U.S. FOOD & DRUG ADMINISTRATION

BsUFA III Regulatory Research Pilot Program:

Interim Report

July 2025

Contents

The Regulatory Science Research Pilot Program Under BsUFA III

The third authorization of the Biosimilar User Fee Act (Fiscal Years (FY) 2023–2027) (BsUFA III) includes a commitment for FDA to pilot a regulatory science research program to further enhance regulatory decision-making and facilitate science-based recommendations in areas foundational to biosimilar development.[1] The BsUFA III Commitment Letter identified two aims, or demonstration projects, for the BsUFA III regulatory research pilot program, herein referred to as the Pilot Program: 1) advancing the development of interchangeable products; and 2) improving the efficiency of biosimilar product development. In addition, FDA agreed, as one of the Pilot Program deliverables in the Commitment Letter, to post an interim progress report to its website ahead of an interim public meeting to be held on or before October 31, 2025.

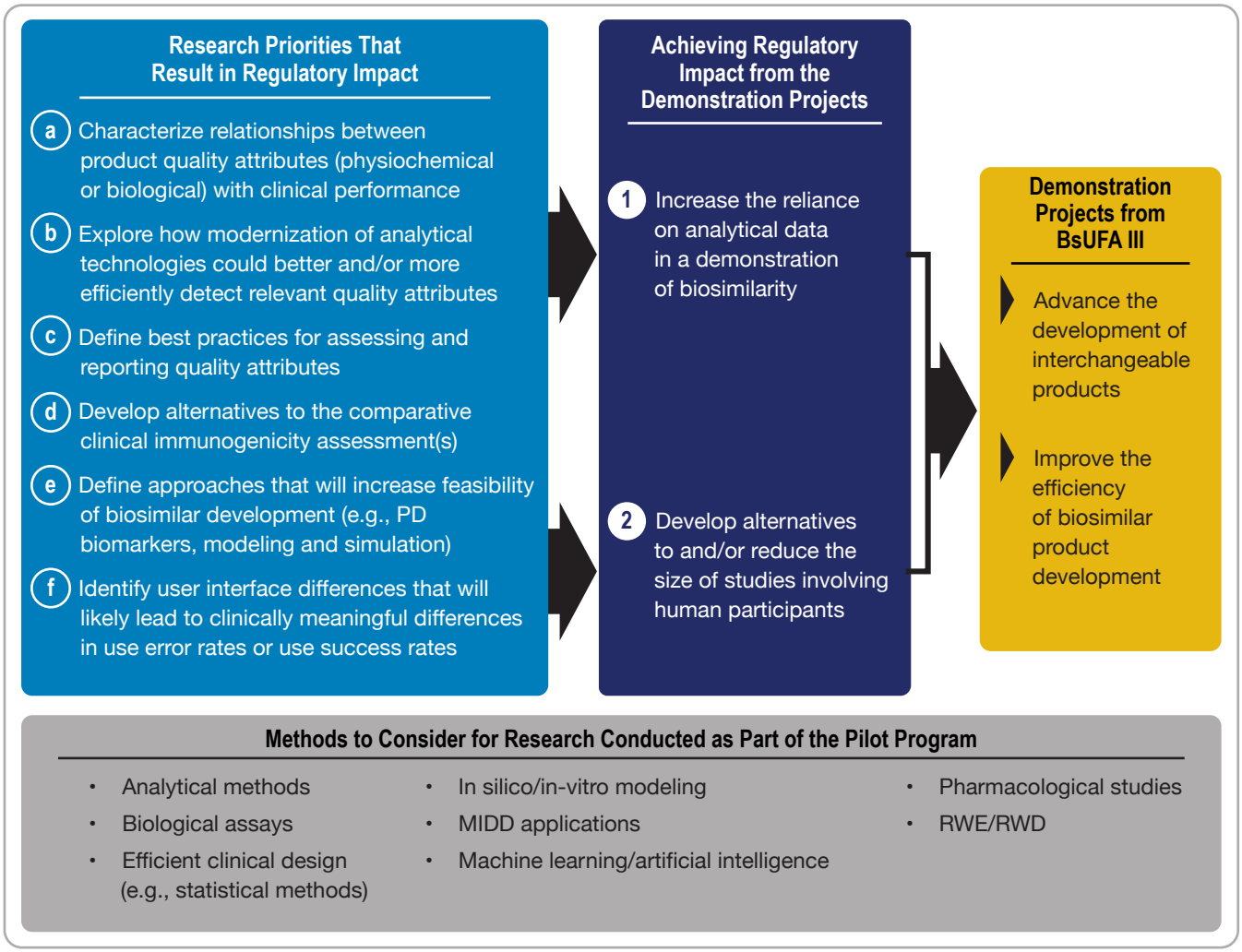
This report meets the BsUFA III commitment of developing an interim progress report and will provide a summary of activities completed in establishing the Pilot Program, an overview of research progress, and a brief discussion of future directions.

Establishing the Regulatory Science Research Pilot Program

RESEARCH PRIORITIES TO ACHIEVE THE DEMONSTRATION PROJECTS

A draft research roadmap that identified research priorities for the Pilot Program was first made publicly available in January 2023. During the subsequent year, stakeholders were invited to provide input on the identified research priorities and a revised research roadmap was published in January 2024 (Figure 1). As shown in Figure 1, all six research priorities (light blue box) and

Figure 1: Pilot Program Research Priorities



'regulatory impact' goals (dark blue box) support both demonstration projects indicated in the BsUFA III Commitment Letter (yellow box) – 'Advance the development of interchangeable products' and 'Improve the efficiency of biosimilar development'. Please see the BsUFA III Regulatory Research Pilot Program: Revised Research Priorities for additional information on the research priorities and goals for the Pilot Program.

The Pilot Program's Operational and Decision-Making Structure

At the beginning of BsUFA III, FDA formed an internal, multidisciplinary team with expertise in the disciplines relevant to biosimilar regulatory review (herein referred to as the Regulatory Science Subcommittee or RSSC). The RSSC conducted a preliminary survey of ongoing research programs at the Agency and identified the need to establish a unique operational structure for the Pilot Program that met the Commitment Letter timeline and established a cross-discipline decision-making framework for research oversight and evaluation. As such, the Pilot Program's operations were developed to encompass three phases that cycle over the course of every FY, which includes: Phase 1) 'Stakeholder Engagement and Priority Setting' for that FY's upcoming funding announcements; Phase 2) 'Submission and Evaluation of New Research Proposals', concluding with funding decisions, if any; and Phase 3) 'Regulatory Impact and Return on Investment Analysis' of ongoing research to understand how the Pilot Program is meeting its goals (Figure 2).

