U.S. FOOD & DRUG ADMINISTRATION

# Biosimilar User Fee Act (BsUFA) III Regulatory Science Pilot Program

## ANNUAL REPORT

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## Check if this report is Progress or Final Report:

☐**Progress report** ☒ **Final report**

# REPORT OVERVIEW

**Table 1:** Project Overview

| | |
|---|---|
| **Project Title:** | Landscape Assessment of Biosimilar Submissions |
| **Investigator:** | Jeff Florian |
| **Organization:** | OTS/OCP/DARS |
| **Grant No. (if applicable)** | 75F40123F19020 CDER-2023-118257 |
| **Project Objective:** | Conduct a landscape analysis to determine how FDA can answer questions about whether differences in analytical assessments in biosimilar development programs do or do not corelate with clinical data. |

| Specific Aim(s) | Progress | Outcomes | Communication Timeline |
|---|---|---|---|
| 1. Explore if analytical data from a defined set of biosimilar and reference products correlate with clinical data. | • Collected data for 9 adalimumab and 5 trastuzumab biosimilars<br>• Analyzing and visualizing data to understand any comparative differences and their resolution | Developing a draft manuscript for eventual publication that could promote internal review consistency and inform discussions regarding future product development programs. | • Drafting sections for future manuscript publication (Fall 2024)<br>• Developing slide decks with overview of methods and results for future presentations (Summer 2024) |
| 2. Survey ongoing biosimilar database efforts across CDER where available analytical, PK/PD, and comparative clinical data from submitted 351(k) applications are being collected. | • Interviewed 23 staff across OTS/OCP, OND/OTBB, and OPQ<br>• Reviewed 8 CDER-wide IT systems and 15 Office-specific databases and tools containing biosimilar data | Outlining assessment findings, including the feasibility and value of a future state database, in an internal report. | Internal report will be delivered to FDA in September 2024 |

# PROGRESS SUMMARY

The objective for this project is to conduct 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. See Table 2 for an overview of our project's phases, milestones, and current status.

**Table 2:** Project Milestones, Timeline, and Current Status

| Phase | Aim(s) | Activities & Milestones | Status (Month Completed) |
|---|---|---|---|
| **Initiation and Planning** | Aims 1 & 2 | Lead project kickoff meeting | Complete (October 2023) |
| | | Develop project plan and evaluation materials | Complete (December 2023) |
| **Conduct Assessment** | Aim 1 | Collect quality & clinical data for adalimumab + trastuzumab biosimilars | Complete (March 2024) |
| | | Clean, harmonize, and QC data | Complete (May 2024) |
| | Aim 2 | Conduct FDA stakeholder interviews | Complete (May 2024) |
| | | Review existing biosimilar databases | Complete (June 2024) |
| | Aims 1 & 2 | Analyze data and summarize findings | Complete (June 2024) |
| | Aim 1 | Collect quality & clinical data for additional biosimilar product classes | Not yet started (Expected September 2024) |
| **Develop Manuscript and Report** | Aims 1 & 2 | Develop manuscript and report outlines | Complete (June 2024) |
| | Aim 1 | Develop first draft of Methods and Results sections for manuscript | Complete (July 2024) |
| | Aim 1 | Facilitate FDA internal reviews of draft manuscript sections | Ongoing (Expected August 2024) |
| | Aim 2 | Develop findings, including future database feasibility, in an internal report | Ongoing (Expected September 2024) |

# Aim 1: Explore if analytical data from a defined set of biosimilar and reference products correlate with clinical data

**Background**: Comparative analytical assessments are foundational in biosimilar development to detect potential differences between products. When differences are present, it is critical to understand whether and how they impact clinical outcomes. Advancing FDA's understanding of analytical methods and their impact on clinical performance is a key research priority for the BsUFA III Regulatory Science Pilot Program. Our team is conducting a study to explore the following research questions:

1. Are quality data, combined with clinical PK data, sufficient to establish biosimilarity between candidates and their reference products (RPs)?
2. In cases where differences are present, what steps are taken to determine that they do not preclude a determination of highly similar?

