U.S. FOOD & DRUG ADMINISTRATION

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

ANNUAL REPORT

December 2025

Contents

Report Overview[1]

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

Project Title:	**Evidence-based approach to the design of clinical pharmacology studies**
Investigator:	Yow-Ming Wang
Organization:	OTS
Grant No. (if applicable)	N/A
Project Objective:	To increase the efficiency of biosimilar development programs by leveraging clinical pharmacology studies

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. Biosimilar development considerations for therapeutic proteins (TPs) with limited systemic exposure **The original aim "TPs with challenges in conducting CES where PD biomarkers may improve efficiency of biosimilar development" was revised to align with ongoing effort to streamline biosimilar development (IPRP Workshop and Final Report), and there was no further activity since annual report of 2024.*	TPs with limited systemic exposure were identified, potential PD biomarkers were investigated, and biosimilar development considerations were provided.	Identified 19 approved TPs with limited systemic exposure (not feasible to assess PK similarity): • 4 TPs not suitable for biosimilar pathway, • 1 TP with the potential option of using PD similarity approach, • 14 TPs may rely on CES with special study design considerations for 10 of 14 TPs.	• (Revised aim) Results have been presented at the Biologics Oversight Board (BOB) of Office of Clinical Pharmacology (OCP) in June 2025 and will be presented at conference if resource allows. • (Original aim) Results have been presented at BOB and OCP Day in 2023 and 2024 ASCPT annual meeting. • Manuscript in preparation.

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

Specific Aim(s)	Progress	Outcomes	Communication Timeline
2. Develop Best Practices for Bioanalytical Methods Used to Measure Biomarkers in Biosimilar Programs.	Collected and summarized information about biomarkers that were included in BLAs of neurology products and enzyme replacement therapy (ERT), including specific information regarding PD biomarker, clinical studies, endpoint type and context of use information, bioanalysis method types, validation parameters, and other relevant information. Developed one internal review resource (with points to consider for reviewing biomarker assays) which can also assist reviewer in communication through information request (IR) for PD biomarker bioanalysis – a key task for the second year.	• Created a database of biomarkers in BLAs of two therapeutic areas. • Created dynamic excel dashboards to facilitate an interactive knowledge sharing experience.	• Internal presentation at 2023 OCP Day. • Presented at 2024 ASCPT annual meeting (findings on neurology products) • Accepted for poster presentation at 2024 ACCP (ERT products) • Published the review resource in TBP SharePoint site • Manuscript in preparation
3. Compare PK and immunogenicity data across products in 351(k) submissions & seek explanations for observed differences	Establish a dataset of failed PK similarity studies and identified factors or reasons for the failed studies.	15 PK studies from 13 BLAs had at least one primary PK endpoints not meeting prespecified acceptance criteria. Higher-than-expected PK variability is the most cited reason for not meeting PK similarity criteria. Difference in immunogenicity or drug content are also mentioned.	• Presented findings at the 2023 OCP Day • Presented at 2025 BsUFA III Regulatory Science Pilot Program Interim Public Meeting • Manuscript in preparation

Specific Aim(s)	Progress	Outcomes	Communication Timeline
4. Investigate factors that contribute to differences in PK performance of autoinjectors (AI) compared to prefilled syringes (PFS) & develop an evidence-based approach to bridge these two devices among BLAs of monoclonal antibodies (mAbs) and Fc-fusion proteins	• Collected clinical data supporting the approval of AIs in 351(a) and 351(k) BLA of mAbs. • Identified the AI platforms used for and collected device and product information. • Summarized the parameters of AI devices and products as well as the PK comparability study outcomes.	• Identified 3 major platforms for AI devices and collected their parameters. • Produced a database on approved mAbs with AIs. • Summarized the AI device parameters, product information, and results of PK comparability studies.	• Published a paper reporting the 7 non-BE PK studies in 351(a) BLA mAbs. • Presented at 2025 BsUFA III Regulatory Science Pilot Program Interim Public Meeting • Manuscript in preparation

Progress Summary

Aim 1: (Revised) To provide biosimilar development considerations for therapeutic proteins (TPs) with limited systemic exposure