Under this operational structure, the following decision-making processes have been established:

Research review process for research proposals: Research proposals seeking funding from the Pilot Program in Phase 2 of the Pilot Program's operations are reviewed based on both a: 1) technical (subject matter expert or SME) evaluation; and 2) programmatic/strategic evaluation prior to funding decisions (see Appendix A). All final funding decisions are made by the BsUFA III Steering Committee (SC) within the context of all BsUFA III, of which the Pilot Program is only one component. All research proposals, both internal and external to FDA, are evaluated and ranked using similar criteria. As such, the review cycles for internal and external research are now run and evaluated in parallel, as depicted in Figure 2.

Research evaluation model for funded research: Research progress is monitored through annual reports submitted by all awardees, which are made available to the public. Funded projects led by principal investigators external to FDA also have FDA program officers (PO) to monitor research progress on an ongoing basis. Permission from external-to-FDA investigators is required to post their annual reports. In Phase 3 of the Pilot Program's operations, the annual reports and input from POs are used to evaluate the regulatory impact and return on investment (ROI) of the BsUFA III research portfolio based on the BsUFA III Revised Research Priorities and Commitment Letter (Figure 3). The Pilot Program defined terms, such as regulatory impact and ROI, for the purposes of these evaluations (Appendix B).

Figure 2: Annual Timeline of Internal and External Reviews

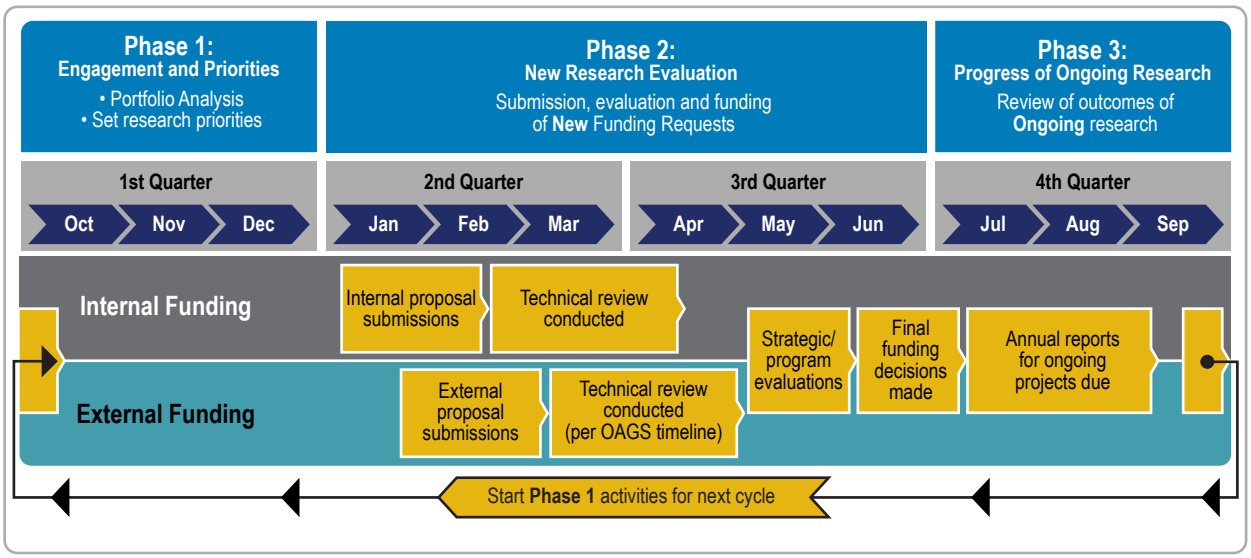
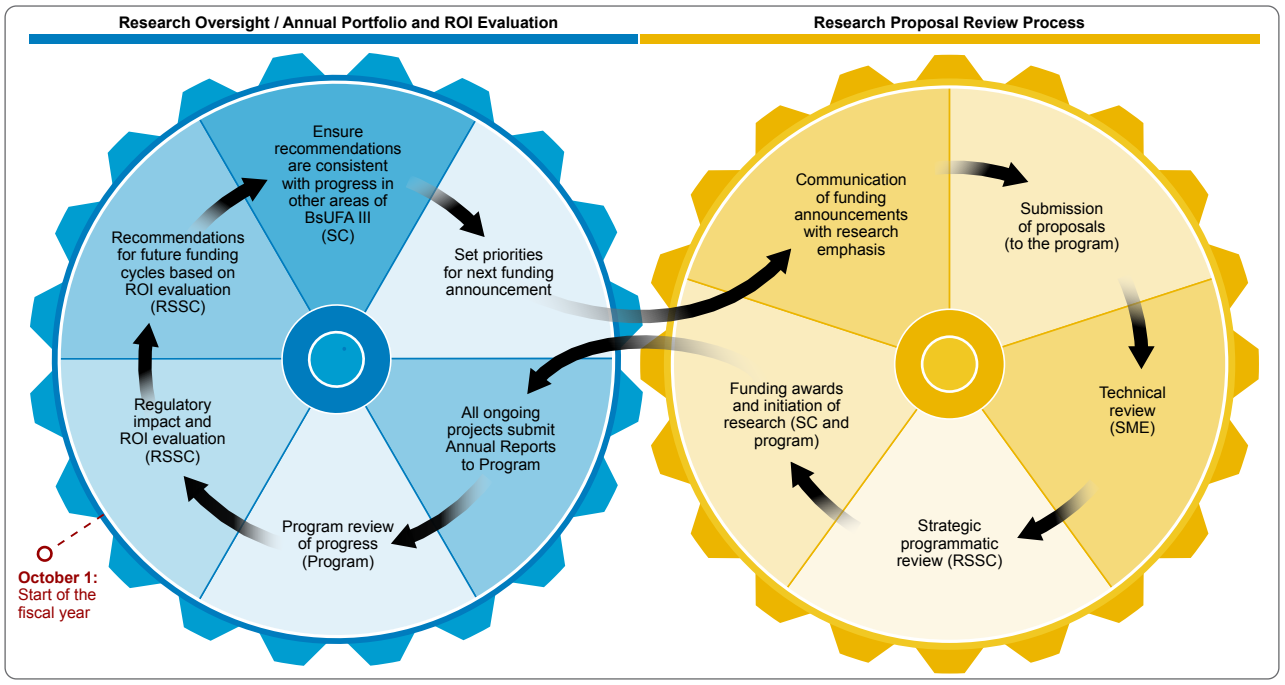


Figure 3: BsUFA III Regulatory Science Program Portfolio Analysis Process



Infrastructure for knowledge management and reporting: The Pilot Program required the development of a unique information technology (IT) framework for its operations and lifecycle management of its research. For Pilot Program operations, an information management system was built and now handles all Pilot Program workflows for developing and executing process improvement activities, monitoring research project workflows and ad-hoc requests, communicating with applicable stakeholders in relation to program activities, and applying change, risk, and resource management. For lifecycle management of research, a second IT framework was built based on the BsUFA III Revised Research Priorities and BsUFA III Commitment Letter that captures standardized data elements, such as project objectives, outcomes, regulatory impact, and ROI. These data elements are used to cross-populate across different research efforts, enable portfolio and gap analyses that inform future directions of the Pilot Program, and report the Pilot Program's activities to internal (i.e., internal to FDA, such as FDA assessors) and external stakeholders (e.g., other Federal Government agencies, private sector, academia).

