Biosimilar Submissions (analytical, PK, PD, and comparative studies)**

   Lead FDA Super Office: OTS
   Collaborating FDA Super Office(s): Office of Pharmaceutical Quality (OPQ) and Office of New Drugs (OND)
   Expected Timeline for Project Completion: 1 year from Fall 2023

   Project Objective (as described by lead office): The project objective is a landscape analysis to determine how FDA can answer questions about whether differences in analytical assessments in biosimilar development programs do or do not correlate with clinical data. Advancing understanding of analytical methods and their impact on clinical performance has been identified as key research priority for the BsUFA III Regulatory Science Pilot Program both internally to FDA (Revised Regulatory Research Road Map Priority A) and from external stakeholders (public comments on draft research roadmap). Additionally, our global regulatory counterparts are undertaking similar efforts.

   The analyses in this project will focus on a defined set of IgG1 monoclonal antibody reference products, e.g., with at least two approved biosimilar products, and include data from biosimilar and reference products as well as available data from non-US comparator.

[1] The projects are sorted under the revised roadmap research priorities presented during the SBIA Webinar on October 16, 2023 (Link to webinar: BsUFA III Regulatory Science Pilot Program - 10/16/2023 | FDA). The revised research roadmap is undergoing internal FDA clearance.

Research Priority B: Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes.

Total Amounted Awarded for Research Priority B: $2,598,958 USD.

2. **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**

   Institute: U.S. Pharmacopeia
   Principal Investigator: Diane McCarthy
   Expected Timeline for Project Completion: 2 years from Fall 2022

   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.

   Link to annual report dated 28Jun2023[2]

[2] *Publicly posting annual reports from external awardees requires written permission from the awardee. Any annual report that is made available to post publicly is posted publicly.*

3. **Establishment of A Feasible Method to Quantify Major Glycoforms of Human IgG1 mAb Drugs and their Biosimilars in Culture Media as a Component of Process Analytic Technology**

Lead FDA Super Office: OPQ
Expected Timeline for Project Completion: 2 years from Summer 2023

Project Objective (as described by lead office): Human IgG1 mAb drugs produced from CHO cells often contain three major glycoforms due to heterogenous N-glycosylation at Asn297 residue in their Fc domain: 1) aFucosylated; 2) Fucosylated; and 3) High-mannose. N-glycosylation is a critical quality attribute (CQA) for many IgG1 mAb drugs as it impacts their effector function-related activities, such as ADCC, and PK/ PD, and thus needs to be controlled and monitored. A small fraction of IgG1 mAb is not N-glycosylated (non-glycosylated) and consequently lacks effector activity. Mass spectrometry (MS) and (U)HPLC are the current tools for analysis of these glycoforms of the purified mAbs, which is not practical for an in-process analytical characterization such as PAT (process analytical technology) during biosimilar manufacturing process development, production cell line development and advanced manufacturing. To address the unmet analytical need, we generated two sets of mouse mAbs that specifically recognize non-glycosylated and glycosylated human IgG1, respectively. Our initial characterization and ELISA testing indicated that the different glycoforms of human IgG1 mAbs could be measured individually with these mouse mAbs. In this new project, we will further characterize these mouse mAbs, and establish a Bio-Layer Interferometry (BLI) method to quantify major glycoforms of human IgG1 mAb in unprocessed production media. Successes of the project will facilitate the production cell line development and process development at pilot scales of biosimilars by optimizing conditions to get the glycan profiles they are targeting. The clinical link for biosimilars is that the ability to optimize the manufacturing conditions to better match glycan profiles reduces uncertainty about the clinical performance of the drug and therefore reduces the need for clinical studies. At large scale it allows monitoring of product quality by using the technology as an in-process testing method.

