U.S. FOOD & DRUG ADMINISTRATION

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

ANNUAL REPORT

CONTENTS

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☒ **Progress report** ☐ **Final report**

1. REPORT OVERVIEW[1]

Project Title:	Model development and verification to evaluate minimum stability data required for biosimilar submissions
Investigator:	Thomas O'Connor, Uriel Ortega-Rodriguez, Mari Lehtimaki
Organization:	FDA/CDER/OPQ/OPQR
Grant No. (if applicable)	
Project Objective:	**Determine the minimum amount of stability data required to accurately predict long term stability and support biosimilar product's shelf-life.**

Specific Aim(s)	Progress	Outcomes	Communication Timeline
1. Survey modeling approaches used in all biotechnology regulatory applications using regulatory databases and internal review documents	A survey of regulatory applications (BLA and IND's) in which stability modeling was used to support shelf life of biotechnology drug product has been completed.	More than 20 examples in which kinetic modeling, or extrapolation of limited stability data was used to support stability of biotechnology drug products were identified. The context in which modeling was used, and the areas of consideration identified during the assessment of the stability modeling strategies were investigated, and the factors that led to successful or unsuccessful outcomes were identified.	The findings of the regulatory database search on stability modeling in biotechnology are being drafted into a manuscript for publication in 2025.
2. Produce kinetic stability data for kinetic modeling	Pilot accelerated stability studies were performed to optimize the conditions of analytical assays, and to identify which stability indicating attributes of trastuzumab and insulin lispro are amenable to modeling. The data from these studies are being used establish preliminary frequentist kinetic models.	Pilot data which were amenable for modeling included loss of main peak, coupled with an increase in high or low molecular weight species from both size exclusion chromatography experiments, and capillary electrophoresis, sodium dodecyl sulfate (CE-SDS) experiments. Additionally, an increase in acidic charge variants, and the loss of the main charge variant over time by Imaged capillary isoelectric focusing (icIEF) were also determined to be prime candidates for modeling. Other analytics are which assess site-specific degradation, and bioassay/potency are currently underway.	The long-term accelerated stability arm of the project is on track to be completed in Spring 2025, and the data will be fed into the preliminary kinetics models, to refine the models. The long-term real-time stability arm of the project will be completed in 2026.

[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
3. Create predictive models from the data collected using a frequentist and Bayesian approaches.	The pilot data from SEC-UPLC, CE-SDS, icIEF analytics have been provided to the kinetics modeling team, and preliminary model building is in progress.	Preliminary model assessment based on available pilot stability data is in progress.	The final statistical models will be available in 2027.

2. PROGRESS SUMMARY

Project Objective: Determine the minimum amount of stability data required to accurately predict long term stability and support biosimilar product's shelf-life.

Aim 1: Survey modeling approaches used in all biotechnology regulatory applications using regulatory databases and internal review documents.

A comprehensive survey of regulatory applications in which stability modeling was used to support shelf life of biotechnology drug product using internal review databases was completed in late Fall of 2023. The findings of the database search were communicated in an internal presentation to regulatory staff in CDER/OPQ/OPQAIII in late spring of 2024, and a manuscript summarizing the results of the survey will be drafted in 2024 and published in 2025.

Aim 2: Produce kinetic stability data for kinetic modeling.

The ICH Q5C consistent timepoints for real time study (0, 1, 3, 6, 12 and 24 months), and accelerated and stress studies (weekly for 1 month and monthly for 6 months) are used to monitor purity, potency, protein aggregation and common degradant profiles to track specific degradation pathways to enable the development of improved kinetic models. Data from a 24-month experimental study design at intended real time storage conditions and 6 months of accelerated and stress conditions of trastuzumab and insulin lispro originator and biosimilar products will be used. Pilot accelerated and real-time stability studies were conducted in early Spring of 2024, using trastuzumab and insulin lispro for 1 month (collected weekly), to optimize the conditions for size exclusion chromatography (SEC-UPLC), reducing and non-reducing capillary electrophoresis, sodium dodecyl sulfate (CE-SDS) and charge variant analysis by Imaged capillary isoelectric focusing (icIEF). The pilot studies were conducted at various temperatures (4°C, 25 °C, 40°C, 50 °C, and 55 °C, to obtain at least 20% degradation of stability indicating attributes in order to develop the kinetic models. These experiments were used to identify which stability indicating attributes of trastuzumab and insulin lispro were amenable to modeling. Further optimization of other precision analytical assays, including Fc-binding by Bio-layer interferometry (BLI), multi-attribute monitoring to track and identify site-specific degradants on trastuzumab and insulin lispro peptides which are stability indicating, and dynamic light scattering (DLS) to monitor protein aggregation. Optimization of all analytics will be completed prior to initiation of the long term accelerated (24 months) and real-time studies (6-months), which will begin in mid-September 2024.

