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**

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

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. To identify potential PD biomarkers for therapeutic proteins that face challenges in conducting CES and in need of PD biomarkers for biosimilar programs	Identification and characterization of TPs associated with challenging factors have been completed; PD biomarker investigations for prioritized TPs are ongoing.	(Completed Part I) Identified >120 (49%) approved TPs to be associated with challenging factors. These results along with additional considerations (i.e., TPs with certain challenges [e.g., unclear MOA, limited systemic exposure]) have informed TP prioritization for Part II - PD biomarker identification - which is ongoing.	Internal (e.g., OCP Day, OCP internal forum) and external (e.g., conference abstract, poster, presentation) communication within 1 year of funding, manuscript publication within 2 years of funding

[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 neurologic and enzyme replacement therapy (ERT) products, including specific information regarding PD biomarker, clinical studies, endpoint and context of use information, bioanalysis method types, parameters, and other relevant information. Currently, summarizing the results to inform the best practice framework	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 neurological products) Accepted for poster presentation at 2024 ACCP (ERT products) 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 is completed; the factors or reasons for the failed studies are identified.	15 PK studies from 13 351(k) BLAs had at least one of primary PK endpoints not meeting prespecified acceptance criteria. All programs had a follow-up study that met the prespecified criteria.	Presented preliminary findings at the 2023 OCP Day; plans to communicate in future internal and external via posters and podium presentations and/or manuscript within 2 years of funding.
4. Investigating factors that contribute to differences in PK performance of autoinjectors (AI) compared to prefilled syringe (PFS) & develop evidence-based approach to bridging 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 351(k) BLA and currently collecting device and product information for each AIs platform. Summarized the parameters of AIs on one platform, and currently investigating other AI platforms. Ongoing investigations - the relationship, if any, between the AI device parameters, product characteristics, and the PK comparability study outcomes.	Identified 3 major platforms for AI devices. Produced a database on approved mAbs with AIs. Summarized results of PK comparability studies that bridged AI to another approved presentation.	We published a paper reporting the 7 non-BE PK studies in 351(a) BLA mAbs. Findings from the rest of the study will be communicated in internal and external venues via abstract, posters, presentations and/or manuscript within 2 years of funding.

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.*

Aim 1: To identify potential pharmacodynamic (PD) biomarkers for therapeutic proteins (TPs) that face challenges in conducting comparative efficacy study (CES) and in need of PD biomarkers for biosimilar programs

- Identify novel TPs (approved by the end of 2023) associated with challenges in conducting CES based on defined challenging factors **– Status:** completed
- Examples of challenging factors include: 1). long study duration for primary efficacy endpoint evaluation; 2) challenging sample size (n≥1000) or (n≤100; very rare disease); 3) young pediatrics only (e.g., ≤12 years)
- Characterize identified TPs (e.g., challenging factor numbers, approval year, disease area, TP type) **– Status:** completed
- Investigate PD biomarker role and provide case examples for addressing each defined challenging factor **– Status:** completed
- Access additional considerations. For example, alternative ways to address challenges of CCS besides PD biomarker approach when PD biomarkers are not available, and challenges remained (e.g., most TPs indicated for young pediatrics only require innovative development pathway due to ethical and safety concern) **– Status:** completed
- Summarize Part I results and start Part II: prioritize products and investigate potential PD biomarker(s) for at least 10 TPs **– Status:** ongoing

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:** ongoing
- Extract best practices as a review protocol and foundations for information requests (IRs) in interaction with Sponsors **– Status:** ongoing

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

- Establish a dataset of 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 for failed PK similarity studies **– Status:** partially completed pending for immunogenicity information
- Identify the factors or reasons for the failed studies **– Status:** completed
- Document noticeable difference between the failed studies and the follow-up passed ones **– Status:** ongoing
- Identify the factors by making comparison between the failed studies and the successful ones from other submissions using the same reference product **– Status:** ongoing

Aim 4: To investigate factors that contribute to differences in PK performance of autoinjectors (AI) compared to prefilled syringe (PFS) & Develop 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 parameters of the devices **– Status:** completed for one of three AI platforms and ongoing for other platforms of AIs
    - Data supporting the approval of AI **– Status:** completed the survey for the approved AIs of mAbs
    - The design and the results of comparative PK studies **– Status:** completed for studies comparing PFS and AI of mAbs
- 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:** ongoing

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.