**Methods**: Our team has collected, reviewed, and analyzed the quality (i.e., from comparative analytical assessments) and clinical data (i.e., from pharmacology and comparative efficacy and safety studies) for adalimumab and trastuzumab biosimilars approved by FDA as of November 1, 2023. These product classes were selected as representative examples of widely used biologics (i.e., IgG1 mAbs) covering autoimmune and oncology indications. Comparative quality data and clinical study results were manually extracted from FDA review documents (e.g., Product Quality Reviews and Biosimilar Multidisciplinary Evaluation and Reviews) of the original 351(k) biologics license applications (BLAs) and organized in a data collection instrument that our team developed and iteratively modified to ensure efficient and consistent collection of pertinent information. Data collected include the following:

- **Comparative Analytical**: batch-level data to determine percentage of lots demonstrating high similarity to the US RP, as well as reviewer explanations regarding resolution of identified differences

- **Clinical Pharmacology**: summary results of PK and immunogenicity endpoints
- **Clinical Efficacy and Safety**: summary results of primary and secondary efficacy endpoints as well as rates of various adverse event categories

Following an internal quality control process to verify data accuracy, our team harmonized the nomenclature (e.g., quality attribute names, test methods) for each class and developed a data dictionary to visualize quality attribute names from each biosimilar. Throughout this process our team has sought guidance and incorporated feedback from an interdisciplinary project advisory group (PAG)—consisting of scientific and policy experts from CDER's OCP, OPQ, and OTBB—across all phases of the project including conceptualization, methods development, data collection and analysis, and presentation of results.

**Progress and Current Status:** As of June 2024, we have collected all comparative analytical, clinical pharmacology, and clinical efficacy/safety study data for adalimumab (9) and trastuzumab (5) biosimilars and completed our nomenclature harmonization and QC process. We have also completed our initial analysis and visualization efforts across all quality and clinical datasets, developing figures to show the results of comparative analytical assessments and clinical studies and facilitate comparisons within the product class. In addition, in cases where differences between the biosimilar and its RP existed, we assessed regulatory review documentation, extracted information about how those differences were resolved, and identified patterns across the product class. We have presented initial results to our PAG, with follow-up meetings and other internal FDA presentations to disseminate results in July and August 2024. In addition, our team is currently drafting Methods and Results sections for a manuscript that we intend to pass over to FDA in September 2024.

# Aim 2: Survey ongoing database efforts across CDER

**Background**: Across CDER, organizations are collecting and curating datasets independently from one another, using multiple databases, systems, and approaches to do so. To evaluate the possibility of streamlining these efforts, our team has evaluated existing databases and other knowledge management tools within CDER. This includes information from analytical assessments, clinical PK/PD, and comparative efficacy studies for submitted biosimilars. Additionally, we documented other data requirements (e.g., data standards), evaluated any limitations in current databases, explored considerations for a potential future centralized database solution, and described and analyzed our team's own quality and clinical data collection processes outlined in the section above.

**Methods**: We first developed a three-phased Assessment Plan and Evaluation Framework to identify the types of data sources, objectives, and overall outputs of the feasibility assessment. We also developed a discussion guide to assist capturing information regarding types of data already being collected, perceptions around data gaps and opportunities, databases currently used and in development, and preferences for a potential new database or other recommendation. To support the collection of these findings, we created a data collection tool to facilitate data and information gathering and analysis.

Our team then conducted a formal review of relevant documents and IT systems and databases/tools and led stakeholder interviews with FDA staff across OCP, OPQ, and OTBB to (1) assess specific data collection and analysis requirements, (2) evaluate challenges in current databases, systems, and processes, and (3) identify opportunities for a future database solution or other recommendation(s). Our team also used Visio to develop a process flow to document complexities (i.e., data inputs and outputs, purposes, descriptions, decision trees, actions and approaches, caveats and recommendations, time and effort analysis) as well as an SOP as supporting documentation describing each step of the quality data and clinical data collection processes completed in Aim 1 above. Following an analysis of the themes identified from the stakeholder interviews, database and tool reviews, and process flow documentation, we began synthesizing our findings in an internal draft report.

**Progress and Current Status**: As of June 2024, we have finished our FDA stakeholder interviews as well as reviews of CDER IT systems and Office/team-specific databases and tools containing biosimilar information used across OCP, OTBB, and OPQ. This includes an inventory of the various systems and databases/tools used, their purpose, and (if applicable) a summary of its contents, current maintenance status, and data entry frequency and responsibility. Our team has also synthesized FDA stakeholders' experiences and sentiments expressed during interviews, such as strengths and limitations of existing databases as well as potential considerations for a future state. One overarching challenge, expressed in various ways by a majority of interviewees, identified that many IT systems and Office-specific databases/tools with biosimilar data already exist, each containing discrete types of information needed to support their work. In addition, variations in data formatting, standardization of nomenclature and endpoints, and staff needs across the different disciplines – for example, clinical pharmacology

study results are structured and assessed differently than comparative analytical data – would present complex challenges when trying to develop a consolidated future state solution. This suggests that developing and building an additional IT system or database for the particular purpose described in Aim 1 may be more infeasible and of more limited practical value than originally envisioned.