4. **OnePotGlycan - A chemoenzymatic method for simultaneous profiling of N and O-glycans in one-pot format**

Lead FDA Super Office: OPQ
Expected Timeline for Project Completion: 2 years from Fall 2023

Project Objective (as described by lead office): Glycosylation, including N-glycosylation and O-glycosylation is generally characterized and controlled as a critical quality attribute for therapeutic glycoproteins because glycans can impact protein drug product efficacy, half-life, stability, and safety. Analytical procedures to characterize N-glycans are relatively well-established, but the characterization of O-glycans is challenging due to the complex workflows and lack of enzymatic tools. Traditional methods for structural N- and O-glycomics involves the enzymatic release and separation of the N-glycans from O-glycopeptides/O-glycoproteins which undergo separate processing to release O-glycans. The manipulation and analysis of N- and O-glycans is a separate process from two different samples, and the analysis of the N-and O-glycans is exclusive. Therefore, determining the relative quantity of N- to O-glycans, and the total PK-relevant glyco-determinants on the same glycoprotein drug samples is challenging. Specifically, for biosimilars, the similarity to the reference products in both glycan

profiles within the same class of glycosylation, and the ratio between two class of glycosylation need to be determined. Herein, we are developing a simplified chemoenzymatic method to simultaneously profile N- and O-glycans from the same sample using a one-pot format by mass spectrometry (MS). N-glycans were first released by PNGase F, followed by O-glycopeptide generation by Proteinase K, selective N-glycan reduction, and O-glycan release by β-elimination during permethylation of both N- and O-glycans. Glycan structural assignments, the relative quantity (%) of different glycan species, the ratio of total O-glycans versus N-glycans, and the sialylated species versus neutral glycans can be determined based on their individual peak intensities/area in the one-pot MS spectra. The one-pot method will be further optimized and validated as a reproducible and robust approach that will provide industry a better control strategy for the glycosylation of their biosimilars and facilitate the quality assessment of the biosimilar products.

Research Priority C: Define best practices for assessing and reporting quality attributes.

Total Amount Awarded for Research Priority C: $6,614,692 USD.

5. **Model development and verification to evaluate minimum stability data required for biosimilar submissions**

   Lead FDA Super Office: OPQ
   Expected Timeline for Project Completion: 3 years from Fall 2023

   Project Objective (as described by lead office): Comparative analytical data provide the foundation of biosimilar development. Per FDA guidance, appropriate physicochemical and functional comparison of the stability profile of the proposed product and reference product are expected to establish a direct stability comparison of the biosimilar with the reference product. The accrual of real-time data from primary stability batches can be a rate limiting factor for submission of biosimilar drug applications. Science- and risk-based strategies are being used by sponsors to leverage prior knowledge and modeling techniques to propose shelf-life and stability-related specifications for well-characterized drug molecules. Simple statistical extrapolation and complex modeling approaches could potentially result in decreased and targeted real-time stability data which would facilitate quicker submission, evidence-based regulatory assessment, and faster access of biosimilars to patients. We propose to conduct both basic statistical and confirmatory experimental studies to investigate the validity and robustness of models currently in use for biologic drug products and apply them to compare biosimilar drug product stability. A collaborative approach will be taken to address the analytical techniques, modeling strategies and regulatory risk assessments.

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

   Institute: National Institute for Pharmaceutical Technology and Education (NIPTE)
   Principal Investigator: Raj Suryanarayana
   Expected Timeline for Project Completion: 2 years from Fall 2022

   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 approach 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.

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

Institute: University of Michigan – Ann Arbor
Principal Investigator: Anna Schwendeman
Expected Timeline for Project Completion: 2 years from Fall 2022

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.

8. **The Bioassay Initiative: Enhanced biosimilar testing capabilities**

Lead FDA Super Office: OPQ
Expected Timeline for Project Completion: 2 years from Fall 2023

Project Objective (as described by lead office): Our goal is to continue to establish and standardize cell-based biological activity assay capabilities in OBP to support regulatory research, development, assessment, and harmonization of these biosimilar drug products.

Research Priority D: Develop alternatives to the comparative clinical immunogenicity assessment(s).

Total Amount Awarded for Research Priority D: $7,111,952 USD.

