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

Project Title:	Bridging the Gap: Using Foreign Real-World Data to Inform Interchangeable Biosimilar Approvals
Investigator:	Catherine M. Lockhart, PharmD, PhD
Organization:	Academy of Managed Care Pharmacy
Grant No. (if applicable)	1-U01FD008041-01
Project Objective:	Demonstrate the feasibility and fitness of using real-world data (RWD) from European countries to inform US regulatory decisions

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. Evaluate the feasibility and validity of a biosimilar switching study using RWD from the US and non-US sources	Initial assessment of data sources is complete; Protocols for target trial emulation designs for insulin glargine and adalimumab are in preparation.	Descriptive analysis of patient cohorts from different countries; Assessment of the feasibility and fitness for purpose using non-US data to apply to US regulatory needs;	Three abstracts will be submitted in Q4 of 2024 or Q1 of 2025; Two manuscripts will be prepared for peer-reviewed submission in Q2 or Q3 of 2025;
2. Develop recommendations for FDA describing how to address challenges of using non-US RWD for regulatory decisions	Not yet begun	Comprehensive recommendations describing opportunities and solutions for leveraging non-US data	One abstract will be submitted in Q2 of 2025; One manuscript will be prepared for peer-reviewed submission in Q3 of 2025

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.*

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

Project Objective:

To assess feasibility and fitness for use of real-world data (RWD) from outside the US 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: Evaluate the feasibility and validity of a biosimilar interchangeability (e.g., switching) study using real-world data from the United States and sources from outside the United States.

Aim 1, Task 1: Assess the quality of RWD from US and non-US data sources.

This task is complete, and a brief report is in preparation. We assessed a large claims-only database in the US, regional claims data from Italy, and the broad health and demographic data available from Denmark. See timeline in **Table 2**.

Aim 1, Task 2: Develop a common data model (CDM) and harmonize data.

This task is ongoing and is informing protocol development (Aim 1, Task 3). Comparison between data sources is part of the protocol in preparation, and specifications for a CDM will be described in the statistical analysis plan (SAP). We selected target trials examining reference to biosimilar switching in patients treated with insulin glargine, and patients treated with adalimumab products. From these target trials we have identified all variables needed for successful emulation for each product. Many biosimilar interchangeability or other switching studies use pharmacokinetic (PK) or pharmacodynamic (PD) measures as surrogates for treatment effect. These are rarely conducted in usual clinical practice, so even in databases where rich laboratory data are available, PK/PD information is unlikely to be present. This is one limitation of using secondary data sources for research, as those data were collected for the purpose of health care delivery (e.g., recording clinical care, submitting for reimbursement), so other solutions that measure treatment effect in different ways are necessary. The opportunity for RWD lies in the fact that PK/PD measures are also surrogates and used to predict treatment effect, so there are often other ways to capture the same information in different ways. For example, in patients with diabetes who are treated with insulin, the goal is glycemic control and to avoid hypo- or hyper-glycemic events. If we are able to identify whether one of these events occurred, that provides appropriate information for decision-makers to understand whether one product offers the same safety and effectiveness as another. This is the foundation of using RWD for trial emulation or to answer questions that are important to regulatory decision-makers. See timeline in **Table 2**.

Aim 1, Task 3: Design an emulation of a clinical study.

Detailed study designs and protocols are in development to assess the feasibility of using RWD from outside the US to assess biosimilar interchangeability (e.g., switching) using the test cases of insulin glargine and adalimumab. We chose insulin glargine as one test case because we have sufficient utilization of biosimilar and follow-on biologic products to allow for analysis, and the outcome measures important for patients with diabetes, such as hypo- and hyper-glycemia, are readily measurable in claims data. Some variables like glycosylated hemoglobin (HbA1c) and other laboratory values are available at some data sites so this also allows assessment of how differing data availability impacts questions of treatment effect that are relevant for regulatory purposes. We chose adalimumab as a second test case because even though there are many biosimilars available, utilization in the US is not yet available in most secondary data sources due to a typical data lag; however, adalimumab biosimilars have been used widely in Europe. We wanted to demonstrate application of our approach to a scenario where data are not widely available for biosimilar use in the US, but non-US data could be particularly informative. We also want to examine the similarities and differences in data completeness and fitness from each site as well as

alternative study designs that will allow utilization of treatment effects that are measurable within the available data sources.