We are currently documenting our findings in an internal report which we intend to deliver to FDA in September 2024.

# RESEARCH OUTCOMES

A key outcome of this project is to develop a drafted manuscript for publication in a peer-reviewed journal, visualizing and identifying trends in analytical similarity assessment and clinical study results, which will promote internal review consistency and inform discussions about future biosimilar development programs. The analysis, included in the manuscript, will systematically compare quality attribute data across biosimilars within the two product classes, alongside rationale for resolving observed differences in quality attributes between each biosimilar and its RP. The manuscript will further summarize clinical PK and safety/efficacy study results for each biosimilar as well as describe (1) cases where individual endpoints fell outside pre-defined margins and (2) correlations between comparative analytical and clinical data.

This outcome achieves the project objective of conducting a landscape analysis to determine how FDA can answer questions about whether differences in analytical assessments in biosimilar development programs correlate with clinical data. Analysis of quality and clinical data, including visualization of quality attribute data trends across biosimilars, not only answers questions about whether differences in analytical assessments in biosimilar development programs correlate with clinical data, but also informs ongoing discussions regarding the role and value of the various types of clinical studies in regulatory decision making.

Comparing quality attributes collected, comparison approaches, and the comparative analytical assessment result outcomes across biosimilars (see Figure 1 as a representative depiction) more clearly visualizes observed differences in analytical assessments, facilitating the assessment of correlations between quality and clinical data. For example, preliminary results for adalimumab indicate high similarity across all quality attributes, and explainable differences in the post-translational modifications, glycosylation, and charge variant categories. In addition, all adalimumab biosimilars demonstrated no clinically meaningful differences, although in three cases a second clinical pharmacology study with a larger sample size was required, likely due to the higher observed variability for certain PK endpoints than originally anticipated. Nevertheless, all comparative clinical studies showed similar safety and efficacy results and raised no new issues requiring additional investigation. These results, alongside resolutions for observed differences, advance FDA's understanding of how certain quality attributes affect clinical outcomes and inform regulatory policy discussions.

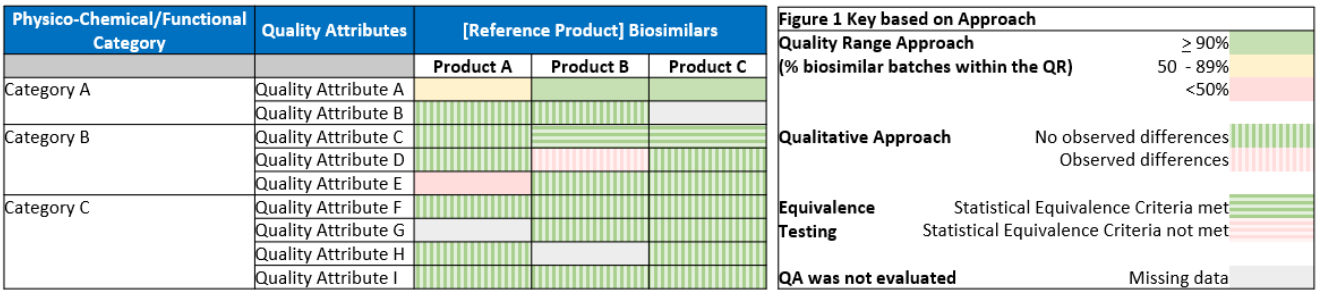


**Figure 1:** Representative Visualization of Comparative Analytical Results

The additional outcome, outlining our assessment findings regarding the feasibility and value of building a future state database, lays the groundwork for determining how FDA can best answer questions regarding whether observed differences in quality attributes correlate with clinical outcomes. This potential future state could provide FDA with a tool to automate comparison of quality and clinical data across different biosimilars of the same product class going forward. However, given the time involved and scope of data sources used to collect quality and clinical data for the products included in the manuscript alone, it was determined that designing, building, and populating a future-state database is a lower priority than collecting quality and clinical data for additional product

classes covering different indications and disease areas. These outcomes further facilitate achieving the longer-term objectives of facilitating evidence-based discussions about the utility of clinical studies during biosimilar development and improving internal review alignment, consistency, and efficiency, while informing regulatory guidance and future policy development.