Ongoing Stakeholder Engagement and Transparency

Given that biosimilar development is an ever-evolving field due to ongoing product development, regulatory review, and policy development, the Pilot Program takes an agile, transparent, and collaborative approach to communication and engagement with its multiple stakeholders. Table 1 provides a summary of FDA-initiated engagements that served as forums for the Pilot Program to better understand the perspectives, priorities, and challenges faced by researchers, industry, patients, and providers. Input from these engagements directly informs the funding priorities, subsequent funding announcements, and next steps for the Pilot Program. Additionally, as mentioned above; to facilitate these interactions, the Pilot Program posts the annual research progress reports publicly to allow stakeholders to remain abreast of the Pilot Program's research. For example, input from the Small Business and Industry Assistance webinar held in October 2023 and the Reagan-Udall Foundation roundtables held in Fall 2024 (Table 1) contributed to selecting Research Priority F (see Figure 1) as the research funding focus for the FY 2025 funding cycles.[2]

Table 1: FDA-Initiated Stakeholder Engagements for Regulatory Science Research Pilot Program

Title of Effort and Date	Purpose
BsUFA III Regulatory Research Pilot Program Request for Comment on Research Roadmap Docket Posted on January 25, 2023	To achieve the demonstration projects outlined for the Pilot Program, FDA published a research roadmap to highlight scientific areas where advancement is expected to impact science-based recommendations and regulatory decision making. The FDA sought input from patients, researchers, non-profit organizations, companies, and other stakeholders on the research strategy and priorities and any additional regulatory science research gaps.
BsUFA III Regulatory Science Pilot Program October 16, 2023 (Virtual) and October 26, 2023 (In-Person)	The two-part meeting provided an overview and discussion of the Pilot Program's status as it relates to the BsUFA III commitments. The virtual public component of the meeting included presentations and panel discussions by FDA staff, as well as internal and external awardees conducting research projects under the Pilot Program, and highlighted updates to the BsUFA III regulatory science research priorities based on comments from the public docket. During the in-person portion of the meeting, round table discussions focused on progress, feedback, and recommendations to improve regulatory impact of the demonstration projects outlined under the Pilot Program's research priorities.
Reagan-Udall Foundation Biosimilar Roundtables August 6, 2024; August 27, 2024; September 18, 2024; October 8, 2024; October 30, 2024	The Reagan-Udall Foundation for the FDA conducted a series of six closed-door virtual roundtable conversations with biosimilar developers to explore emerging areas of regulatory science and to create a space for active discussion and exploration among biosimilar developers. FDA was an observer of the discussions.
BsUFA III Regulatory Science Pilot Program: Progress Update January 22, 2025	This virtual meeting provided a recap of the activities of the Pilot Program since the October 2023 engagement. The webinar included a status update on the current research portfolio as it relates to the BsUFA III commitments as well as presentations and panel discussions by FDA staff. FDA staff also presented the next steps planned for the Pilot Program.

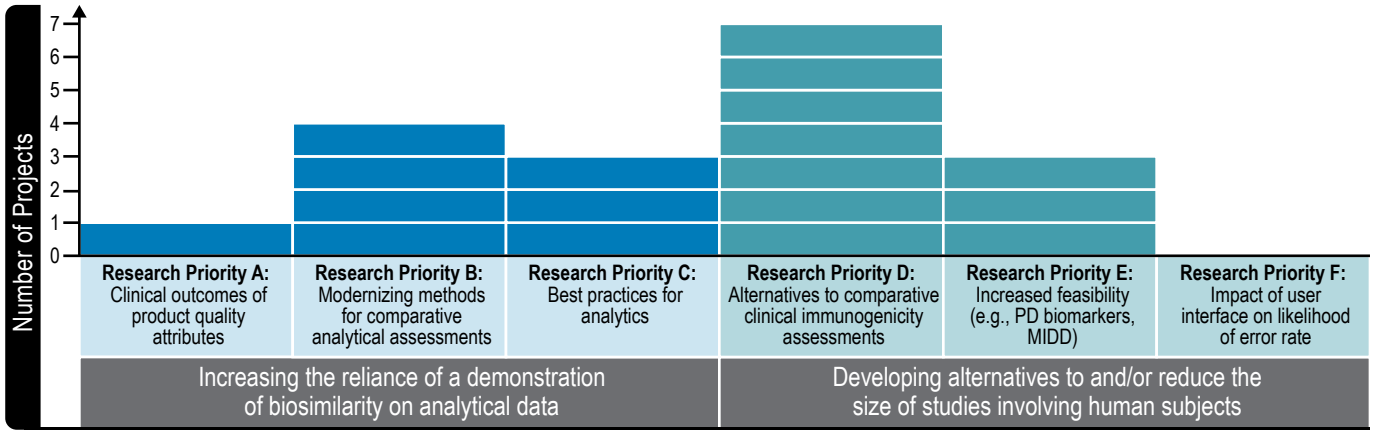
Overview of Research Progress

SUMMARY OF COMPLETED FUNDING CYCLES

The Pilot Program conducted several funding cycles that have resulted in the current portfolio of 18 different projects across both internal and external researchers that fall under the two regulatory impacts and six research priorities (Figure 4). For external funding calls, both the cooperative agreement and Broad Agency Announcements mechanisms were used, and timelines defined by the FDA Office of Grants and Acquisition Services were followed.[3,4,5,6] As mentioned above, for internal researchers, the review process mirrored and was conducted in parallel with external funding cycles as closely as possible. Given that all these funding cycles were run concurrently with the activities needed to establish the operations and decision-making structure of the Pilot Program, both the development of funding cycle processes and the operational and decision-making processes informed each other in real time.

The remainder of this section will provide an overview of the 18 funded research projects. Each research project will be summarized under the regulatory impact and the research priority that it was expected to address at the time of the funding award. Please see the BsUFA Revised Research Priorities[7] for additional context and rationale about the research impact and priorities. Each research project's summary of progress provides a brief description of its purpose, the researchers' approach, and key findings or next steps, when applicable. A complete list of projects addressing each research priority, as well as the research institution, primary investigator, initial funding year and duration, and a link to their annual report(s) can be found in Appendix C.

Figure 4: Number of Research Projects Addressing Each Research Priority



Regulatory Impact #1: Increase the Reliance on Analytical Data in a Demonstration of Biosimilarity

RESEARCH PRIORITY A: CHARACTERIZE RELATIONSHIPS BETWEEN PRODUCT QUALITY ATTRIBUTES (PHYSIOCHEMICAL OR BIOLOGICAL) WITH CLINICAL PERFORMANCE

The project under Research Priority A aims to leverage FDA experience to explore the effect that differences in product attributes have on clinical performance across FDA approved biosimilars. This work is intended to add to the global evidence base and ongoing conversations regarding the usage of clinical data in biosimilarity evaluations.

