U.S. FOOD & DRUG ADMINISTRATION

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

ANNUAL REPORT

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Contents

Report Overview[1]

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:	**Bridging the Gap: Using Foreign Real-World Data to Inform US Regulatory Decisions for Biosimilars**
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 data assessment is complete, and a detailed assessment is underway; Protocols for target trial emulation designs for insulin glargine and adalimumab are being revised according to recommended project and scope changes.	Descriptive analyses of patient cohorts from different countries; Assessment of the feasibility and fitness for purpose using non-US data to apply to US regulatory needs;	One abstract was accepted for poster presentation at the ISPE 41st Annual Meeting (August 2025); At least two additional abstracts will be submitted, one in Q4 2025 and the second by Q3 2026; At least two manuscripts will be prepared for peer-reviewed submission, one by Q4 2025 and a second by Q2 of 2026;
2. Design and conduct observational studies (e.g., descriptive analyses, target trial emulation, transportability estimation) to assess the ability to answer and interpret meaningful questions on biosimilars using US and non-US RWD.	Data and feasibility assessment, and protocol revisions are underway	Comprehensive recommendations describing opportunities and solutions for leveraging non-US data	One abstract will be submitted by Q3 2026; At least one manuscript will be prepared for peer-reviewed submission in Q4 of 2026

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

Progress Summary

Project Objective:

To assess the feasibility and fitness for use of real-world data (RWD) from outside the US to inform FDA regulatory decisions, and to provide recommendations for overcoming challenges and strategies for applying non-US RWD in a US regulatory context. We intend to thoroughly assess data sources from two European (EU) countries (Italy and Denmark) for quality, completeness, fitness for purpose, and generalizability to a US setting, and to determine the potential of non-US data to answer relevant US regulatory questions, using biosimilar switching as a test case.

Aim 1: Evaluate the feasibility, quality, validity, and fitness of RWD from one source within the US and two sources from outside the US to answer US regulatory questions on biosimilars.

We have identified two test cases: one with biosimilar products on the market and in use in both the US and the EU, and one used primarily in the EU. Specifically, we chose the therapeutic areas of diabetes (insulin glargine) and inflammatory diseases (adalimumab) because we believe there are important lessons to learn from these test cases. For each product, we have conducted an initial assessment across data sources to determine all available variables relevant to clinical trials related to the selected therapeutic areas.

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 the 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 the applicability 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, and alternative study designs that will allow for the assessment 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 the biosimilar infliximab, its market share was over 95% (Jensen et al., 2020). 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 the 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 originator 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 the standard use of propensity scores. Since the biosimilar transition was 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.

A scoping review of the literature is underway to identify all studies that supported biosimilar approval for the two test-case drugs (insulin glargine, adalimumab). We will extract the common data elements (demographics, exposures, outcomes) for all studies. These data elements will be evaluated in each data source (i.e., US, Italy, Denmark) to assess data availability, completeness, and quality. This work will result in a detailed inventory of which data are available, the level of completeness (e.g. proportion of records that contain valid values), and available notes or commentary exploring any gaps or contingencies related to data quality. In the final report we will include an assessment of what applications are (or are not) currently feasible using RWD.

Aim 2: Design and conduct observational studies (e.g., descriptive analyses, target trial emulation, transportability estimation) to assess the ability to answer and interpret meaningful questions on biosimilars using US and non-US RWD.

This activity is underway and will be conducted in several steps outlined as follows:

Task 1: Perform descriptive analyses on cohort of users of two test cases, by applying meaningful inclusion/exclusion criteria for the selection of study cohorts. As the focus is not in truly demonstrating interchangeability, but on learning how to leverage non-US data for US decisions (or where it is not appropriate), we will emphasize, thorough descriptive analyses, how the available data lead to the strengths and weakness of interpretation or application to regulatory or clinical decision-making. This will include a detailed assessment of the similarities and differences in patient populations across countries, including patterns of reference product and biosimilars use, and the success or failure of conducting meaningful analyses to inform how RWD in general may be used. Furthermore, we will provide a description of process limitations in data access that should be considered when exploring both US and non-US data sources for research purposes. Detailed protocols are currently being updated to reflect this detail.

Task 2: Conduct a feasibility assessment according to FDA Guidance (US Food and Drug Administration, 2018, December, 2023, August, 2023, December-a, 2023, December-b, 2024, July) to establish whether an appropriate target trial emulation is possible using RWD from the US, Italy and Denmark. This will include a detailed report, and recommendations, strengths, and

limitations expected to impact the successful completion of an emulation. This work is currently in progress.

Task 3: Based on the feasibility assessment in Task 2, if possible, design a target trial emulation that could be conducted at each site using a parallel protocol approach. Subsequently, across sites a detailed evaluation of strengths and limitations of using RWD to inform regulatory or clinical decisions. This will include a summary of the challenges of designing the emulation studies (i.e., identify the gaps) in the context of non-medical switching.

Task 4: Conduct emulation studies and data analyses at each site using a parallel protocol approach, followed by detailed evaluation across sites of strengths and limitations of using RWD to inform regulatory or clinical decisions. Evaluate the feasibility of conducting transportability of outcomes across countries.

Task 5: Prepare a detailed report outlining our findings.

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, and therefore the therapeutic areas or other specific assessments must be specified prior to requesting data access. 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 have access to data from approximately 25,000 Italian General Practitioners, which 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 distributed geographically 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. These descriptive analyses will examine how treatment patterns and patient characteristics compare between countries, and to evaluate whether non-US analyses are likely to be predictive of outcomes in a US population.