- Identify and characterize TPs with limited systemic exposure. **Status:** Completed.
- Evaluate if identified TPs are well characterized and suitable for biosimilar development. **Status:** Completed.
- For TPs well characterized, investigate if suitable PD biomarkers are available and provide biosimilar development considerations (i.e., PD biomarker approach vs. CES). **Status:** Completed.
- If no suitable PD biomarker, investigate if there are challenges for evaluating clinical efficacy endpoints and provide considerations for CES (e.g., endpoint, population, duration). **Status:** Completed,
- Note: There was no further activity for the old aim “TPs with challenges in conducting CES where PD biomarkers may improve efficiency of biosimilar development” since annual report of 2024.

Aim 2: To develop Best Practices for Bioanalytical Methods Used to Measure Biomarkers in Biosimilar Programs

- Establish a database of bioanalytical methods for biomarkers used to make regulatory decisions, e.g., labeling, exposure-response analysis, approval decision. **Status:** Completed.

- Identify the timing of validation data submission. **Status:** Completed.
- Review the quality of biomarker validation and reviewer comments including IRs if any. **Status:** Completed.
- Align the submission time, validation quality and review comments on the method validation. **Status:** Completed.
- Developed one internal review resource to assist reviewer in the review and the preparation of information request (IR) for PD biomarker bioanalysis. **Status:** Completed.

Aim 3: To compare Pharmacokinetics (PK) and immunogenicity data across products in 351(k) submissions & seek explanations for observed differences

- Establish a dataset of both passed and failed PK similarity studies with data collection on the study design, primary endpoints, sample size, study population, dose, route of administration, sampling time, statistical method, and immunogenicity. **Status:** Completed.
- Identify factors or reasons for the failed studies. **Status:** Completed.
- Document noticeable differences between the failed studies and the follow-up successful ones. **Status:** Completed.
- Identify factors by making comparison between the failed studies and the successful ones from other submissions using the same reference product. **Status:** Completed.

Aim 4: To investigate factors that contribute to differences in PK performance of autoinjectors (AI) compared to prefilled syringes (PFS) & Develop an evidence-based approach to bridging these two devices

- Produce a database with all the precedent PFS to AI presentation changes, including the following information for further analysis:
    - The devices parameters. **Status:** Completed.
    - Data supporting the approval of AI. **Status:** Completed.
    - The design and results of comparative PK studies. **Status:** Completed.
- Summarize the findings to inform a roadmap that can serve as a communication tool for further dialogues with industry scientists to advance this area of knowledge gap as well as for regulatory interactions. **Status:** Completed.

Research Outcomes

Aim 1:

1. Identified 19 TPs with limited systemic exposure among 272 TPs approved as of May 2025.

2. Characterized these TPs: 1) by disease areas: neuropsychiatric (37%), inflammation and immune (32%) diseases; 2) by TP type: toxin (37%), protein mixture (21%), and enzyme (16%); 3) by dosing route: all for local effect.
3. Identified 4 TPs not suitable for biosimilar pathway and provided rationales.
4. Identified 1 TP which could rely on PD similarity approach and provided biosimilar development considerations compared to CES.
5. Identified 14 TPs which could rely on CES and provided biosimilar development considerations regarding study design (e.g., alternative population, shorter study duration, specific patient selection among multiple indications).

Note: There was no further activity for the old aim "TPs with challenges in conducting CES where PD biomarkers may improve efficiency of biosimilar development" since annual report of 2024.

Aim 2:

- Identified a total of 100 PD biomarkers from 36 BLAs that encompassed neurology products and enzyme replacement therapy (ERT); specifically, 65 PD biomarkers from 16 BLAs of neurology products and 35 biomarkers from 20 BLAs of ERT products. We further evaluated the clinical pharmacology application of PD biomarkers (phase of clinical studies, endpoint type, and context of use) and their corresponding method validation profiles including method types, parameters, and other relevant information.
- Aligned the PD biomarkers and their application in clinical pharmacology studies and compared their bioanalytical method validation profiles with current biomarker assay validation guidance and industry white papers.
- Summarized the findings in the following categories to aid in informing future best practice:
    - The current landscape of PD biomarkers and their method validation profiles.
    - The relationship between PD biomarkers, clinical study phase, endpoint type, context of use, method type, and parameters.
    - The adherence to guidance recommendations regarding validation parameters.
    - Differences in the approaches taken between therapeutic areas and bioanalytical method types.
- Developed an internal review resource and write the manuscript to enhance the standardization of the PD bioanalysis from review recommendation to industry practice. The review resource can serve as a review aid and a tool for regulatory communications.