Landscape Assessment of Biosimilar Submissions

- **PI Institution:** Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Applied Regulatory Science (DARS)
- **Summary of Progress:** A team of multidisciplinary researchers led by Center for Drug Evaluation and Research's (CDER) OCP catalogued how the Agency evaluated differences in product quality attributes identified in comparative analytical assessments (CAA) for FDA-approved biosimilars. To achieve this, the researchers investigated analytical and clinical data from a defined set of biosimilar and reference products, which included collecting, standardizing, and visualizing data from nine adalimumab and five trastuzumab biosimilar development programs. The preliminary findings from the project are generally consistent with those of other efforts from other global regulatory bodies and, as of Spring 2025, are in preparation for publication.

RESEARCH PRIORITY B: EXPLORE HOW MODERNIZATION OF ANALYTICAL TECHNOLOGIES COULD BETTER AND/OR MORE EFFICIENTLY DETECT RELEVANT QUALITY ATTRIBUTES

The four projects under Research Priority B aim to provide a methodology or approach that, once developed and validated, would provide developers with an option that would more efficiently (e.g., less time and/or cost) obtain the same information as conventional and currently used approaches. Of note, the Agency acknowledges that implementation of a new method(s) also requires resources for developers. However, the findings of these projects suggest that these approaches could increase the efficiency of biosimilar development over time and, if included in an application, FDA assessors will have some experience and/or resource to reference for these approaches.

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

- **PI Institution:** Office of Pharmaceutical Quality (OPQ)/ Office of Pharmaceutical Quality Research (OPQR)
- **Summary of Progress:** This research team is seeking to develop a method of quickly quantifying major glycoforms for human IgG1 antibodies in their production culture media with a high throughput applicability. To do this, mouse monoclonal antibodies (mAb) were generated against glycosylated and non-glycosylated human IgG1 and then their affinities to specific glycoforms of human IgG1 mAb were determined using Biolayer Interferometry (BLI) at ~100 nM range. The preliminary results from the BLI method also showed reproducible and consistent quantification of the major glycoforms of human IgG1

mAb biological products. This group is now working to optimize the BLI method with different products and their biosimilars, as well as with production media. Once this method is developed, the project aims to conclude with validation and communication of this method in the public domain for both FDA assessors and drug developers. Once validated, this approach could facilitate product cell line development and provide a mechanism of real time feedback during manufacturing that could help address chemistry, manufacturing, and controls considerations for biosimilar manufacturers.

OnePotGlycan - A Chemoenzymatic Method for Simultaneous Profiling of N and O-glycans in One-Pot

- **PI Institution:** OPQ/OPQR
- **Summary of Progress:** The same group in OPQ/OPQR aims to develop and validate a method that simultaneously profiles N- and O-glycosylation of therapeutic proteins in the same samples. The researchers have established a method to simultaneously profile and measure relative abundance of N- and O-glycans from purified proteins and therapeutic proteins in a 'one-pot' format.[8] The researchers are currently working on validating and advancing this method, which could allow the use of one method when previously two were needed for the same information.

Assessment of the Performance of MAM vs Conventional Quality Control (QC) Methods for Evaluation of Product Quality Attributes of Adalimumab and Etanercept

- **PI Institution:** U.S. Pharmacopeia
- **Summary of Progress:** Researchers from U.S. Pharmacopeia seek to evaluate the performance of the mass spectrometry (MS)-based Multi-Attribute Method (MAM), in comparison to conventional analytical methods for measuring product quality attributes for CAAs and quality control (QC). The team from U.S. Pharmacopeia conducted forced degradation of a mAb (adalimumab) and a fusion protein (etanercept) from three sources under thermal and chemical stress conditions. They then assessed product quality attributes (e.g., charge variants, glycosylation, oxidation, other post translational modifications) by both conventional QC methods and the MAM workflow. Finally, they evaluated the same samples for differences in function and structure. As of Spring 2025, data collection and analysis has been completed and the researchers are preparing presentations and scientific publications on their work.

Model Development and Verification to Evaluate Minimum Stability Data Required for Biosimilar Submissions

- **PI Institution:** OPQ/OPQR
- **Summary of Progress:** The bioanalytics and protein stability group in OPQ/OPQR aims to determine the minimum amount of stability data required to accurately predict long-term stability. To accomplish this, the researchers first surveyed kinetic modeling approaches that have been included in biotechnology regulatory applications and are now producing the kinetic stability data that will be used to develop predictive models for a protein (insulin lispro) and a mAb (trastuzumab) and their biosimilars using frequentist and Bayesian approaches. Once complete, these models aim to inform recommended review practices for modeling of stability in regulatory submissions and provide knowledge and training to support biosimilarity assessments. Ultimately, the ability to accurately predict shelf life of 24-36 months with limited stability data could expedite availability of biosimilars to patients.

RESEARCH PRIORITY C: DEFINE BEST PRACTICES FOR ASSESSING AND REPORTING QUALITY ATTRIBUTES

The three projects under Research Priority C aim to provide publicly available information about aspects of biosimilar development that could help an inexperienced biosimilar developer make more informed choices about their development programs. Research under this priority aims to give FDA additional capability to define benchmarks for certain testing methods relevant to biosimilar development that will enable faster and more consistent guidance from the Agency, which can streamline biosimilar development and regulatory review over time.

Platform for Reliable Characterization and Evaluation of Comparability of Biosimilar Drug Products in Lyophilized and Liquid Formulations

- **PI Institution:** National Institute for Pharmaceutical Technology and Education (NIPTE)
- **Summary of Progress:** The NIPTE group is characterizing how formulation composition may influence the stability of mAbs against physical stressors and/or methods used for product characterization and

comparability studies.[9,10,11] Upon completion of the project, the researchers are aiming to publish several manuscripts and/or a white paper summarizing their observations to inform consideration of biosimilar candidate formulations by developers.

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

- **PI Institution:** University of Michigan at Ann Arbor
- **Summary of Progress:** The work by this research group aims to examine product quality attributes across a range of FDA-approved biosimilar and reference product(s) for insulins, trastuzumabs, and rituximabs using standardized methods in a single lab. These findings will be published in the public domain to serve as a reference for biosimilar developers attempting to evaluate 'how similar is similar.' Additionally, these researchers used the National Institute of Standards and Technology mAb and, as such, their results could be used as a benchmark during early biosimilar development. In this group's final research aim, they sought to collect feedback about any technical and regulatory challenges in interchangeable product development. As of Spring 2025, interviews with industry representatives are ongoing.

