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]

Project Title:	Translating Clinical Pharmacology Biosimilar Research Findings into Best Practices for Industry and FDA Review Staff
Investigator:	David Strauss
Organization:	U.S. Food and Drug Administration
Grant No. (if applicable)	N/A
Project Objective:	Closeout of bioanalytical and omics related project activities from the 'Pharmacodynamic Biomarkers for Biosimilar Approval' project

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. Finalizing reports and publishing manuscripts for bioanalytical and proteomics activities conducted as accompaniment to previously completed FDA-led clinical studies	Bioanalytical methods development and validation reports have been completed for all drugs and pharmacodynamic biomarkers from completed studies. Proteomics sample analysis, data analysis, and methods reports have been completed for all omics analyses.	One bioanalytical manuscript is in draft and will be submitted for publication in fall of 2024. Two proteomics manuscripts describing observations from completed clinical studies and lessons learned are in draft and will be submitted for publication in fall of 2024.	Previous objectives from the project have been communicated as publications, SBIA webinars, journal podcasts, or outward facing summaries on FDA.gov. Remaining publications will be submitted and revised (as needed) for publication with no additional communication plans.
2. Developing and discussing best practices for bioanalytical and proteomics assays at internal meetings and seminars for reviewer education	Presentations and best practice documents were prepared and have been discussed at internal Office of Clinical Pharmacology meetings.	Best practices for bioanalytical and proteomics methods have been discussed at internal meetings (e.g., reviewer training seminars, scientific interest groups) for reviewers to utilize in review of biosimilar submissions.	Reviewer trainings were completed in the spring and summer of 2024. Slide decks and recordings from meetings were shared with FDA reviewers.

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

2. Progress Summary

Development of biosimilar biological therapeutics is critical for spurring competition of drug pricing, while ensuring safe and effective treatment options for patients. To encourage innovation and competition in the market for biological products and facilitate their development, FDA developed the Biosimilars Action Plan (BAP) to outline agency's commitments and focuses on biosimilar biological product development. This multi-year project was designed based on strategic priorities and goals outlined in the BAP, specifically improving the efficiency of biosimilar and interchangeable product development and approval processes. This multi-year project has previously completed major milestones including i) a public workshop on use of pharmacodynamic biomarkers in biosimilar development, ii) a publication of an evidentiary framework, iii) completion of multiple trials for justifying pharmacodynamic selection for use in biosimilar development, and iv) publications of clinical findings from these studies. References for these publications are included at the end of the report.

For the final year of this multi-year project, aims were: i) finalizing reports and publishing manuscripts for bioanalytical and omics activities conducted as accompaniment to previously completed FDA-led clinical studies; and ii) developing and discussing best practices for bioanalytical and omics assays at internal meetings and seminars for reviewer education. Under i), specific tasks included finalizing bioanalytical reports for the interferon beta-1a, IL-5, and PCSK9 studies (to be completed by September 2024), drafting of at least one manuscript describing methods development and validation for one of the completed clinical studies (targeting manuscript submission by September 2024), finalizing omics reports for the interferon beta-1a, IL-5, and PCSK9 studies (to be completed by September 2024), publishing a manuscript on remaining dose levels from the interferon beta-1a clinical study (targeting manuscript submission by September 2024), and drafting a manuscript describing lessons learned utilizing proteomics approaches for characterizing PD biomarkers for biosimilars and other applications (targeting manuscript submission by September 2024). Under ii), specific tasks included drafting a lessons learned training document to support clinical pharmacology reviewer assessment of bioanalyses in biosimilar submissions (to be completed by September 2024), providing at least one reviewer training on these materials at internal Office of Clinical Pharmacology meeting (to be completed by September 2024), drafting a lessons learned training document to support clinical pharmacology reviewer assessment of proteomics analyses in regulatory submissions (to be completed by September 2024), and providing at least one reviewer training on these materials at internal FDA meetings (to be completed by September 2024).