Aim 3:

1. Identified fifteen studies in thirteen 351(k) BLAs that had at least one primary PK endpoint deviated from the pre-specified 80-125% acceptance range, which are PK similarity studies (n=6), PK/PD similarity studies (n=6), or comparability studies (n=3).

2. Established a database for these studies, including study design, primary endpoints, sample size, study population, dose, route of administration, statistical method, and the geometric mean and the variability of PK endpoint as well as the corresponding 90% confidence interval (CI) of geometric mean ratio of PK endpoints. Most failed PK studies had parallel design in healthy subjects and are for subcutaneously administered products.
3. Gathered the applicants' explanations for the deviation from acceptance range. Frequently cited potential explanations include high PK variabilities and differences in immunogenicity or drug content between the biosimilar product and the reference product. Conducting a subsequent study with a larger sample size is a common approach taken to achieve a successful study outcome which suggests that the initial studies were not appropriately powered statistically. Other approaches adopted in the subsequent studies have implemented include utilizing partial reference-replicate design to address high intra-subject variability, implementing ANCOVA to control imbalance of covariates such as body weight or trial sites, or adding restrictions for enrolling subjects to control variability among others.
4. The sample size of the failed studies is smaller compared to those of the successful ones in biosimilar BLAs that share the same reference product. The geometric mean ratios of PK parameters that failed to meet similarity criteria often deviate from unity by more than 10% (i.e., <0.9 or > 1.1).

Aim 4:

1. Identified three major AI platforms used for 351(k) BLA mAbs: Ypsomate, SHL AI (Scandinavian Health Ltd), and BD Physioject.
2. Produced a database for 351(a) and 351(k) BLA mAbs with AIs approved, which currently contains injection depth, injection time, injection rate, and the viscosity of drug products.
3. Documented the PK comparability studies of these AIs. Our preliminary analysis suggests that these parameters individually are not associated with the outcome of PK comparability.

Regulatory Impact

Aim 1:

Ongoing effort of biosimilar framework modernization may lead to waiving CES for well-characterized TPs and concluding that they can rely on CAA + PK approach to support approval. However, the approach does not apply to TPs with limited systemic exposure or TPs not well-characterized, and currently there is limited experience for their biosimilar development. This research can proactively identify TPs with limited systemic exposure and provide key considerations to facilitate their biosimilar development. In addition, the findings will provide scientific considerations for the revision of biosimilar guidance.

Aim 2:

The quality of bioanalytical method is the foundation facilitating the applications of biomarkers in PD similarity studies to support biosimilars approval. Developing a best practice will facilitate standardization of regulatory review of biomarker assays. The investigation covers various types of biomarkers that use different technology platforms, as such the research findings will support developing a best practice framework and ensure the quality of biomarker assay performance (e.g., improving the performance characteristics of biomarker assays). The benefit will manifest in reducing the variability of data in PD similarity studies, thereby, improving the efficiency of biosimilar development.

Aim 3:

Inefficiencies in biosimilar development programs can be related to the failure to demonstrate PK or PK/PD similarity on the first attempt, requiring repeat studies to support the regulatory approval of biosimilar products. Biosimilar programs have had such experience in 10% of the studies which highlights the need to better understand the cause for study failure. Identifying potential factors that could lead to increasing risk of study failures is critical to facilitate providing regulatory recommendations to proactively address the risk thereby improve the efficiency of biosimilar development. The data suggests that sample size increases are often the primary approach for addressing failed BE studies, particularly when high variability is the root cause. In addition, sophisticated approaches involving study design modifications and statistical adjustments could be utilized when appropriate to implement by pre-specification in the study protocol. Recognizing that an increasing number of PK similarity studies utilizes ANCOVA, OCP developed a review tool to assess PK similarity with covariate adjustment in the statistical analysis.