Bioassay – Enhanced Biosimilar Testing Capabilities

- **PI Institution:** OPQ/OPQR
- **Summary of Progress:** This OPQ/OPQR project aims to provide the Agency with a better capability to define, standardize, and harmonize expectations for assessing and reporting product attributes, while reducing inconsistencies and unnecessary testing. The researchers are obtaining international reference standards to provide a benchmark across laboratories and agencies for the comparison of biosimilar products. Current and future work focuses on the development and validation of cell-based orthogonal assays for insulins and mAb products.

Regulatory Impact #2: Develop Alternatives to and/or Reduce the Size of Studies Involving Human Participants

RESEARCH PRIORITY D: DEVELOP ALTERNATIVES TO COMPARATIVE CLINICAL IMMUNOGENICITY ASSESSMENT(S)

A key safety concern for all biological products is the generation of an unwanted immune response or immunogenicity. The effect of these unwanted immune responses can range from no deleterious clinical impact to significant alterations in the safety and effectiveness profile of a product. Although there has been substantial progress toward understanding risk factors contributing to eliciting an unwanted immune response, to date, immunogenicity in patients cannot be predicted to a level of certainty to meet regulatory standards of safety and effectiveness. As such, for innovator biological products, safety evaluations for immunogenicity always include a clinical evaluation.

A biosimilar product and its reference product generally have the same primary amino acid sequence. Therefore, the risk of immunogenicity of the biosimilar, via an adaptive immune response, can be based on the measurement of incidence and titer of anti-drug antibody (ADA) and neutralizing antibodies of the reference product, which is generally publicly available in the prescribing information. However, as indicated above, not all the underlying mechanisms leading to an unwanted adaptive immunogenic response are fully understood. Also, there are other factors that may impact a differential generation of an immune response, including the presence of process-related impurities, such as host cell proteins, DNA, or activators of the innate immune response. Therefore, knowledge about the reference product alone does not necessarily address ongoing gaps around predicting the incidence and impact of immunogenicity for a biosimilar product from a regulatory perspective.

Biosimilar development is designed to leverage product quality and CAA as both the: 1) most sensitive; and 2) least resource-intensive methods to detect differences that could potentially lead to clinically meaningful differences. However, there remains a paucity of these 'more sensitive' and 'less resource intensive' analytical methods for immunogenicity to enable a comparison of probability and consequence of an unwanted immune

response between a biosimilar candidate and its reference product. As such, for innovator products to date, comparative immunogenicity assessments for biosimilars generally have been evaluated through clinical studies. Of note, a growing body of literature is showing that these clinical studies have not demonstrated different immunogenicity concerns between a biosimilar candidate and its reference product if the biosimilar candidate was shown, through a thorough CAA, to be highly similar to its reference product.[12,13,14,15,16,17,18]

The Pilot Program identified the lack of comparative tools for immunogenicity as a key gap that regulatory science could attempt to address. The Pilot Program heavily invested in exploring an array of approaches that included in silico prediction of major histocompatibility complex (MHC) presentation, innate immune and adaptive immune in vitro assays, and humanized mouse models to understand how and when this 'toolbox' could identify differences in the probability and consequence of an unwanted immune response without having to conduct a clinical study with primary data collection. The Pilot Program's investment also included real-world data (RWD)/real-world evidence (RWE) from post-market or global experience with a biosimilar(s) to ensure the Pilot Program's investment in these methods were comprehensive. Additionally, exploration of RWD/RWE in biosimilar development is highlighted in the BsUFA III Commitment Letter.

The seven projects under Research Priority D collectively aim to collate and understand the current state of regulatory applications for alternative methods to clinical studies with primary data collection (including secondary use of RWD) for immunogenicity assessments for biosimilar development and, in turn, to develop and subsequently evaluate the potential for their future contributions. The Pilot Program's accumulated experience under this research priority indicates that there is a potential for these approaches to deepen our understanding of immunogenicity itself and transform immunogenicity risk assessments and evaluations across drug development, including biosimilar development.

In Vitro Prediction of Innate Immune Response:

Develop Acceptance Parameters and Standards for the Innate Immune Response Modulating Impurities (IIRMI) Assays in the Biosimilar Space

- **Institution:** OPQ/OPQR
- **Summary of Progress:** This OPQ/OPQR project aims to develop an in vitro assay that can be used to assess immunogenicity risk of process- or product-related impurities on eliciting an innate immune response. To this point, the project has evaluated the impact of protein parameters on assay performance (glycosylation, host cell protein (HCP) levels, oxidation, aggregation, etc.). The investigators are also developing a set of reference standards that can be used by sponsors to benchmark their assays, which is a critical need for assay development and interpretation because no harmonized testing protocol exists.

In Silico Prediction of Adaptive Immune Response:

ISPRI-HCP: CHO Protein Impurity Immunogenicity Risk Prediction for Improving Biosimilar Product Development and Assessing Product Interchangeability

- **Institution:** Epivax, Inc.
- **Summary of Progress:** The project from Epivax, Inc. aims to explore the correlation between in silico prediction of MHC presentation to results from peripheral blood mononuclear cells (PBMC)-based in vitro assays measuring an adaptive immune response, such as T cell proliferation and/or cytokine release.[19] As of Spring 2025, 65 HCPs derived from Chinese hamster ovary (CHO) proteins reported in the published literature have been analyzed in silico. Peptides for the in vitro assays have been designed and obtained. In a preliminary in vitro analysis, the immune responses of peripheral blood mononuclear cells (PBMC) from donors to standard controls such as Phospholipase B-like 2 (PLBL2), memory T cell epitopes (e.g., "CEFT" epitopes), and human albumin were validated. Further studies are being performed to quantify in vitro PBMC responses to 30 of the 65 HCP and determine whether anticipated modifications to the ISPRI-HCP algorithm will align with in vitro results.

In Vitro Prediction of Adaptive Immune Response:

Addressing Fundamental Issues for In Vitro Immunogenicity Testing

- **Institution:** OTS/OCP/DARS
- **Summary of Progress:** This project aims to identify the current methods being used for PMBC-based in vitro immunogenicity assays in regulatory submissions. Thus far, six unique assays have been used for in vitro assessment of immunogenicity across biosimilar applications; none of which were used in regulatory decision making. Next steps will include developing best practices and standardization for these approaches.

Animal Model Prediction of Adaptive Immune Response:

Validation of a Non-Clinical Immunogenicity Model

Production and Optimization of Humanized Mice

- **Institution:** OTS/OCP/DARS
- **Summary of Progress:** Two similar projects aim to establish a protocol for producing immune humanized mice for the two most frequently used humanized mouse models and then evaluate the ability of humanized mice to serve as a nonclinical immunogenicity model by evaluating several biological products (with known moderate to high immunogenicity in the clinic). To this point, analysis of phenotypic and functional data is complete, while ADA assays that can be used with chimeric serum samples to evaluate for the presence of ADAs to mAbs and therapeutic protein products are in development. Next steps include finalizing analysis of the assays and sharing project findings.