Aim 1

1. Identified 123 of 252 (49%) TPs approved by Dec. 2023 associated with challenges in conducting CES for further investigation.
2. Assessed scenarios where the use of PD biomarkers can address the challenges (e.g., long duration, large sample size, low sensitivity) and scenarios where PD biomarkers may not be helpful (e.g., TPs indicated for young pediatrics only, safety concern for conducting PD similarity study in healthy adults).
3. Identified case examples where other approaches (besides using PD biomarkers) are helpful to address the challenges e.g., alternative population, study endpoint, or duration.
4. Prioritized TPs for PD biomarker identification considering identified challenging factors.

Aim 2

1. Identified a total of 100 PD biomarkers from 36 BLAs that encompassed neurologic and enzyme replacement therapy (ERT) products; specifically, 65 PD biomarkers from 16 BLAs of neurologic 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.
2. Aligned the correlation between PD biomarkers and its application in clinical pharmacology and compared their bioanalytical method validation profiles with current biomarker assay validation guidance and industry white papers.
3. Summarizing 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

Aim 3

1. Identified fifteen PK similarity studies (6), PK/PD similarity studies (6) or comparability studies (3) for thirteen 351(k) BLAs that had at least one primary PK endpoints deviated from the pre-specified 80-125% acceptance range.
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 explanation 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. Evaluated the utility of alternative statistical approach for data analysis, e.g., ANOVA versus ANCOVA.

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 Ypsomate AIs approved (n=15), which currently contains device parameters, e.g., injection depth, injection time, injection rate, and the product parameters, e.g., the viscosity of drug products.
3. Summarized results of PK comparability studies that compared AI to another approved presentation. See our publication for some examples, including adjustments to AI device parameter such as the spring force.

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).

Aim 1:

This research will help increase biosimilar development and approval for more reference products by preemptively addressing challenges in conducting CES, including the use of PD biomarker approach. Although there are ongoing global discussions to re-evaluate the need of CES, the new proposal may not apply to all approved TPs. This research will facilitate biosimilar guidance revision by providing case examples for TPs with challenges in waiving CES and will facilitate biosimilar development programs by providing science-based recommendations for potential PD biomarkers and study design considerations for those TPs.

Aim 2:

The bioanalytical method quality is the foundation of 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 uses 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:

Inefficiency in the biosimilar development programs can be related to the failure to demonstrate PK or PK/PD similarity in the first attempt and requiring a repeat study to support the regulatory approval of a biosimilar products. Biosimilar programs have had such experience in 10% of the studies which highlights the need to better understand the cause. 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.

Aim 4:

Many sponsors (of biosimilars & stand-alone biologics) have asked whether a PK comparability study can be waived if the newly proposed AI presentation contains the same PFS and drug product, or whether an AI platform approved for one product can be adopted by a new product without a PK comparability study. This project aims to develop an evidence-based approach to address these regulatory review questions. So far, the root cause of why some AIs did not achieve comparability with PFS largely remained unclear. Investigating factors such as device design, drug characteristic and study design that may contribute to the lack of PK comparability is important to minimize the need for PK studies in human.

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).

Aim 1:

1. Office of Clinical Pharmacology (OCP) presentation at an internal forum (November 2023)
2. American Society for Clinical Pharmacology & Therapeutics (ASCPT) travel award abstract/poster presentation on March 27-29, 2024

   "Approved Therapeutic Proteins with Challenges in Clinical Endpoints Evaluation where Pharmacodynamic Biomarkers may Improve Efficiency of Biosimilar Development".
3. Manuscript for Part I "Approved Therapeutic Proteins with Challenges in Clinical Endpoints Evaluation where Pharmacodynamic Biomarkers may Improve Efficiency of Biosimilar Development" under preparation

Aim 2:

Communication and dissemination of results from this project were submitted as abstracts and presented as posters at the following events.

1. FDA OCP Day 2023 (October 2023)
   - *A Snapshot of Pharmacodynamic Biomarkers Bioanalysis in 16 BLAs Approved for Neurology Indications*
2. American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2024 Annual Meeting (March 2024)
   - *A Snapshot of Pharmacodynamic Biomarkers Bioanalysis in 16 BLAs Approved for Neurology Indications*
3. American College of Clinical Pharmacology (ACCP) 2024 Annual Meeting (September 2024)
   - *A Survey of Pharmacodynamic Biomarkers Bioanalysis In 20 Biologics License Applications Approved for Enzyme Replacement Therapy Indications*

Aim 3:

1. Characterizing the Clinical Pharmacology Studies in Biosimilar Biologics License Applications (BLAs) - OCP Day poster (October 2023)

Aim 4:

1. Manuscript of the 24 AIs approved under the 351(a) BLA pathway is published in Journal of Clinical Pharmacology & Therapeutics (March of 2024), https://doi.org/10.1002/cpt.3145
2. Student Scientific Research Day at FDA poster "A Landscape Survey for the Presentations Approved for Subcutaneous Protein Products" (August 2024)

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).