Aim 4:

1. Our project was inconclusive regarding critical AI device parameters that can influence PK performance when each parameter was evaluated separately.
2. Limited data suggest:
    - AI injection time > 19 sec may be of high risk for PK not comparable (vs. PFS).
    - AI's spring force may be a factor.
    - Using the same AI device (or platform) to deliver different products may not consistently achieve comparable PK (vs. PFS).
    - PK performance of AI device is likely dependent on multifactorial interactions between multiple device parameters, product characteristics, and proper user handling.
3. Results suggest the need for further investigation; for instance, by expanding the list of AI device parameters and product parameters that may influence PK performance of autoinjector devices.

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)
Aim 1			
Biosimilar development considerations for TPs with limited systemic exposure	Presentation	BOB meeting	N/A
Biosimilar development considerations for therapeutic proteins with limited systemic exposure	Manuscript	Under preparation	N/A
Approved Therapeutic Proteins with Challenges in Clinical Endpoints Evaluation where Pharmacodynamic Biomarkers May Improve Efficiency of Biosimilar Development	Poster and podium presentation	OCP Day	N/A
Role of PD biomarkers in biosimilar development and approval	Presentation	ASCPT Network & Community Experience (NCE)	N/A
Approved TPs with Challenges in Clinical Endpoints Evaluation where PD Biomarkers May Improve Efficiency of Biosimilar Development	Presentation	BOB meeting	N/A
Approved Therapeutic Proteins with Challenges in Clinical Endpoints Evaluation where Pharmacodynamic Biomarkers May Improve Efficiency of Biosimilar Development	Poster	ASCTP travel award poster	N/A
Aim 2			
A Snapshot of Pharmacodynamic Biomarkers Bioanalysis in 16 BLAs Approved for Neurology Indications	Poster	FDA OCP Day 2023 (October 2023)	N/A

Title	Type of Communication (e.g., poster, manuscript, presentation)	Source	Link (if available)
A Snapshot of Pharmacodynamic Biomarkers Bioanalysis in 16 BLAs Approved for Neurology Indications	Poster	American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2024 Annual Meeting (March 2024)	N/A
A Survey of Pharmacodynamic Biomarkers Bioanalysis In 20 Biologics License Applications Approved for Enzyme Replacement Therapy Indications	Poster	American College of Clinical Pharmacology (ACCP) Annual Meeting (September 2024)	N/A
Clin Pharm Comments on Bioanalysis of PD Biomarker	Internal review resources	TBP sharepoint	N/A
Aim 3			
Characterizing the Clinical Pharmacology Studies in Biosimilar Biologics License Applications (BLAs)	Poster	OCP Day poster (October 2023)	N/A
Characterizing the Covariates and their Impacts on Statistical Evaluations of Clinical Pharmacology Studies in the 351(k) Biologic License Applications	Poster	American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting (September 2024)	N/A
Aim 4			
Pharmacokinetics-Bridging Between Autoinjectors and Prefilled Syringes for Subcutaneous Injection: Case Examples Revealing a Knowledge Gap	Manuscript	Clinical Pharmacology & Therapeutics	Pharmacokinetics-Bridging Between Autoinjectors and Prefilled Syringes for Subcutaneous Injection: Case Examples Revealing a Knowledge Gap
Molecule-Independent Device Bridging Approach (MIDBA)	Presentation	Biologics Oversight Board meeting, 9/5/2025	N/A

Title	Type of Communication (e.g., poster, manuscript, presentation)	Source	Link (if available)
A Landscape Survey for the Presentations Approved for Subcutaneous Protein Products	Poster	FDA scientific research day, 8/7/2024	N/A
A Landscape Survey for the Presentations Approved for Subcutaneous Protein Products	Poster	ASCPT, 5/26/2025	N/A

Scientific and Technical Challenges

Aim 1:

The research aims had to be revised to focus on TPs with limited systemic exposure to align with the current regulatory thinking. There have been ongoing global discussions to re-evaluate the need of CES or PD similarity study, and the proposal is to rely more on CAA and PK similarity study.[1] The potentially revised regulatory thinking may reshape biosimilar development plan, including no need to evaluate clinical endpoint or PD biomarker for most TPs. The new proposal will rely on CAA+PK approach which has a huge impact on the original research aims (i.e., to identify TPs with challenges in CES and to investigate potential PD biomarkers for them). Therefore, the aims were adjusted timely to focus on finding TPs for which CES is still needed, and PD biomarker approach may serve to streamline the CES approach.