Use of Real-World Data/Evidence to Identify Differences in Adverse Immunogenic Responses:

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

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

- **Institution:** Academy of Managed Care Pharmacy (AMCP), Inc.
- **Summary of Progress:** The first of the two AMCP projects aims to evaluate the feasibility of using RWD, as it exists now in the U.S., to inform biosimilar and interchangeable biosimilar regulatory assessments. Reports that summarize a literature review and two expert panels are being finalized for public dissemination, along with an assessment of three U.S.-based data sources regarding quality, completeness, and fitness for use in generating RWE for regulatory purposes. Additionally, a target trial emulation of a switching study using RWD available in the U.S. has been conducted to determine whether the results are suitable for regulatory decisions for biosimilars or interchangeable biosimilars. The results are finalized, and a summary and recommendations has been prepared to describe how to best use RWD for biosimilar and interchangeable products. A report summarizing the findings is being finalized for public dissemination.[20,21,22]

  A companion project led by the same team aims to study the feasibility and fitness of using RWD from European countries to inform scientific considerations in demonstrating biosimilarity. The initial assessment of data sources is complete, while target trial emulation designs for insulin glargine and adalimumab are in preparation. Next steps for this study include finalizing the protocol and conducting the planned data analyses and communication plan to understand whether RWD from European countries are fit-for-use.

RESEARCH PRIORITY E: DEFINE APPROACHES THAT WILL INCREASE FEASIBILITY OF BIOSIMILAR DEVELOPMENT (E.G., PD BIOMARKERS, MIDD INCLUDING ARTIFICIAL INTELLIGENCE AND/OR MACHINE LEARNING)

Although uptake of biosimilars is starting to generate savings across the U.S. healthcare field,[23] there are still concerns that many biological products will not have a biosimilar. This is hypothesized to be due to a variety of reasons, with the most cited reason being that the size of a certain patient population does not justify the cost and time required to develop a biosimilar under the current regulatory paradigm.[24] As such, this priority aims to identify and/or develop new or alternative approaches, not covered by the other five research priorities, that could reduce the size or need for comparative clinical studies in a biosimilar development program, and therefore, possibly increase the feasibility of development of biosimilars for all reference products.

Translating Clinical Pharmacology Biosimilar [PD Biomarker] Research Findings into Best Practices for Industry and FDA Review Staff

- **Institution:** OTS/OCP/DARS
- **Summary of Progress:** A team of FDA researchers initially embarked on a project as outlined in the 2018 Biosimilar Action Plan (BAP),[25] which was folded under the Pilot Program in its last year as part of the implementation of the Pilot Program's operational and oversight models. Over the duration of this entire project, research outcomes included: 1) a public workshop on the use of pharmacodynamic (PD) biomarkers in biosimilar development[26,27] 2) a publication of an evidentiary framework;[28] 3) development of internal reviewer resources; 4) completion of multiple exemplar trials for justifying PD selection for use in biosimilar development; and 5) publications of clinical findings from these studies.[29,30,31] These outcomes facilitated the communication of information on bioanalytical and proteomics work completed under FDA-led clinical studies, including the dissemination of best practices during FDA-internal events to promote reviewer education on these topics. Next steps include submission of multiple manuscripts for publication and continued application of the lessons learned to future biosimilar applications when biosimilar developers express interest in utilizing PD biomarkers as part of their development program.

Critical Factors for Standardization and Accuracy of PK Assays of PEGylated Biosimilars

- **Institution:** OTS/OCP/DARS
- **Summary of Progress:** This project seeks to provide guidance and best practices to industry for evaluating pharmacokinetics (PK) associated with biosimilars that are conjugated to polyethylene glycol (PEG). The research team at FDA has worked to validate existing assays used by biosimilar sponsors for pegfilgrastim PK and developed an alternate pegfilgrastim PK assay as a proof of concept. Next steps are to publish the remaining manuscripts and provide a seminar to reviewers regarding assay development and aspects of assay performance that could affect the approval of biosimilar PEGylated products.

Evidence-Based Approach to the Design of Clinical Pharmacology Studies

- **Institution:** OTS/OCP
- **Summary of Progress:** The project from OCP aims to explore and identify areas for increased efficiency for biosimilar development from a clinical pharmacology perspective. The researchers are employing a multi-pronged approach including: 1) identifying potential PD biomarkers for biosimilar programs for which conducting comparative efficacy studies can be challenging; 2) developing best practices for bioanalytical assessment of biomarkers; 3) seeking explanations for differences between PK and immunogenicity data among 351(k) submissions; and 4) investigating factors that contribute to device-related differences in PK performance. Work is ongoing in all four areas.

RESEARCH PRIORITY F: IDENTIFY USER INTERFACE DIFFERENCES THAT WILL LIKELY LEAD TO DIFFERENCES IN USE ERROR RATES OR USE SUCCESS RATES IN THE CONTEXT OF PHARMACY SUBSTITUTION

As of Spring 2025, the Pilot Program has not funded any research proposals that address Research Priority F. During the Pilot Program's stakeholder engagement events, both the Agency and its stakeholders emphasized that research in this area remains a high priority. Specifically, at the in-person component of the two-part public meeting FDA hosted in October 2023, attendees highlighted that additional information about which differences in devices or delivery systems could be considered meaningful would increase the efficiency of biosimilar development. Examples given included differences in the shape of the injector, the number of steps required for injection, the number of doses delivered, and physical characteristics or aspects of clinical performance.

Interim Program Evaluation and Future Planning

PROGRESS OF THE PROGRAM

Using the timeline outlined in the Commitment Letter, FDA is approximately 3 years into piloting a regulatory science program that is '*broadly applicable to facilitating biosimilar and interchangeable biological product development.*'

To date, from an operational and strategic perspective, the Pilot Program has:

- Identified, sought feedback on, and revised the research priorities.[32]
- Developed and implemented a cross-office operational and decision-making structure including both a proposal review process and a research oversight model (Figure 3).
- Designed and developed information management systems for tracking, reporting, and evaluating research under the Pilot Program (see section titled *'Infrastructure for knowledge management and reporting'*).
- Engaged in transparent and ongoing stakeholder engagement that includes posting the research progress reports used by the Pilot Program to conduct its ROI analysis (Table 1).
- Conducted four funding calls for external-to-FDA research proposals and three funding calls for internal-to-FDA research proposals, and received a total of 60 research proposal submissions (as of December 2024).[2,3,4,5]
- Developed criteria for and conducted technical and strategic reviews on all proposal submissions (Appendix A), which resulted in less than 30% of submitted projects receiving funding awards.
- Developed reporting templates, implemented annual reporting for all awardees, and posted annual reports publicly (as permitted for external-to-FDA awardees).[33]
- Developed and began implementing annual ROI analysis for the Pilot Program itself and for BsUFA III in its entirety.