In Denmark, the transition to the use of biosimilars has been unusually rapid and strong. Virtually all secondary care is publicly funded, and procurement of expensive drugs is highly centralized. Six months after the launch of biosimilar infliximab, its market share was over 95% (https://pubmed.ncbi.nlm.nih.gov/31677117/). This poses a challenge to conducting a trial emulation. There is only a short time interval during which there will be clinical equipoise for the choice between the original and biosimilar product, and this narrow time window accounts for a very small proportion of the total use of biologics. If use of the original product is modest in the later part of the study period, it can be assumed that the users are atypical and therefore not suitable for inclusion in a trial emulation. We will address this by employing a modified trial emulation design, where the timeframe is shifted between initiators of original and biosimilar products. Considering that the choice of biosimilar products is administrative rather than clinically determined, we would expect differences in baseline characteristics to be modest and largely correctable through standard use of propensity scores. Since the biosimilar transition applied equally to new and prevalent users of biologics, the Danish scenario poses a unique opportunity to address the clinical consequences of biosimilar switching in patients who are already treated with biologics.

We anticipate finalized protocols will be complete by the third quarter of 2024. See timeline in **Table 2**.

Aim 1, Task 4: Conduct the emulation and analyses independently at each site.

This activity is not yet underway and will begin once the protocols from Aim 1, Task 3 are finalized. We anticipate beginning the process of building data sets and identifying patient cohorts in the third quarter of 2024, followed by analysis in the fourth quarter of 2024 and into the first quarter of 2025. See timeline in **Table 2**.

Aim 1, Task 5: Compare emulation results to existing clinical research.

This activity has not yet begun; however, studies for trial emulation have been selected for insulin glargine and adalimumab and are informing the study designs (Aim 1, Task 3). We will complete this task once the analyses conducted in Aim 1, Task 4 are complete. We anticipate reaching this milestone in the first quarter of 2025. See timeline in **Table 2**.

Aim 1, Task 6: Detailed comparison of results across sites.

This activity has not yet begun but will be conducted as part of the overall project analysis after the trial emulations are complete. We anticipate reaching this milestone in the first quarter of 2025. See timeline in **Table 2**.

Table 2. Timeline for Aim 1 milestones

Milestone	**2023**			**2024**												**2025**							
	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Aim 1	X	X	X																				
Task 1 – Assess RWD quality				X	X	X																	
Task 2 – Develop CDM										X	X	X											
Task 3 – Protocol							X	X	X	X	X	X											
Task 4 – Conduct analyses												X	X	X	X	X							
Task 5 – Compare benchmarks																	X	X	X				
Task 6 – Compare across sites																	X	X	X				

Aim 2: Develop recommendations for the FDA on the use of real-world data from outside the United States in its regulatory decision-making processes for biosimilars.

Aim 2, Task 1: Identify potential stakeholders and obtain feedback on the recommendations.

The FDA develops guidance and recommendations through the federal rule-making process: they analyze regulatory issues, draft proposed rules, seek and receive feedback, and finalize the rules.[4] The preamble to the rule on "using foreign clinical studies not conducted under an investigational new drug application" provides an example of this process.[5] Our study's question about the use of OUS *RWD* is similar to the question of the use of OUS *clinical* data in terms of the recommendation development process. We will follow the FDA's model of proposal, feedback, and finalization. We will identify potential stakeholders, such as healthcare professionals, patient advocacy groups, and pharmaceutical companies, and obtain feedback on the recommendations developed in Aim 1. The feedback will help refine the recommendations and ensure that they are practical and feasible to implement. This task has not yet begun. We anticipate reaching this milestone in the first or second quarter of 2025. See timeline in **Table 3**.

Aim 2, Task 2: Evaluate the feasibility and potential impact of the recommendations.

This task will involve evaluating the feasibility and potential impact of the recommendations in the context of the FDA's regulatory decision-making processes. The evaluation could include assessing the resources required to implement the recommendations and their potential impact on the FDA's ability to make timely and evidence-based regulatory decisions. We will use the information from the framework developed in a recent systematic review of European use of RWD in regulatory decision making to describe the current state of the field.[5] This task has not yet begun. We anticipate reaching this milestone in the second quarter of 2025. See timeline in **Table 3**.

Aim 2, Task 3: Develop implementation guidelines for the recommendations.