Regulatory Impact

Our study will advance the development of biosimilars by demonstrating whether RWD, including leveraging non-US data, could lead to alternative approaches other than clinical trial to meet FDA evidentiary needs and to inform clinical decisions that could advance biosimilar utilization in the US. This will increase the efficiency of reviewing and approving biosimilars and interchangeable biosimilars in the United States. The regulatory impact of our work stems from its use of multiple

RWD databases, to increase the efficiency of conducting biosimilar studies and thus increase biosimilar adoption and use in the US. As one major deliverable of this study, we will develop practical recommendations for the FDA to guide the feasibility of using non-US RWD to increase the amount of data available to the US for 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 US and non-US RWD in regulatory decision-making that can be applied to other therapeutic areas.

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), leading to mature RWD that is available in 2025 describing their biosimilar experience. The emphasis of this study is in identifying how, and in what circumstances, non-US data could be used to answer US regulatory questions, or in informing clinicians and patients on real-world utilization and relevant outcomes. 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.

Communication and Dissemination

Table 2: Summary of communications and dissemination of information, results, outcomes, etc. related to this study.

Title	Type of Communication (e.g., poster, manuscript, presentation)	Source	Link (if available)
Can observational studies replace experimental transition (or switching) studies for evaluating the interchangeability of biological drug reference and biosimilars? Methodological challenges and considerations	Poster	International Society for Pharmacoepidemiology (ISPE) 41st Annual Meeting. August 22-26, 2025. Washington, D.C.	N/A

The scope and direction of this project has changed, and as a result we are presenting our first related abstract as a poster at the International Society for Pharmacoepidemiology (ISPE) 41st Annual Meeting held on August 22-26, 2025, in Washington, D.C. We have one manuscript in preparation to describe our unique, multi-national study design and approach to using

international RWD to assess biosimilars and anticipate submitting it for peer-reviewed publication in late 2025. We have a robust plan for public dissemination and communication to describe our experience and findings. Specifically, we anticipate submitting abstracts to describe our data feasibility assessment, descriptive analyses comparing patient cohorts from different countries, and, if feasible, the design and conduct of target trial emulations to demonstrate how non-US RWD could be leveraged for US evaluation. Manuscripts intended for peer-reviewed publication will also be prepared for each of these topic areas. The timing of these submissions will align with deadlines for relevant scientific and professional meetings, as shown in Table 3.

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

Year	**2025**						**2026**							
Month	**J**	**A**	**S**	**O**	**N**	**D**	**J**	**F**	**M**	**A**	**M**	**J**	**J**	**A**
Abstract submissions														
Study design	X	X												
Feasibility analyses						X	X	X						
Descriptive analyses						X	X	X						
Emulation design (if appropriate)								X	X					
Manuscript preparation														
Study design			X	X	X									
Feasibility analyses							X	X	X	X				
Descriptive analyses									X	X	X	X		
Emulation (if appropriate)														X

Scientific and Technical Challenges

Originally, the purpose of this study was "…to assess and improve [multiple-database studies] and to determine the potential of [non-US] RWD to improve the power and generalizability of US regulatory studies to determine interchangeability." However, the reduced emphasis on requiring switching clinical trials to support an interchangeability designation has inspired a modified approach. The goal remains to evaluate the availability, quality, completeness, and generalizability of non-US data for fitness and appropriateness in a US regulatory context. Our emphasis remains in identifying how, and in what circumstances, non-US data could be used to answer US regulatory questions, or in informing clinicians and patients on real-world utilization and relevant outcomes and remains not to demonstrate interchangeability directly. We therefore modifyied the study objective from "…develop tools and guidance for US regulatory research to access [non-US] RWD for **demonstrating biosimilar safety and effectiveness**" to "…**thoroughly assess non-US data sources for quality, completeness, fitness, and generalizability** to a US setting, and to determine the potential of [non-US] RWD to answer **relevant US regulatory questions using biosimilar switching as a test case**."

To achieve these modified goals, we are grateful for input from our FDA colleagues, and propose the following modified Specific Aims and related Tasks:

Aim 1: Evaluate the feasibility, quality, validity, and fitness of RWD from one source within the US and two sources from outside the US to answer US regulatory questions on biosimilars. This activity will be conducted in several steps outlined as follows:

Task 1: Evaluate the availability, completeness, and data quality across three data sources (US, Italy, Denmark), using clinical trials for insulin glargine and adalimumab biosimilars as the test case. This work will result in a detailed inventory and notes exploring any gaps or contingencies related to data quality. In the final report we will include an assessment of what applications are (or are not) currently feasible using RWD.

Aim 2: Design and conduct observational studies (e.g., descriptive analyses, target trial emulation, transportability estimation) to assess the ability to answer and interpret meaningful questions on biosimilars using US and non-US RWD.

Task 1: Perform descriptive analyses on cohort of users of the two test cases (insulin glargine, adalimumab), including a detailed assessment of the similarities and differences in patient populations across countries, patterns care, and identify strengths and limitations of applying RWD.

Task 2: Conduct a detailed data feasibility assessment to generate recommendations, strengths, and limitations expected to influence whether we can complete an emulation.

Task 3: Based on the feasibility assessment, if possible, design a target trial emulation using a parallel protocol approach.

Task 4: Conduct emulation studies, followed by detailed evaluation across sites of strengths and limitations of using RWD. Evaluate the feasibility of conducting transportability of outcomes across countries.

Task 5: Dissemination.

Next Steps

The scope and approach to this study has been changed, based on FDA recommendations. Changes include the plan to include a formalized data feasibility assessment, and to use that to determine whether a target trial emulation would be possible or meaningful. We believe there is utility in this thorough assessment and remain confident that our approach will yield valuable learnings to advance the use of RWD for regulatory and clinical decisions. Therefore, our next steps are to complete this feasibility assessment within, and across, the three participating data sites, followed by revision of our initial protocols according to our decision to pursue a full target trial emulation.

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