Aim 1:

Currently there are ongoing global discussions to re-evaluate the need of CES or PD similarity study, and the proposal is to rely more on comparative analytical assessment (CAA) and pharmacokinetic (PK) similarity study.[1] The potentially revised regulatory thinking may reshape biosimilar development plan, including the need to evaluate clinical endpoint or PD biomarker for some products. In addition, our research has identified a large number (>120) of TPs associated with challenges in performing CES. To address these challenges, TPs with difficulties in both waiving CES and conducting CES will be prioritized for PD biomarker investigation.

Aim 2:

The main project specific challenge was 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 neurologic 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 neurologic products, it was thought that expanding the focus of the project to include ERT products would provide the following.

- Larger data set of information to display 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 present challenges encountered

- The reasons provided by applicant for failed PK studies often lack supporting evidence. This makes it difficult to evaluate their impact on PK results.
- Applicant 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:

- PK results have big variations but are mostly contained within 80-125%, making it hard to investigate the relationship between the PK results against device or product parameters. We may need to develop models to interpret the subtle impact from each one the contributing factors.
- In some cases, a second PK comparability study will follow a previously failed one. We are investigating 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 site of injection, etc., making it hard to identify whether the critical contributing factors are associated with changes in the device or the study design.
- There are limited knowledge and availability of device parameters as well as product characteristics that are critical to the in vivo PK performance.

NEXT STEPS

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

Aim 1:

1. Identify TPs with challenges in waiving CES (e.g., unknown/unclear mechanism of action [MOA], inadequate CAA due to complex or unique MOA; within those, TPs also associated with challenges in conducting CES (results from research Part I) will be prioritized for PD biomarker identification
2. Identify additional scenarios for TPs where PD biomarker may help (e.g., TPs with limited or no systemic exposure)
3. Investigate potential PD biomarker based on PD biomarker database, clinical study report (CSR), and literature
4. Evaluate PD biomarker based on FDA recommended five characteristics
5. Provide PD biomarker and study design recommendation
6. Communicate research findings internally and externally through presentation and/or publication

Aim 2:

1. Conduct in-deep data analysis of
    - 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 between therapeutic areas and bioanalytical method types
2. Write a manuscript to summarize the results to help inform future best practice in biomarker bioanalysis in hope of reducing the variability of data in PD similarity studies, thereby, improving the efficiency of biosimilar development.

Aim 3:

1. Collect and analyze additional failed PK or PK/PD studies in 351(k) submitted after December 2023.
2. Document noticeable difference between the failed studies and the follow-up passed ones.
3. Identify the factors by making comparison between the failed studies and the successful ones from other submissions using the same reference product
4. Prepare a manuscript to report the findings and present the results at FDA internal meetings and national conferences

Aim 4:

1. Investigate AI devices that use other platforms, such as SHL AI and BD Physioject.
2. Summarize the parameters of the other AIs platforms AIs and consult with collaborators in CDRH.
3. Investigate the relationship, if any, between the AI device parameters, product characteristics, and the PK comparability study outcomes.
4. Consult modeling experts in OCP for a computational way to simulate the impact of device and product parameters on PK.
5. Write a manuscript to report our findings and present this project at FDA internal meetings and national conferences.

REFERENCES

References used in progress report.

Aim 1:

2023 FDA IPRP workshop: Increasing the Efficiency of Biosimilar Development Programs--Reevaluating the Need for Comparative Clinical Efficacy Studies (URL).

Aim 2:

None

Aim 3:

None

Aim 4:

Li Z. et al. Pharmacokinetics-Bridging Between Autoinjectors and Prefilled Syringes for Subcutaneous Injection: Case Examples Revealing a Knowledge Gap. Clin Pharmacol Ther. 2024 Mar;115(3):404-407. https://doi.org/10.1002/cpt.3145

APPENDIX A: ADDITIONAL MATERIAL

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

APPENDIX B: ABBREVIATIONS

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

ABBREVIATION	DEFINITION
AI	Autoinjector
ASCPT	American Society for Clinical Pharmacology & Therapeutics
BE	Bioequivalence
BLA	Biologics license applications
CAA	Comparative analytical assessment
CDRH	Center for Devices and Radiological Health
CES	Comparative efficacy study
CI	Confidence interval
CSR	Clinical study report
IPRP	International Pharmaceutical Regulators Programme
MAb	Monoclonal antibody
MOA	Mechanism of action
OCP	Office of Clinical Pharmacology
PD	Pharmacodynamics
PFS	Pre-filled syringe
PK	Pharmacokinetics
SHL	Scandinavian Health Ltd
TP	Therapeutic protein