Aim 3: Create predictive models from the data collected using a frequentist and Bayesian approaches.

We plan to test the accuracy of the models using the real-time stability data to assess the feasibility of accelerated and stress stability data to support biosimilar product's shelf-life determination. Preliminary model building is in

progress using the pilot data from SEC-UPLC, CE-SDS, icIEF analytics. The first model based on the loss of the main charge variant of trastuzumab has been assessed.

3. RESEARCH OUTCOMES

Research Outcomes Aim 1: More than 20 examples in which kinetic modeling, or extrapolation of limited stability data was used to support stability of biotechnology drug products were identified in submissions. Stability modeling was used for various contexts, including in-use stability, in process control strategies, specification setting, new manufacturing site comparability and others. Additionally, stability modeling was used during various stages of the manufacturing process, including the final drug product, drug substance and drug substance intermediates. A variety of modeling approaches were identified, including machine learning algorithms, Bayesian statistical models, modified Arrhenius equations, and simple linear regression. The attributes modeled in the applications, varied in a product-specific manner, and were based on the data from a variety of analytical assays, including SEC-UPLC**,** CE-SDS**,** icIEF, DLS, potency, site-specific degradants and others, which support the validity of our study design. The areas of consideration identified during the assessment of the stability modeling strategies were investigated, and the factors that led to successful or unsuccessful outcomes were identified.

Research Outcomes Aim 2: Data acquired during pilot stability studies include SEC-UPLC, CE-SDS, icIEF at 4°C, 25 °C, 40°C, 50 °C, and 55 °C. The data amenable for modeling included loss of main peak, coupled with an increase in high or low molecular weight species from both SEC-UPLC, and CE-SDS experiments. Additionally, the loss of the main charge variant, associated with an increase in acidic charge variants, over time, which were prominent at elevate temperatures, as detected by icIEF, were also determined to be prime candidates for modeling. Other analytics which assess site-specific degradation by high resolution liquid chromatography tandem mass spectrometry (LC-MS/MS), and bioactivity assessment by biolayer interferometry, and cell-based bioassays are underway.

Research Outcomes Aim 3: All pilot stability data were provided to the kinetics modeling team, and preliminary model assessment is in progress. A sample model has been produced based on a time and temperature dependent loss of the main charge variant of trastuzumab by icIEF.

4. REGULATORY IMPACT

We will employ a combination of precision analytics, and advanced kinetic modeling to establish tools to facilitate regulatory assessment of biosimilarity in support of BsUFA Research Priority c “improve on and/or develop new analytical technologies”.

Per FDA guidance, appropriate physicochemical and functional comparison of the stability profile of a biosimilar and reference product are expected to establish a direct comparison between the two. The recommendation of stability data to support the proposed shelf life of the product with “sufficient real time, real condition stability data” at the time of biosimilar product 351(k) application submission is outlined in the FDA Guidance document “Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product - Guidance for Industry. “

Generally, at least 12 months of real-time data are submitted to support the shelf-life of a biosimilar product. The requirement for long term stability testing can translate into a waiting period of at least a year after commercial scale manufacturing is established. Therefore, stability testing can be the bottleneck in biosimilar development in which only abbreviated clinical data are expected. Our regulatory assessments have informed us that Sponsors are starting to implement stability modeling approaches to provide support for the proposed self-life of biotechnology drug products. Statistical extrapolation and complex modeling approaches could potentially result in decreased and targeted real-time stability data which would facilitate quicker submission, evidence-based regulatory assessment, and faster access of biosimilars to patients. However, there have been limited uses of these strategies in biological drug product applications, and questions regarding the accuracy and precision of stability modeling remain.