Taken together, one of the Pilot Program's major accomplishments was setting up the fundamental infrastructure and setting the precedent for transparent, responsive, and methodological approaches to running the program and meeting the BsUFA III commitment by September 30, 2027. Given that biosimilar regulatory review occurs across offices in CDER, the Pilot Program's research framework is serving as a mechanism by which disciplines can convene, discuss gaps outside the structure of a regulatory review, and align ongoing and future research efforts.

As of Spring 2025, due to the nature and timeline of the research process, most of the 18 research projects under the Pilot Program are ongoing and/or have needed no-cost extensions. The regulatory impact and/or ROI of these projects will be assessed at the end of the Pilot Program.

To date, the Pilot Program expects the following interim results, when finalized, to inform regulatory decision-making and facilitate science-based recommendations at the Agency. Of note, this list is a snapshot as of Spring 2025 and changes/additions may occur as projects mature.

- An FDA publication that will add to the global conversation about the use of and need for clinical data to address residual uncertainty in biosimilar development. (*Project: Landscape Assessment of Biosimilar Submissions*)
- Information about the efficiency of a MAM approach for biosimilar developers and FDA assessors. (*Project: Assessment of the Performance of MAM vs Conventional Quality Control (QC) Methods for Evaluation of Product Quality Attributes of Adalimumab and Etanercept*)
- Comparisons of product quality attributes of US-approved biosimilars using the same methodology. (*Project: Systematic Analytical Characterization of Innovator and Biosimilar Products with the Focus on Post-Translational Modifications*)
- Broad assessment of the current state of comparative immunogenicity methods in relation to biosimilar development. *(All Projects under Research Priority D)*
- Identification of gaps that must be addressed to integrate RWD/RWE in biosimilar development. (*Projects: 'Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data' and 'Bridging the Gap: Using Foreign Real-World Data to Inform Interchangeable Biosimilar Approvals'*)

- Understanding that PD biomarkers may not necessarily increase the efficiency of most biosimilar development programs. (*Project: Translating Clinical Pharmacology Biosimilar [PD Biomarker] Research Findings into Best Practices for Industry and FDA Review Staff*)

As noted above, there have not yet been any projects funded to Research Priority F, '*Identify user interface differences that will likely lead to differences in use error rates or use success rates in the context of pharmacy substitution.*' During the Pilot Program's stakeholder engagements, this priority has consistently been identified as a challenge for biosimilar developers, and streamlining the data needed to support acceptable differences in user interfaces would increase the efficiency of biosimilar development. The Pilot Program continues to conduct targeted outreach to elicit more proposals for this priority.

THE ROLE OF REGULATORY SCIENCE RESEARCH FOR BIOSIMILAR DEVELOPMENT

As outlined in the Commitment Letter, the goal of the Pilot Program is to explore the use of regulatory science to enhance FDA's regulatory decision making and to facilitate FDA's science-based recommendations. The final deliverable of the Pilot Program will be a *'comprehensive strategy document outlining specific actions the Agency will take to facilitate the development of biosimilar and interchangeable biological products'* regarding the role of regulatory science research for biosimilar development. Although this final deliverable ultimately will be informed by the entirety of the Pilot Program, a few preliminary themes are emerging as of the publication of this interim report, which are listed below.

- There is a lengthy multi-step process to: 1) identify questions that can potentially impact regulatory decision-making; 2) develop detailed research project(s) to address these questions; 3) conduct the studies and analyze the results; and 4) formulate regulatory implications from the results. Although regulatory research outcomes can inform and facilitate policy development, the importance of a strategic and intentional regulatory science framework around research efforts and ensuring sufficient time to bring efforts to fruition, is clear.
- When translating research outcomes to regulatory impact, maintaining flexibility regarding alternative or future approaches is as desirable as the potential transparency and predictability that guidance or 'standard setting' may offer to the biosimilar development community.
- On a related note, fundamentally, the core utility of a regulatory science program in support of FDA's regulatory process is in facilitating science-based recommendations and decision-making; it is not just to obtain new scientific knowledge. Therefore, elucidating how scientific information may or may not translate to regulatory applications is a useful focus.

At this interim timepoint in the Pilot Program, FDA is encouraged by the progress made in establishing the infrastructure and strategic vision underlying the regulatory science program and by the work done and lessons learned from the experiences of Pilot Program participants, as well as valuable feedback obtained from other biosimilar development stakeholders. FDA also looks forward to the final reports from Pilot Program projects and the conclusions and implications that they may support. Moving forward, FDA envisions a biosimilar-related regulatory science research program that is nimble enough to respond to acute needs. Additionally, the strength of a biosimilar-related regulatory research science program may lie in the anticipation and identification of probable regulatory issues associated with upcoming biosimilar development efforts (e.g., for therapeutics or therapeutic modalities with upcoming expiration of exclusivity).

This forward-looking approach could allow a research program to prospectively collaborate, explore, and communicate research findings to increase the efficiency of biosimilar development before inefficiencies drive up resource utilization. This approach is also more aligned with when biosimilar developers are making decisions about their biosimilar portfolio and, as such, would benefit from continued input from industry stakeholders to help identify and inform research priorities.

Appendix A: Broad Agency Announcement Review Process

As of 11/12/2024

SME TECHNICAL EVALUATION

- Is there a need/problem/gap?
- Does the proposed study address the need/problem/gap with scientific rigor?
- Are there resources to be successful?

1. **Significance to development and/or regulation of biosimilar products**
    a. Does the project address an important problem or a critical barrier to progress in biosimilar development or regulation?
    b. Is the rationale/prior research/justification that supports for the proposed project rigorous and compelling?
    c. If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or regulatory practice be advanced and/or more efficient?
    d. How will scientific knowledge, technical capacity and/or regulatory practice identified in #1c above change the field of biosimilar development and regulation?
2. **Investigator(s) and environment**
    a. Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise? Are their leadership approach, governance, and organizational structure appropriate for the project?
    b. Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment, and other physical resources available to the investigators adequate for the project proposed?
3. **Methods and approach**
    a. Is the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
    b. Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility, and will particularly risky aspects be managed?

REGULATORY SCIENCE SUBCOMMITTEE STRATEGIC/PROGRAMMATIC EVALUATION

- Alignment with research priorities?
- Proximity to regulatory impact?
- How innovative?

1. **How aligned are the research outcome(s) of the project to achieving ONE or BOTH of the following?**
    a. One or more of the BsUFA III revised regulatory research priorities and/or a critical milestone toward one or more of the BsUFA III revised regulatory research priorities?
    b. A tangible effect on regulatory decision-making for biosimilar development programs
2. **If the research outcomes are achieved, how much effort will be needed to translate that outcome into the project objective and/or regulatory impact at the FDA?**
3. **Are the concepts, approaches or methodologies, instrumentation, or interventions in the research proposal novel or do they challenge a current paradigm in the field of biosimilar development or regulation?**

Appendix B: Definitions

TERM OR PHRASE	DEFINITION
Regulatory Impact	A research outcome(s) that is expected to inform science-based recommendations and regulatory decision-making at FDA.
Research Outcome(s)	The data or work product that results from the specific research activities.
Research Project	A focused investigation (or set of investigations) addressing a regulatory or regulatory science objective and is financed or will be financed, in part or in full, by ANY amount of BsUFA III funds for biosimilar development.
Research Project Objective	The regulatory or regulatory science issue or gap that the research is trying to address.
Return on Investment (ROI)	How the research outcome(s) achieved the regulatory impact, and to what extent (i.e., once the project is closed out, how are FDA science-based recommendations and regulatory decision-making changing?) relative to the BsUFA Regulatory Science Pilot Program resources used.

