U.S. FOOD & DRUG ADMINISTRATION

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

ANNUAL REPORT

CONTENTS

Check if this report is Progress or Final Report:

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

1. REPORT OVERVIEW[1]

Complete table 1 below based on the information provided in the subsequent sections of this report. This table will be used verbatim (i.e., copy/ paste) in any summary materials to evaluate the return on investment of the project.

Table 1: High-level overview of the project objective, aim(s) progress, outcomes, and timelines for communication and regulatory impact (1-2 sentence max per table cell).

Project Title:	Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data
Investigator:	Catherine M. Lockhart, PharmD, PhD
Organization:	Academy of Managed Care Pharmacy
Grant No. (if applicable)	1U01FD007757-01
Project Objective:	Demonstrate the feasibility of using real-world data (RWD) to inform biosimilar and interchangeable biosimilar regulatory assessments.

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. Determine the quality of RWD and relevance of RWE for regulatory decisions	Complete; Report(s), abstract(s) and manuscript(s) in preparation	Guidance on selecting a data source based on research needs and available data features; Comprehensive analysis of where RWD has, or could be, used for regulatory decisions	Two abstracts have been submitted in Q2 of 2024 and an additional one is planned for submission in Q4 of 2024 or Q1 of 2025; Two manuscripts will be prepared for peer-reviewed submission in Q2 or Q3 of 2025;
2. Use RWD to emulate an FDA evaluation of interchangeability	Protocol finalized; Data extraction and analysis underway	We will conduct a modified target trial emulation that will demonstrate how RWD could be used for biosimilar regulatory purposes, including recommendations describing challenges and opportunities.	Two abstracts will be submitted in Q4 of 2024 or Q1 of 2025; Four manuscripts are planned or in preparation for peer-reviewed submission in Q3 of 2024, and an additional two planned for submission in Q1 of 2025

[1] This section will be used by program for broader research portfolio and regulatory impact analysis by the BsUFA III steering committee.

2. PROGRESS SUMMARY

Describe the overall project objective, aims, for this study. These must be the same objective and specific aims from funded spend plan/application. Include milestones and activities with timelines for each aim (What was accomplished under each aim?) (No word max). *Note, text in this section should directly support content in the 'Progress' column in table 1.*

Project Objective:

To assess feasibility and fitness for use of real-world data (RWD) to inform FDA regulatory decisions, using switching studies for biosimilar interchangeability as a test case, and to provide recommendations for overcoming challenges and strategies for applying non-US RWD in a US regulatory context.

Aim 1: Determine the quality of RWD and the relevance of RWE for regulatory decision-making.

Aim 1, Task 1: Literature review. This task is undergoing final analysis, and the report and manuscript are behind our original timeline as we met with some personnel challenges that required the Principal Investigator (PI) and other colleagues to repeat substantial portions of the screening and data extraction. However, we have enlisted help from our co-investigators to get this work back on track. We anticipate finalizing the report in the second quarter of 2024. We will also submit a second abstract for presentation at a scientific or professional meeting in the fourth quarter of 2024.

Aim 1, Task 2: Expert panel. This task is complete and a final report and manuscript for peer-reviewed publication is in preparation. We anticipate submitting an abstract describing our findings in the second quarter of 2024 in anticipation of scientific meetings to be held in the Fall of 2024.

Aim 1, Task 3: Quality of RWD This task is complete and a final report and manuscript for peer-reviewed publication is in preparation. We will submit an abstract describing our findings in the second quarter of 2024 to present at a scientific meeting in the Fall of 2024.

Aim 1, Task 4: Relevance of RWE This task is complete and was conducted in tandem with Aim 1, Task 3.

Aim 2: Use RWD/RWE to emulate an FDA evaluation of interchangeability of a biosimilar drug.

Aim 2, Task 1: Test case selection. This task is complete and informed the study design and protocol development. We chose a granulocyte-colony stimulating factor (G-CSF) product, specifically pegfilgrastim reference and biosimilars based on utilization patterns that suggest adequate sample sizes for meaningful analysis, our extensive experience in identifying relevant cohorts, and the ability to measure the primary outcome of interest – febrile neutropenia – using claims data. The clinical trial "Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy" will serve as the target trial this study will emulate.[32] This study is the only available study evaluating the switching of a G-CSF biosimilar (filgrastim-sndz) with reference filgrastim. To date, no switching studies of pegfilgrastim biosimilars compared to reference pegfilgrastim have been published. We will use the filgrastim switching study for our emulation, adjusting for differences associated with pegfilgrastim.