The guidelines could include detailed procedures for collecting, standardizing, and validating OUS RWD, as well as guidelines for using appropriate analytical techniques to ensure the data's accuracy, reliability, and applicability to regulatory decision-making. The guidelines could also address any regulatory hurdles that the FDA may need to overcome when using OUS RWD. This work will ensure that the recommendations are applied consistently and effectively across the FDA's regulatory decision-making processes. This task has not yet begun. We anticipate reaching this milestone in the third quarter of 2025. See timeline in **Table 3**.

Table 3. Timeline for Aim 2 milestones

Milestone	**2023**			**2024**												**2025**							
	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Aim 2																							
Task 1 – Stakeholder feedback																		X	X	X			
Task 2 – Draft recommendations																			X	X	X		
Task 3 – Implementation guide																					X	X	X

3. RESEARCH OUTCOMES

We began this study with a descriptive assessment comparing available data across the three participating sites. As expected, the Danish databases are extremely rich with available data across 34 registries including the Central Person Register containing demographic information and a variety of healthcare registries including medical encounters, laboratory results, and medication use. Data fields are requested based upon study needs. In Italy, regional claims data are available that include fields used for billing and reimbursement similar to claims databases in the US. In Italy we also are negotiating access to data from approximately 25,000 Italian General Practitioners, which also includes a diabetology registry that will be valuable for our proposed insulin glargine study. The data source we are utilizing in the US leverages claims that are broadly, geographically representative across the country. While some demographic data such as race or ethnicity are not well captured in this database, some algorithms have been implemented to capture census level information at the level of three-digit ZIP code such as race and ethnicity cross section, median household income, and education level. This assessment is informing our study design and protocol development, including site-level modifications that we can apply to leverage available data.

As part of the data assessment activities, we identified clinical trials and relevant studies that examined reference-to-biosimilar switching with insulin glargine and adalimumab. We used the selected studies to develop our inclusion and exclusion criteria, outcome measures, and clinical or demographic variables that are relevant for each product. This allowed us to establish a common data model (CDM) that unifies our three sites, and to identify areas where we also wish to deviate from the CDM based upon differing data available in each country. This work is informing two protocols with a shared structure and overall study design are in preparation: one to assess switching from insulin glargine reference to a biosimilar or follow-on biologic, the second to assess adalimumab switching as described in Aim 1, Task 3 above. The adalimumab study will examine switching in the Italian and Danish settings and compare patient characteristics and demographic information with the US to evaluate whether non-US analyses are likely to be predictive of outcomes in a US population.

4. REGULATORY IMPACT

Our study will advance the development of biosimilars and interchangeable biosimilar products by developing alternative approaches than a switching clinical trial to meet the standard for interchangeable products using RWD from outside the US. This will increase the efficiency of reviewing and approving interchangeable biologics in the United States. The regulatory impact of our work stems from its use of multiple RWD databases, including databases from outside the United States, to increase the efficiency of biosimilar switching studies and thus increase biosimilar adoption and use in the United States. As one major deliverable of this study, we will develop practical recommendations for the FDA to guide the use of non-US RWD to increase the amount of data available to the United States for the FDA regulatory process. These recommendations will be valuable assets to be used by the FDA in the FDA's rule making and guidance development process. Our research will pave the way for guidance on more efficient and cost- effective biosimilar switching studies and provide a model for utilizing RWD in regulatory decision-making that can be applied to other therapeutic areas.

RWD from other countries can help identify any differences in the safety and efficacy of biosimilar products compared with their reference products and to other biosimilars, which can inform the development of appropriate regulatory requirements and guidelines in multiple countries. Other countries, particularly in Europe, have enjoyed robust biosimilar utilization beginning in 2005 when the first biosimilar was approved by the European Medicines Agency (EMA). In this study we will demonstrate the feasibility and fitness for purpose of non-US data to inform biosimilar and interchangeable biosimilar regulatory decisions. The use of RWD from countries outside the United States could also help to reduce the cost and time associated with conducting clinical trials in the US. For example, by using RWD to support regulatory decisions, regulators may be able to reduce the burden (by reducing the size)

of clinical trial requirements on manufacturers, which could lead to lower costs and faster development of biosimilar products. If the proposed aims are achieved, our work will advance the field by detailing foreign data, comparing study results, and comparing European populations to a US population.