9. **Addressing Fundamental Issues for In-vitro Immunogenicity Testing**

   Lead FDA Super Office: OTS
   Expected Timeline for Project Completion: 1 year from Fall 2023

   Project Objective (as described by lead office): The objective is to validate methods for in vitro immunogenicity testing that could be used by industry to reduce/eliminate the need for clinical trials assessing immunogenicity for biosimilar drug products.

10. **Bridging the Gap: Using Foreign Real-World Data to Inform Interchangeable Biosimilar Approvals**

    Institute: Academy of Managed Care Pharmacy, Inc
    Principal Investigator: Catherine Lockhart
    Expected Timeline for Project Completion: 2 years from Fall 2023

    Abstract from Grant Application: This study will use real-world data (RWD) from the U.S., Italy, and Denmark to evaluate alternative approaches to meet the standard for interchangeable products (Area 2.ii.). The long-term objective is to develop recommendations for the FDA on using foreign RWD to improve regulatory processes. The study will determine the potential of RWD from outside the U.S. to improve the power and generalizability of U.S. regulatory studies. Researchers will use an observational/non-interventional retrospective cohort design to address two specific aims with the following methods:

    Aim 1: Evaluate the feasibility and validity of a biosimilar interchangeability (e.g. switching) study using real-world data from the U.S. and sources from outside the U.S. The study will evaluate the quality of RWD from two foreign sources and develop a common data model to harmonize the data. The Principal Investigator (PI) will design a shared protocol. Co-Investigators will conduct emulations of a switching study of a biosimilar product at U.S., Italian, and Danish sites. The PI will compare the results at each site and compare the results with an existing study to validate our findings.

    Aim 2: Develop recommendations for the FDA on how to address the challenges of using real-world data from outside the United States in its regulatory decision-making processes. Based on learnings from Aim 1, the PI will propose guidance for the FDA to consider. The guidance will recommend strategies to address the unique challenges associated with collecting, standardizing, and validating RWD from international sources.

    This study will show how using foreign RWD can significantly improve the efficiency of the FDA regulatory process, leading to increased adoption of safe and effective biosimilar products. This innovative approach could also serve as a model for using RWD from outside the U.S. in regulatory decision-making across different therapeutic areas. This study will help the FDA advance its mission of making safe and effective drugs available to patients.

11. **IIRMI Assay Standards - Develop acceptance parameters and standards for the Innate Immune Response Modulating Impurities (IIRMI) assays in the biosimilar space**

    Lead FDA Super Office: OPQ
    Expected Timeline for Project Completion: 3 years from Fall 2023

    Project Objective (as described by lead office): Overall objective is to develop in vitro systems that better predict differences in immunogenicity risk between biosimilars. As part of this effort, we will 1) To provide guidance/best practices to industry for evaluating product and process related impurities that may impact on immunogenicity risk. 2) Establish suitability controls that can be used by industry to benchmark their own assays and aid in the interpretation of data derived from these assays across studies.

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

    Institute: Academy of Managed Care Pharmacy, Inc
    Principal Investigator: Catherine Lockhart
    Expected Timeline for Project Completion: 2 years from Fall 2022

    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.

    Link to annual report dated 30Jun2023[3]

[3] *Publicly posting annual reports from external awardees requires written permission from the awardee. Any annual report that is made available to post publicly is posted publicly.*

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

Institute: Epivax, Inc
Principal Investigator: Anne Degroot
Expected Timeline for Project Completion: 2 years from Fall 2022

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.

Link to annual report dated 1Jul2023[3]

14. **Production & Optimization of Humanized Mice**

Lead FDA Super Office: OTS
Expected Timeline for Project Completion: 1 year

Project Objective (as described by lead office): We are producing humanized mice to answer important questions related to pharmacokinetics, pharmacodynamics, immunogenicity and adverse events that have not been successfully addressed with other models. If successful, these mice could be used by industry to assess drugs from the discovery to post-marketing phase, enabling products to enter the market more rapidly and to assess post-marketing concerns as they arise. Funding for this project supports the production these mice used to the evaluate immunogenicity and adverse events.