Aim 2, Task 2: Emulation. The study protocol based on the publication identified in Aim 2, Task 1 has been finalized, and programming is underway at each site to build our study dataset. We anticipate programming and data extraction to be complete in the early part of the third quarter of 2024.

Aim 2, 3: Data analysis. A detailed cohort specifications document has been developed along with the study protocol and will be applied once cohorts and datasets are established. We anticipate the data analysis will be complete by the end of grant Year 2.

Table 2. Timeline for Aim 2 milestones

Milestone	2024												2025							
	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Aim 2																				
Task 1 – Test case selection	X																			
Task 2 – Protocol	X	X	X	X	X															
Task 2 - Emulation						X	X													
Task 3 – Data Analysis							X	X	X											

3. RESEARCH OUTCOMES

Describe project specific outcomes since the start of the budget cycle or last report inform or achieve the project objective (500-word max). *Note, text in this section should directly support content in the 'Outcomes' column in table 1.*

In addition, if there is a concern about public dissemination of the research outcomes prior to completion of the project, notify the BsUFA III regulatory science pilot program *immediately* to discuss either 1) requesting that this section is redacted from the publicly posted version or 2) only including abstract-level detail.

Since our last annual report, we have completed all activities related to Aim 1, although reports and publications are still in preparation. Specifically, we have finalized a data assessment to provide guidance and recommendations for researchers to select the most appropriate type of data based upon a variety of research questions, with a report and manuscript planned for public dissemination. We are also preparing reports summarizing the results of two expert panel discussions to describe opportunities and challenges in using RWD for regulatory purposes, as identified by the panel. We have finalized a study protocol designed to conduct a

switching study to identify where RWD can produce results suitable for regulatory decisions for biosimilars or interchangeable biosimilars.

4. REGULATORY IMPACT

Describe project specific regulatory impact. This section should clearly identify and describe how the project will inform or impact biosimilar development or regulation (500-word max).

RWD/RWE has the potential to improve the efficiency of regulatory decision-making for biosimilars. This study will determine whether the currently available RWD from administrative claims and current observational research methods are ready to use in biosimilar product development or whether more work must be done to improve the quality and rigor of the data or study approach. The results of this study will be impactful to the FDA as they consider additional guidance documents for the use of RWD/RWE for biosimilar development.

Our work will aid biosimilar manufacturers, regulatory decision-makers, and the research community to leverage RWD/RWE for biosimilar development and licensure, specifically in the test of interchangeability. This study will advance the development of interchangeable products by providing new information on the quality of the data in multiple claims databases and developing new analytical tools for the evaluation of interchangeability. These analytical tools will provide generalizable strategies to leverage relevant RWE in regulatory science. New analytical tools and a proposed framework for incorporating RWD/RWE into product development will include data harmonization, patient matching, and data provenance for the elements we will identify and use in this study to complement existing data models and analytical tools. These will be valuable assets that could be used by drug sponsors for future regulatory approvals and designations as interchangeable biosimilars.

5. COMMUNICATION AND DISSEMINATION

Describe project specific communication and dissemination for this study. Include citations for any publications, abstracts, talks/speaking events etc. *Note, text in this section should directly support content in the 'Communication Timeline' column in table 1.*

If the contents of Section 3 are either be redacted or written at an abstract-level detail due to concerns about public dissemination of the results and outcomes prior to completion of the project (see Section 3), this section ***must*** include the plan and timeline for communication of all the results and outcomes of the project (500-word max).

There are five abstracts and manuscripts submitted, in preparation, or planned for submission in Year 2 of this project.

One abstract describing interim results of our literature review was presented as a poster at the ISPOR Europe meeting in Copenhagen, Denmark, held on November 12-15, 2023. We have a robust plan for public dissemination and communication for the remaining completed and continuing activities described above.

(**Table 3**). Specifically, we have prepared an abstract reflecting a unique, informative approach to assessment of the richness and fitness for purpose of three databases included in this study to help researchers choose which features and capabilities are necessary to successfully answer a variety of research questions. This abstract will be submitted in June 2024 for presentation at ISPOR Europe to be held on November 17-20, 2024, in Barcelona, Spain. We also prepared and submitted an abstract reflecting the results of our expert panel discussions for presentation at ISPOR Europe 2024. We have three additional abstracts planned, describing the final results of our literature review, detailing our study design, and the results of the trial emulation. We anticipate these three abstracts will be submitted in the fourth quarter of 2024 or first quarter of 2025, aligning with spring scientific and professional meetings.