# REGULATORY IMPACT

As part of this project, the analytical and clinical data submitted for approval of adalimumab and trastuzumab biosimilars were consolidated, standardized, and are currently being analyzed to address if analytical data correlate with clinical data. This process demonstrates the degree of biosimilarity and how the differences in analytical data were resolved (e.g., role of additional analytical testing and clinical data), ensuring they did not preclude the determination of highly similar. This information will enhance FDA's understanding across review disciplines about comparative analytical assessment process, facilitating internal review alignment and consistency. In addition, when the study results are made available via publication in a peer-reviewed journal, it will promote transparency and stakeholder engagement, ultimately increasing efficiency of biosimilar development.

Comparative efficacy studies (CESs) are frequently conducted for regulatory review prior to product licensure and are one of the key contributors to the cost and time associated with biosimilar development. Therefore, there is a growing interest in reexamining the use of CESs to reduce the cost and enhance the efficiency of biosimilar development. This project analyzes the value of PK studies as well as CESs in resolving differences identified in comparative analytical assessments. The conclusions will facilitate evidence-based discussions, not only internally but also globally, about the need for CESs in demonstrating biosimilarity. The information will also contribute significantly to the growing body of scientific evidence that supports a tailored approach for clinical data requirements rather than default requirements and may eventually facilitate a regulatory review of the standards for clinical data requirements.

One of the key challenges identified during this project, further detailed under "Challenges" below, is the variation in nomenclature (e.g., physicochemical and functional categories, QA names, test method descriptors) and data format that sponsors submit in the quality data package. To address this challenge, aligned with a key BsUFA III Regulatory Science Pilot Program priority, our team undertook a process to harmonize the nomenclature for each class and developed a data dictionary to visualize quality attribute names from each biosimilar. Establishing a standard data reporting structure may expedite regulatory review and decision-making by creating consistency in 351(k) BLA submissions. Harmonization of quality attribute descriptors as part of this project could inform ongoing efforts in this direction. Moreover, the information collected for adalimumab and trastuzumab biosimilars and lesson learned could enable similar analyses for other IgG1 mAb reference products covering a wide range of indications.

# COMMUNICATION AND DISSEMINATION

Our team developed a timeline (see Figure 2) to communicate preliminary quality and clinical results to internal FDA stakeholders, develop drafted sections of a manuscript, and presentations to communicate and disseminate results to external audiences. In May 2024 we began presenting findings from our preliminary analysis of quality and clinical data to FDA stakeholders and elicited feedback on drafted figures and tables planned for inclusion in the manuscript. Through these presentations, we discussed patterns identified during data analysis, such as physicochemical categories where differences are more commonly observed and similarities in resolution explanations across biosimilars in the same product class. Following implementation of the feedback and continued discussions with FDA stakeholders, our team began building out the Methods and Results sections of the manuscript and presented these sections internally in June 2024. This step prepared our team to begin tailoring quality evaluation results to external audiences.

Through an iterative and collaborative process, the manuscript will go through several rounds of internal review and all necessary clearance steps. Following completion of this review and clearance process, FDA will submit the manuscript for publication to the selected target journal.

Concurrent with the development, submission, and publication of the manuscript, our team will develop slide presentations of the final adalimumab and trastuzumab quality and clinical data results for external stakeholder audiences, intended for example at conferences or workshops. Presentation materials will include both summary overview and in-depth descriptions of the study results across quality and clinical datasets (e.g., quality attributes with frequent differences identified, correlations with clinical outcomes) as well as discussions regarding the potential short- and long-term impacts of the published results. This presentation will be curated to target diverse populations, such as biosimilar sponsors, health care providers, and patients/advocates, explaining results in a digestible format.

The database feasibility report will be internally distributed to FDA stakeholders and does not feature an external communications plan.