5. COMMUNICATION AND DISSEMINATION

As we are still preparing our study protocol, we have no abstracts or publications to report at this time; however, we have a robust plan for public dissemination and communication that will begin with an abstract reflecting our unique, multi-national study design and approach to assessing biosimilar interchangeability (**Table 4**). We anticipate submitting this abstract in the fourth quarter of 2024 or first quarter of 2025 to align with spring scientific and professional conferences. Once the protocols are finalized, we will begin building cohorts and datasets for analysis. We are planning at least two abstracts related to our analyses: one describing the results of our switching study by site, and a second comparing output between sites. We anticipate submitting these abstracts in the first quarter of 2025 to align with summer scientific meetings. Finally, we plan to submit at least one abstract describing our recommendations, including challenges and opportunities, for using non-US data for US biosimilar and interchangeable biosimilar regulatory decisions. We anticipate submitting this abstract in mid-2025 to align with Fall meetings. All proposed abstracts will be followed by manuscript preparation for submission to peer-reviewed journals and public dissemination after each abstract is presented to adhere to embargo requirements for scientific and professional meetings.

Table 4. Timeline for communication: abstracts and manuscripts for peer-reviewed journals

Milestone	**2023**			**2024**												**2025**							
	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Abstract submission																							
Study design													X	X	X	X	X						
Results by site																X	X	X					
Comparison across sites																X	X	X					
Recommendations																					X	X	
Manuscript preparation																							
Study design														X	X	X	X						
Results																		X	X	X			
Recommendations																						X	X

6. CHALLENGES

To date we have not encountered any specific challenges to our study, and we are progressing as expected. Potential challenges may arise as we implement our study protocols and we have identified some alternative approaches should these issues arise. To minimize selection bias, we will include all eligible patients in the selected RWD sources. We will adjust for potential confounding factors using statistical methods, such as propensity score matching[1] or regression analysis, and perform sensitivity analyses to assess the robustness of the results. We will use standardized definitions and procedures for data collection and analysis and validate the data against external sources or medical records to ensure accuracy and completeness if needed. We will use predefined outcome measures and report all relevant outcomes, including both positive and negative results, to minimize reporting bias and increase the transparency and reproducibility of the study. The proposed approach will help overcome potential challenges in biosimilar switching studies using RWD by using a shared protocol to ensure consistency and comparability of the results across the different data sources, conducting subgroup analyses to identify factors that may influence the outcomes of switching, and comparing the results across

multiple countries to assess the generalizability of the findings. Furthermore, adjusting for potential confounding factors and conducting sensitivity analyses will increase the robustness and validity of the results.

Comparing observational studies like RWD-based studies to clinical trials faces well-documented challenges; however, there are effective strategies to overcome those challenges.[2] It is appropriate to use observational studies for our purpose: A Cochrane systematic review concluded, "On average, there is little evidence for significant effect estimate differences between observational studies and randomized clinical trials, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions."[3] Using the emulation of a target clinical trial helps define the study inception point for our study and maintains the high design standards of clinical trials. We will be able to use the wide net of RWD to capture a comparator group that uses treatments with similar indications and modalities as the group receiving the treatment; this strategy mitigates the risk of unmeasured confounding. Like a clinical trial, we will use propensity score matching or adjustment to account for measurable differences between the treatment and control arms. We will explore automation for the creation of adjusters to further remove potential investigator bias.

The means and consistency of collecting data from healthcare encounters, as well as the variables that are routinely collected, may differ by country and database. This could result in incomplete data or a mismatch of variables across data sets. We will address this potential problem by thoroughly assessing the data (Aim 1, Task 1) and implementing an appropriate study-specific common data model to ensure robust and replicable results across all data sites.

7. NEXT STEPS

Next steps for this study include finalizing the protocol and applying for data independently at our three data sites. Throughout the remainder of 2024 we will conduct our planned data analyses and communication plan as outlined above.

8. REFERENCES

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3. Anglemyer A, Horvath HT, Bero L. (2014) Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014;2014:MR000034.
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6. Bakker, E., Plueschke, K., Jonker, C.J., Kurz, X., Starokozhko, V. and Mol, P.G.M. (2023), Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making. Clin Pharmacol Ther, 113:135-151. https://doi.org/10.1002/cpt.2766.

9. APPENDIX A: ABBREVIATIONS

ABBREVIATION	DEFINITION
CDM	Common data model
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
HbA1c	Glycosylated hemoglobin; hemoglobin A1c
PK	Pharmacokinetic
PD	Pharmacodynamic
Q1	First quarter
Q2	Second quarter
Q3	Third quarter
Q4	Fourth quarter
RWD	Real-world data
US	United States