3. Research Outcomes

Previously, three clinical studies (including interferon beta-1a, IL-5, PCSK9 products) had been conducted with two originator biologics each to characterize known PD biomarkers for each drug from the literature, characterize incomplete information available on variability, time course, and bioanalysis, and to explore the use of new technologies, such as proteomics and small-RNA transcriptomics, for identifying PD biomarkers. Primary study results have been published for all studies with bioanalytical methods for pharmacokinetics and pharmacodynamics following 'M10 Bioanalytical Method Validation and Study Sample Analysis Guidance for Industry'.

Over the past year, final bioanalytical reports for each study and analyte have been completed (last study report completed following internal standard operation procedures and archived in May 2024). A manuscript was drafted for the pharmacokinetic and pharmacodynamic bioanalytical analyses from the interferon beta-1a clinical study and is currently going through internal FDA clearance with plans to submit for publication in the fall of 2024. Lessons learned for bioanalytical analysis were summarized in an internal policy document to serve as a resource for clinical pharmacology reviewers in reviewing biosimilar applications (document finished and added to internal storage repository in April 2024). Finally, these lessons were discussed internally with clinical pharmacology and product quality reviewers at two separate scientific interest group meetings in the spring of 2024.

Separately, prior to this year, proteomics analyses had been completed for all three clinical studies along with publication of the placebo and highest dose results from the interferon beta-1a clinical study. For the current year, a publication was drafted (March 2024) describing data analyses for remaining doses from the previous interferon beta-1a clinical study and an example rationale for selecting and supporting use of PD biomarkers for biosimilar development. Rather than publishing separate manuscripts describing the proteomics analyses from the previous IL-5 and PCSK9 studies, a single joint manuscript describing lessons learned utilizing these omics approaches for characterizing PD biomarkers for biosimilars and other applications (July 2024). Lessons learned for proteomics analysis were summarized internally for clinical pharmacology reviewers in reviewing biosimilar applications. These lessons were also discussed internally with FDA staff involved in the review of proteomics data at internal proteomics working group meetings at the end of 2023 and in the spring of 2024.

4. Regulatory Impact

Research from this multi-year project, designed based on strategic priorities and goals outlined in the BAP, has helped inform FDA's understanding regarding the potential and limitations regarding use of pharmacodynamic biomarkers for biosimilar development. As a result of this project, FDA is better positioned to provide timely feedback to sponsors regarding use of pharmacodynamic biomarkers, novel analytical methods (e.g., omics approaches for supporting use of a potential biomarker), and bioanalysis for biologics and pharmacodynamics biomarkers that may be included as part of a biosimilar development program. It represents an option that sponsors can pursue as an alternative to comparative outcome studies.

Whether a sponsor would ultimately pursue a biosimilar development program utilizing pharmacodynamic biomarkers depends on several factors. Uncertainty regarding potential regulatory acceptance of a pharmacodynamic biomarker or analytical approach may lead to delays in a drug development program and a decision to pursue a more typical biosimilar development involving a clinical outcome study. Pharmacodynamic biomarkers can also be more variable than drug concentration data, necessitating an increase in sample size for a combined pharmacokinetic and pharmacodynamic similarity study or the use of analytical approaches that a drug developer does not have familiarity with. In addition, next generation sequencing costs and complexity together with intrinsic platform biases and reduced small RNA diversity in plasma may limit the utility of small RNA transcriptomics for the reproducible detection of response biomarkers for biologics in plasma. It is recognized that use of pharmacodynamic biomarkers may not offer increased efficiency in development for all biosimilar programs, but it has greatest utility in those cases where clinical outcome studies continue to be requested and where timely acceptance of the approach can be communicated to sponsors.

5. Communication and Dissemination

Previous objectives from the project have been communicated as publications, SBIA webinars, journal podcasts, or outward facing summaries on FDA.gov. Four additional posters and presentations related to overall project (first reference below) and proteomics work (last three references below) that occurred during the final year of the project are listed for completeness.