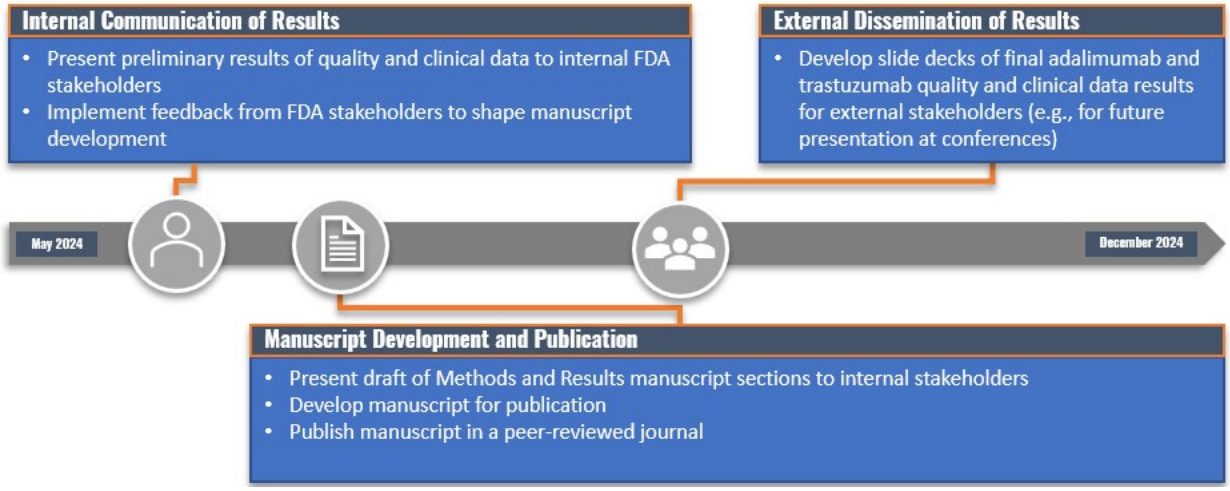


**Figure 2**: Timeline for Communication and Dissemination of Quality Evaluation Results

# CHALLENGES

Impactful preliminary results of the quality evaluation, which emphasized the potential for study findings to inform regulatory policy decisions, led to a shift in FDA's interest in collecting data for additional product classes.

Following internal meetings with FDA stakeholders within CDER and presentation of preliminary quality evaluation results, stakeholders identified a need to collect quality and clinical data for additional biosimilar product classes beyond the two classes (i.e., adalimumab and trastuzumab) included in the initial analysis. This collective interest in collecting additional data led to a shift in the direction of Aim 2. The many already existing IT systems and Office-specific biosimilar databases and tools presents a complex challenge to integrate each of the existing systems to implement a consolidated future state solution. This challenge was quickly realized, and after evaluating resources and the duration of the project, we proposed deprioritizing the design and build a future IT database and instead shift efforts toward collecting quality and clinical data for additional product classes of regulatory focus.

For Aim 1, the main challenge stemmed from the different nomenclature for the physicochemical/functional categories, QA names, and test methods used across different biosimilars in the same product class. Varying data formats and lack of standardization emerged as the root of this challenge. To address this challenge, our team established naming conventions for the purpose of the study to harmonize the QA taxonomy across biosimilars and facilitate product comparisons within each product class. The time required for this targeted approach to this anticipated challenge was accounted for in the project timeline.

# NEXT STEPS

The research team prepared results and summarized preliminary findings to present to CDER leadership within FDA. The next immediate step is to prepare results for presentation to additional CDER stakeholders across multiple offices. Additional next steps for the quality evaluation include developing a manuscript outline and preparing individual sections of the manuscript for FDA to submit for publication. Identifying target journal options, soliciting input from internal FDA reviewers, and proceeding with formatting and clearance processes for manuscript publication are expected steps to follow, as well. Our team will lastly prepare a PowerPoint presentation of the study methods and final adalimumab and trastuzumab quality and clinical data results for FDA to present to external stakeholders.

Alongside efforts to prepare the manuscript for submission and publication, our team is also currently working to complete quality and clinical data collection for biosimilars of additional product classes. Following initial data collection, our team will employ QC measures to verify data entry accuracy. Following this step, we will harmonize the physicochemical/functional category names, QA names, and test method names using the same method developed to harmonize data for the initial two product classes. Our team will then develop a data dictionary using the harmonized data to facilitate future analysis.

# REFERENCES

None

# APPENDIX: ADDITIONAL MATERIAL

| ABBREVIATION | DEFINITION |
|---|---|
| BLA | Biologics License Application |
| BsUFA | Biosimilar User Fee Amendments |
| CDER | Center for Drug Evaluation & Research |
| CES | Comparative Efficacy Studies |
| DARS | Division of Applied Regulatory Science |
| IgG1 | Immunoglobulin G1 |
| FDA | US Food and Drug Administration |
| IT | Information Technology |
| mAb | Monoclonal Antibody |
| OCP | Office of Clinical Pharmacology |
| OND | Office of New Drugs |
| OPQ | Office of Product Quality |
| OTBB | Office of Therapeutic Biologics and Biosimilars |
| OTS | Office of Translational Sciences |
| PAG | Project Advisory Group |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| QA | Quality Attribute |
| QC | Quality Control |
| RP | Reference Product |
| SOP | Standard Operating Procedure |