15. **Validation of a Non-Clinical Immunogenicity Model**

Lead FDA Super Office: OTS
Expected Timeline for Project Completion: 1 year from Fall 2023

Project Objective (as described by lead office): This project evaluates the ability of humanized mice to serve as a non-clinical immunogenicity model by evaluating several biological drug products (with clinically moderate to high immunogenicity) alone or in combination in two commercially available humanized mouse models.

Research Priority E: Define development approaches that will increase feasibility and/ or likelihood of success.

Total Amount Awarded for Research Priority E: $1,270,000 USD.

16. **Critical Factors for Standardization and Accuracy of PK Assays of PEGylated Biosimilars**
    Lead FDA Super Office: Office of Translational Sciences (OTS)
    Expected Timeline for Project Completion: 1 year from Fall 2023

    Project Objective (as described by lead office): To provide guidance/best practices to industry for evaluating pharmacokinetics (PK) associated with approval of biosimilars that are conjugated to polyethylene glycol (PEG).

17. **Evidence-based approach to the design of clinical pharmacology studies**
    Lead FDA Super Office: OTS
    Expected Timeline for Project Completion: 2 years from Fall 2023

    Project Objective (as described by lead office): The aim of this project is to increase the efficiency of biosimilar development programs by leveraging clinical pharmacology studies. Areas to investigate include approaches to minimizing variability in PK and PD measurements (e.g., through assay method enhancements, optimization of statistical analysis), identifying products for which conducting the comparative clinical studies (CCS) in patients is challenging and evaluating potential PD biomarkers, assessing the PK bridge (US-licensed reference product vs. non-US-li censed compactor product), and application of model-informed drug development approaches.

18. **Translating Clinical Pharmacology Biosimilar *[PD Biomarker]* Research Findings into Best Practices for Industry and FDA Review Staff**
    Lead FDA Super Office: OTS
    Expected Timeline for Project Completion: 1 year from Fall 2023

    Project Objective (as described by lead office): This is the final year of a multi-year project that focused on enhancing efficient biosimilar development through developing standards, and methodology for identifying, characterizing, and applying pharmacodynamic biomarkers to support biosimilar development and approval. There are two aims:
    - Developing and discussing internal best practices for bioanalytical analysis of biosimilar clinical trials
    - Developing and discussing internal best practices for bioanalytical assay and data analysis for biosimilar drug development

    The foundational knowledge will come from previously completed work that include i) a public workshop on use of pharmacodynamic biomarkers in biosimilar development, ii) a publication of an evidentiary framework, iii) development of an internal reviewer resources, iv) completion of multiple exemplar trials for justifying pharmacodynamic selection for use in biosimilar development, and v) publications of clinical findings from these studies.

***Previous Publications*:**

Summary Publications

- Advancing innovations in biosimilars. Clin Pharmacol Ther. 2023 Jan;113(1):11-5
- Pharmacodynamic Biomarkers Evidentiary Considerations for Biosimilar Development and Approval. Clin Pharmacol Ther. 2023 Jan; 113(1):55-61.
- Pharmacodynamic biomarkers for biosimilar development and approval: a workshop summary. Clin Pharmacol Ther. 2022 Nov 15
- FDA-Duke Margolis public workshop (https://healthpolicy.duke.edu/events/biosimilar)

Original Research Publications

- Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(II) a randomized trial with IL-5 antagonists. Clin Pharmacol Ther. 2023 Jan;113(1):80-9
- Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(III) a randomized trial with interferon beta-1a products. Clin Pharmacol Ther. 2023 Feb;113(2):339-48
- Evaluating the utility of proteomics for the identification of circulating pharmacodynamic biomarkers of IFNbeta-1a biologics. Clin Pharmacol Ther. 2023 Jan;113(1):98-107
- Considerations for use of pharmacodynamic biomarkers to support biosimilar development--(I) a randomized trial with PCSK9 inhibitors. Clin Pharmacol Ther. 2023 Jan;113(1):71-9