Appendix C: Funded Projects

The projects funded under the Pilot Program are listed in the table below by the research priority they address. The funding institution, primary investigator (PI), link to the most recent available annual report, initial funding year, and the estimated duration of funding (as of December 2024) are included in the table (*Note that timelines are estimated and subject to change and do not account for no-cost extensions or unexpected delays*).

Institution/PI	Title of Project	Initial Funding Year (and Duration)
Research Priority A		
OTS/OCP/DARS (Florian)	Landscape Assessment of Biosimilar Submissions	FY 2023 (estimated 1 year)
Research Priority B		
OPQ/OPQR (Ju)	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	FY 2023 (for estimated 2 years)
OPQ/OPQR (Ju)	OnePotGlycan - A Chemoenzymatic Method for Simultaneous Profiling of N and O-glycans in One-Pot	FY 2023 (for estimated 2 years)
U.S. Pharmacopeia (McCarthy)	Assessment of the Performance of MAM vs Conventional QC Methods for Evaluation of Product Quality Attributes of Adalimumab and Etanercept	FY 2022 (for estimated 2 years)
OPQ/OPQR (Ortega-Rodriguez)	Model Development and Verification to Evaluate Minimum Stability Data Required for Biosimilar Submissions	FY 2024 (estimated 3 years)
Research Priority C		
National Institute for Pharmaceutical Technology and Education (NIPTE) (Suryanarayanan)	Platform for Reliable Characterization and Evaluation of Comparability of Biosimilar Drug Products in Lyophilized and Liquid Formulations	FY 2022 (estimated 2 years)
University of Michigan at Ann Arbor (Schwendeman)	Systematic Analytical Characterization of Innovator and Biosimilar Products with the Focus on Post-translational Modifications	FY 2022 (estimated 2 years)
OPQ/OPQR (Sourbier)	Bioassay - Enhanced Biosimilar Resting Capabilities	FY 2023 (estimated 2 years)

Research Priority D		
OPQ/OBP (Verthelyi)	*Develop Acceptance Parameters and Standards for the Innate Immune Response Modulating Impurities (IIRMI) Assays in the Biosimilar Space	FY 2023 (estimated 2 years)
Epivax, Inc. (DeGroot)	ISPRI-HCP: CHO Protein Impurity Immunogenicity Risk Prediction for Improving Biosimilar Product Development and Assessing Product Interchangeability	FY 2022 (estimated 2 years)
OTS/OCP/DARS (Howard)	Addressing Fundamental Issues for In Vitro Immunogenicity Testing	FY 2023 (estimated 1 year)
OTS/OCP/DARS (Howard)	Validation of a Non-Clinical Immunogenicity Model	FY 2023 (estimated 1 year)
OTS/OCP/DARS (Howard)	Production and Optimization of Humanized Mice	FY 2024 (estimated 1 year)
Academy of Managed Care Pharmacy, Inc. (Lockhart)	Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data	FY 2022 (estimated 2 years)
Academy of Managed Care Pharmacy, Inc. (Lockhart)	Bridging the Gap: Using Foreign Real-World Data to Inform Interchangeable Biosimilar Approvals	FY 2023 (estimated 2 years)
Research Priority E		
OTS/OCP/DARS (Strauss)	Translating Clinical Pharmacology Biosimilar [PD Biomarker] Research Findings into Best Practices for Industry and FDA Review Staff	FY 2024 (estimated 1 year)
OTS/OCP/DARS (Howard)	Critical Factors for Standardization and Accuracy of PK Assays of PEGylated Biosimilars	FY 2024 (estimated 1 year)
OTS/OCP (Wang)	Evidence-Based Approach to the Design of Clinical Pharmacology Studies	FY 2024 (estimated 2 years)

* The link to the annual report for this project will be shared once available.

Endnotes

1 https://www.fda.gov/media/152279/download

2 https://sam.gov/opp/96ecb34be4fa4298a37c02e9730afcae/view

3 https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-22-026.html

4 https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-23-026.html

5 https://sam.gov/opp/26fa501e9b4d4f1ba8e1c2a8314343cb/view

6 https://sam.gov/opp/1811e00d132349d08cebe07ff77497ed/view

7 https://www.fda.gov/media/175799/download

8 https://pubmed.ncbi.nlm.nih.gov/39116882/

9 https://pubmed.ncbi.nlm.nih.gov/38422397/

10 https://pubmed.ncbi.nlm.nih.gov/39798696/

11 https://pubmed.ncbi.nlm.nih.gov/39743160/

12 https://pubmed.ncbi.nlm.nih.gov/37788264/

13 https://pubmed.ncbi.nlm.nih.gov/35881304/

14 https://pubmed.ncbi.nlm.nih.gov/29500555/

15 https://pubmed.ncbi.nlm.nih.gov/37902937/

16 https://pubmed.ncbi.nlm.nih.gov/36546547/

17 https://pubmed.ncbi.nlm.nih.gov/37831324/

18 https://pubmed.ncbi.nlm.nih.gov/35596890/

19 https://pubmed.ncbi.nlm.nih.gov/37697150/

20 https://www.bbcic.org/sites/default/files/2024-12/ISPOREU_BBCIC_FDA1_data_assessment_final.pdf

21 https://www.bbcic.org/sites/default/files/2024-12/ISPOREU_BBCIC_FDA1_expert_panel_final.pdf

22 https://www.bbcic.org/sites/default/files/2023-12/BBCIC_ISPOR_EU_RWD_lit_review_2023.11.03_FINAL.pdf

23 https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027

24 https://pubmed.ncbi.nlm.nih.gov/37542600/

25 https://www.fda.gov/media/114574/download

26 https://healthpolicy.duke.edu/events/biosimilar

27 https://pubmed.ncbi.nlm.nih.gov/36380593/

28 https://pubmed.ncbi.nlm.nih.gov/36178447/

29 https://pubmed.ncbi.nlm.nih.gov/36184697/

30 https://pubmed.ncbi.nlm.nih.gov/36324229/

31 https://pubmed.ncbi.nlm.nih.gov/36308070/

32 https://www.fda.gov/drugs/biosimilars/biosimilars-research-awards

33 https://www.fda.gov/drugs/biosimilars/biosimilars-science-and-research

Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993