Aim 2:

The main project specific challenge was encountered during the initial stage of resource gathering of the BLAs, validation reports, and other supplemental information for products due to the following reasons:

- Older approved drugs were not always located in the electronic database.
- Validation reports and clinical studies mentioned in the BLAs were not always located in the sections of the electronic database that was referred to in the BLA.

Initial focus of the project was on neurology products and their respective PD biomarkers and bioanalytical methods. As the project progressed and after the completion of the data gathering and data analysis of the neurology products, the project was expanded to include ERT products to provide the following enhancements:

- Provide a larger dataset of information on the current landscape of PD biomarkers in regulatory submissions and their method validation profiles.

- Provide insight into potential differences between therapeutic areas, PD biomarker types, and bioanalytical method types.

Aim 3:

The following aspects represent challenges encountered:

- Applicants did not always provide possible reasons for failed PK studies, making it difficult to identify the potential root causes.
- Applicants might not submit all data for the failed studies, making it challenging to analyze the rooting causes for the failure.
- It is difficult to verify/confirm whether immunogenicity is a potential explanation for study failure. Immunogenicity assays used across BLAs varied in their sensitivity, specificity, and drug tolerance, which precludes a meaningful comparison of immunogenicity data in the failed studies to those reported in other studies.

Aim 4:

The challenges of this aim mainly come from the following aspects:

- Completed PK comparability studies were often underpowered, but many studies demonstrated PK comparability despite large PK variability. The finding suggests small sample size may not be a barrier for such studies.
- Device parameters, product characteristics parameters, and study design parameters combined represent many potential influencing factors of the PK comparability results. It is challenging to identify the relationship between the PK comparability study outcome and device or product parameters.
- In some cases, a second PK comparability study will follow a previously failed one. We have investigated the changes of the AI designs that may contribute to the success of the second study. However, changes to the study design in the second study, e.g., increasing sample size, restricting to one injection site, etc., make it hard to identify whether the critical contributing factors are associated with changes in the device or the study design. On the other hand, a few limited cases have suggested that without the device modifications the second study may not have been able to demonstrate PK comparability.
- There is limited knowledge on device parameters as well as product characteristics that are critical to the in vivo PK performance.

Next Steps

Aim 1:

- Present research findings internally to facilitate review team's decisions for relevant products and to contribute to biosimilar guidance revision.

- Save all summary slides in TBP SharePoint as review resources.
- Present research results externally to engage stakeholders to facilitate biosimilar development.

Aim 2:

- Write a manuscript on the research results and inform future best practices in biomarker bioanalysis in hopes of reducing the variability of data in PD similarity studies, thereby improving the efficiency of biosimilar development.

Aim 3:

- Prepare a manuscript to report the findings and present the results at FDA internal meetings and national conferences.

Aim 4:

- Write a manuscript on the research results and present this project at FDA internal meetings and national conferences.
- Save the survey in TBP SharePoint as review resources.

References

- 2023 FDA IPRP workshop: Increasing the Efficiency of Biosimilar Development Programs – Reevaluating the Need for Comparative Clinical Efficacy Studies. https://www.fda.gov/drugs/news-events-human-drugs/increasing-efficiency-biosimilar-development-programs-reevaluating-need-comparative-clinical
- 2024 FDA IPRP workshop summary report https://admin.iprp.global/sites/default/files/2024-07/IPRP_BWG_Final%20IPRP%20Scientific%20Workshop%20Summary%20Report_2024_0506.pdf
- Li, Z., Du, X., Huang, S.M., & Wang, Y.C. (2024). Pharmacokinetics-bridging between autoinjectors and prefilled syringes for subcutaneous injection: Case examples revealing a knowledge gap. Clinical Pharmacology & Therapeutics, 115(3), 404–407. https://doi.org/10.1002/cpt.3145.