The agency needs to provide guidance for the assessment and acceptability of such modeling approaches. This study will help the agency understand the accuracy of advanced kinetic models in predicting real time stability, the minimum amount of data required to accurately predict stability, and suitability of critical quality attributes (CQAs) used for model development., Assessors will benefit from understanding the effect of these variables on kinetic modeling to support biosimilar drug product shelf life. Additionally, broad application of stability modeling

for biotechnology drug products submitted under accelerated approval pathways can lead to faster access of life-saving drugs to patients. This study will help refine the guidance for stability data requirements and stability study design recommendations for use of advanced kinetic modeling in future updates to ICH guidance documents.

5. COMMUNICATION AND DISSEMINATION

Communication and Dissemination Aim 1:

Dr. Uriel Ortega-Rodriguez gave a talk on the findings of the database search (related to aim 1) at the Office of Pharmaceutical Quality Assessment III (OPQA III) all hands meeting on April 2nd, 2024. The presentation, titled "Use of modeling to support stability in biotechnology regulatory submissions," communicated the results from Aim 1 of the project to assessors, and regulatory leadership of OPQAIII. Specific examples on the class of biotechnology products, the modeling strategies and the context in which stability modeling was used, and the regulatory outcome were discussed with stakeholders.

Uriel Ortega-Rodriguez, "Use of modeling to support stability in biotechnology regulatory submissions." OPQA III All Hands Meeting, April 2nd, 2024.

Communication and Dissemination Aim 2:

In progress.

Communication and Dissemination Aim 3:

In progress.

6. CHALLENGES

Changes in the experimental design were made based on scientific assessment and from data acquired during our pilot studies. Briefly, the monoclonal antibody drug product was changed to trastuzumab as the originally chosen drug was not readily available and produced non-ideal degradation patterns in the intended stress conditions. A third temperature was added to the study as predictive modeling generally requires data sets with at least 3 different temperatures (Campa et al. 2021).

The highest temperature conditions for both insulin lispro and trastuzumab products was changed from 55°C to 50°C to reduce the number of stability chambers needed for the study, and to allow efficient use of the analytical equipment. Multiple pilot studies were conducted to ensure the chosen temperatures are appropriate.

We have experienced challenges based on lapses in funding availability, and postponed ordering of materials required for the long term-stability arm of the study. We are preparing an alternate experimental plan to address fluctuation in funding availability.

Personnel changes and internal reorganization of CDER offices have resulted in several challenges that have delayed the official start of the long-term stability study. To mitigate these challenges, we have begun to cross train personnel in many analytical procedures to the greatest possible extent, and the schedule of the long-term and accelerated stability studies have been planned to avoid sampling time points when analysts would not be available (e.g., major holidays). The pilot studies, flexibility in the experimental plan, and extensive scheduling will allow us to proceed with the project at a reasonable pace given the availability of funds allocated to this project.

7. NEXT STEPS

A manuscript related to Aim 1, focused on the survey of modeling approaches used in biotechnology regulatory applications is underway and will be submitted for publication in the next year.

We plan to proceed with the start of the long term and accelerated stability studies in September 2024. The contingency plan to cover identified challenges is being drafted and will be available prior to the start of the main stability study.

Work on the statistical plan and modeling pipeline has begun and our goal is to produce Frequentist and Bayesian models based on 6 month accelerated stability studies by June 2024. We are on schedule to finish the real time stability study in mid-September 2026.

8. REFERENCES

- FDA Guidance: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product - Guidance for Industry, April 2015.
- Campa C et al, Vaccines, 2021

9. APPENDIX A: ABBREVIATIONS

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

ABBREVIATION	DEFINITION
BLA	Biologics License Application
BLI	Bio-Layer Interferometry
BsUFA	Biosimilar User Fee Agreement
CE-SDS	Capillary Electrophoresis Sodium Dodecyl Sulfate
DLS	Dynamic Light Scattering
FDA	Food and Drug Administration
HR-LC MS/MS	High Resolution Liquid Chromatography Tandem Mass Spectrometry
iclEF	Imaged Capillary Isoelectric Focusing
IND	Investigational New Drug application
OPQR	Office of Product Quality Research
SEC-UPLC	Size exclusion chromatography – ultra performance liquid chromatography