We have two manuscripts in preparation or planned (**Table 3**). The complete results of our literature review will be documented in a comprehensive report and prepared as a manuscript. We anticipate having a completed manuscript draft in the third quarter of 2024. A manuscript describing our data assessment is in preparation and we anticipate it will also be complete by the third quarter of 2024. Similarly, a report and manuscript describing the expert panel recommendations is in preparation, anticipated to be complete in the third quarter of 2024. We have three additional manuscripts planned to describe our study design and protocol, the results of our study and data analysis, and a final report and manuscript summarizing our overall findings and recommendations for how RWD can be used in the regulatory decision process. The submission schedule for peer-reviewed journals and public dissemination will occur after each associated abstract is presented to adhere to embargo requirements for scientific and professional meetings.

Table 3. Timeline for communication: abstracts and manuscripts for peer-reviewed journals

Milestone	**2024**												**2025**							
	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Abstract submission																				
Data Assessment						X														
Expert Panel						X														
Literature Review											X									
Study Protocol											X	X	X	X						
Study Results													X	X						
Manuscript preparation																				
Literature Review	X	X	X	X	X	X	X	X												
Expert Panel					X	X	X													
Data Assessment						X	X	X	X											
Study Design						X	X	X	X											
Study Results											X	X	X							
Recommendations										X	X	X	X	X						

6. CHALLENGES

Describe project specific challenges for this study. This section should include:

- Changes in approach and reasons for change.
- Actual or anticipated problems or delays and actions or plans to resolve them.
- Changes that have a significant impact on expenditures.
- Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

(500-word max).

A few challenges have arisen over the course of this study, related in part to personnel and appropriate staffing. First, due to recruitment challenges, the staff research scientist designated to help with this project was hired much later than anticipated. That resulted in a delay in internal support that led to a backlog of work that had to

be resolved by the study PI. Furthermore, the research scientist who joined this project was not a good fit for the required work, which resulted in further delays and in one case required members of the PI and co-investigator teams to step in to re-do some work. In some ways this challenge was unforeseeable; however, as a result we have adjusted some internal processes to ensure adequate staffing is established at the project kickoff. Our partners and collaborators have been able to step in to take on extra tasks to get us back on track.

Second, we faced the unexpected departure of one of our co-investigators from her role as site PI at one of our partner sites. This individual was leading our study design and protocol development efforts. Through the depth of expertise among our collaborators we were able to identify a highly capable individual to take over those tasks. While we have now completed the protocol it did result in a timeline delay.

We had also structured the aims and related tasks that resulted in a large amount of foundational work occurring early in the grant, with the more applied demonstration reserved for the end of the timeline. Some of the early challenges we faced that resulted in some timeline sliding has then inadvertently affected the timeline of the trial emulation and data analysis that is the primary interest of this study. In the future we would propose organizing activities that allow for greater overlap, and to arrange activities to ensure impactful results are produced throughout the timeline.

Overall, the project is still on track for successful completion; however, some of the reporting and dissemination activities have been delayed to the end of the study period.

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7. NEXT STEPS

Describe plans or next steps, especially if there are changes from the original proposal (500-word max).

Next steps for this study are to implement the protocol and conduct the study in three independent data sites. We will conduct a common analysis plan and compare results to expectations from published literature and compare results across sites. Finally, we will draw from our experience to produce a set of recommendations outlining how RWD may be used for biosimilar and interchangeable biosimilar regulatory decisions.

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8. REFERENCES

References used in progress report.

1. Blackwell K, Gascon P, Krendyukov A, Gattu S, Li Y, Harbeck N. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol 2018;29(1):244-249. DOI: 10.1093/annonc/mdx638.

9. APPENDIX A: ADDITIONAL MATERIAL

Include any additional material to support the report content (optional).

10. APPENDIX B: ABBREVIATIONS

This section includes all acronyms used in this document along with a corresponding definition.

ABBREVIATION	DEFINITION
Co-I	Co-investigator
FDA	United States Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
PI	Principal investigator
RWD	Real-world data
RWE	Real-world evidence
US	United States