Remaining publications (one bioanalytical manuscript and two proteomics manuscripts) will be submitted to appropriate journals for the content after obtaining internal clearance. The bioanalytical and proteomics manuscripts related to the interferon beta-1a study are going through internal clearance and with plans to submit to a journal for publication by September 2024. The proteomics manuscript describing lessons learned utilizing proteomics approaches for characterizing PD

biomarkers for biosimilars and other applications is being reviewed by coauthors with plans to also submit for publication by September 2024). The manuscripts will be revised (as needed) for publication, with no additional communication plans. With regards to development of best practice summary materials and providing trainings to clinical pharmacology review staff, these activities were completed in the Spring of 2024. There are no additional communication plans for these activities.

- Chekka M. (2023, October 23). Pharmacodynamic Biomarkers Evidentiary Considerations for Biosimilar Development and Approval. AAPS 2023 PHARMSCI 360, Orlando, FL.
- Chekka M. et al (2023, November 13). Proteomic Derived Longitudinal Pharmacodynamic Biomarkers of Interferon Beta-1A Biologics. American College of Clinical Pharmacy Annual Meeting 2023, Dallas, TX
- Chekka M. et al (2023, November 8). Evaluating the Utility of Proteomics for the Identification of Circulating Pharmacodynamic Biomarkers: A Regulatory Perspective. American Conference of Pharmacometrics 14, National Harbor, MD.
- Chekka M. et al. (2024, March 27). Evaluating the Utility of Proteomics for Identification of Circulating Pharmacodynamic Biomarkers for Biosmilarity – Using PCSK9 Inhibitor Biologics as a Case Study. American Society of Clinical Pharmacology and Therapeutics, Colorado Springs, CO.

6. Challenges

No specific challenges occurred during the final year of this project. Closeout of bioanalytical- and omics-related activities progressed according to internal standard operating procedures, all intended manuscripts were completed and are going through internal clearance, and all planned for internal seminars and trainings were conducted with review staff.

7. Next Steps

No additional work is planned in this area at this time. FDA will apply the lessons learned to future biosimilar applications where biosimilar developers may express interest in utilizing pharmacodynamic biomarkers as part of their development program.

8. References

- Wang, Y.-M. and Strauss, D.G. (2023), Advancing Innovations in Biosimilars. Clin Pharmacol Ther, 113: 11-15.
- Strauss, D.G., Wang, Y.-M., Florian, J. and Zineh, I. (2023), Pharmacodynamic Biomarkers Evidentiary Considerations for Biosimilar Development and Approval. Clin Pharmacol Ther, 113: 55-61.
- Gershuny, V. et al. (2023), Considerations for use of pharmacodynamic biomarkers to support biosimilar development – (II) a randomized trial with IL-5 antagonists. Clin Pharmacol Ther 113, 80–89.
- Sheikhy, M. et al. (2023), Considerations for use of pharmacodynamic biomarkers to support biosimilar development – (I) a randomized trial with PCSK9 inhibitors. Clin Pharmacol Ther 113, 71–79.
- Florian, J., et al. (2023), Considerations for Use of Pharmacodynamic Biomarkers to Support Biosimilar Development – (III) A Randomized Trial with Interferon Beta-1a Products. Clin Pharmacol Ther, 113: 339-348.
- Hyland, P. et al. Evaluating the utility of proteomics for the identification of circulating pharmacodynamic biomarkers of IFNβ-1a biologics. Clin Pharmacol Ther 113, 98–107 (2023).
- US Food and Drug Administration. (2022), M10 Bioanalytical Method Validation and Study Sample Analysis Guidance for Industry. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.
- Florian J. et al. (2023), Pharmacodynamic Biomarkers for Biosimilar Development and Approval: A Workshop Summary. Clin Pharmacol Ther. May;113(5):1030-1035.
- Yu, C. et al. (2024). Lessons learned from regulatory submissions involving endogenous therapeutic analyte bioanalysis. Bioanalysis, 16(3), 171–184.
- US Food and Drug Administration and Duke Margolis Institute for Health Policy (2021). Pharmacodynamic Biomarkers for Biosimilar Development and Approval. September 20-21.
- FDA Biosimilars Action Plan: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf.

9. Appendix: Abbreviations

Abbreviation	Definition
PD	Pharmacodynamic
PCSK9	Proprotein Convertase Subtilisin/kexin type 9
IL-5	Interleukin 5