U.S. FOOD & DRUG ADMINISTRATION

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

ANNUAL REPORT

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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:	**Model development and verification to evaluate minimum stability data required for biosimilar submissions**
Investigator:	Uriel Ortega-Rodriguez & Mari Lehtimaki
Organization:	FDA/CDER/OPQ/OPQR
Grant No. (if applicable)	N/A
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, and EUAS) in which stability modeling was used to support shelf life of biotechnology drug product was completed in 2024. A manuscript based on the findings from the database search has been completed and is pending formal clearance from CDER-OPQ regulatory stakeholders.	Approximately 30 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 have been drafted into a manuscript titled: *"Current landscape of predictive stability modeling in well characterized biotechnology regulatory submissions"* for publication in 2025. The manuscript is currently undergoing internal clearance by CDER.

[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. 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 would be suitable for the long-term and accelerated/stressed stability studies. Based on the optimized conditions from the pilot studies, we initiated a 2-year long-term stability study in October 2024 along with 6-month long accelerated and stressed stability studies. The 6-month accelerated and stressed stability studies were completed in March of 2025, and a variety of stability indicating attributes which include potency, size and charge variants, site specific degradation events, sub visible particle formation events were measured with a panel of advanced analytics. The data from these studies are being used to establish frequentist kinetic models. The pilot data from 2023-2024 are being used as priors for Bayesian model development.	Several candidates for modeling have been identified from data acquired throughout the 6-month stress and accelerated stability studies. Currently, one of the most promising set of data include a time-dependent increase in acidic charge variants which are coupled to the concomitant loss of the main charge variant over time by Imaged capillary isoelectric focusing (icIEF). The time and temperature-dependent increase of acidic variants was observed for both trastuzumab and insulin lispro products, and these data are currently being used for frequentist modeling, and long-term prediction by our modeling team. Additional data that we have identified as candidates for modeling include: a loss of main peak, coupled with an increase in low molecular weight species from both size exclusion chromatography experiments, and capillary electrophoresis, sodium dodecyl sulfate (CE-SDS) experiments for trastuzumab products, and a linear increase in heavy molecular weight species over time for insulin lispro as measured over time by SEC-UPLC. Additionally, we observed site-specific deamidation events on residue A21 of insulin lispro as measured by HR-UV-LC-MS which was identified as a promising candidate for modeling.	The long-term real time stability arm of the project is on track to be completed in Fall of 2026, and the data acquired during the 6-month stability studies will be fed into the preliminary kinetics models. Our team has already published 2 internal technical reports documenting the progress of accelerated and stressed stability studies at the 1 month mark (FY25-OPQR-D4-002-T), and a second technical report which documents the development of a new mass spectrometry-based method to analytically assess deamidation events of A21 in Insulin Lispro products, and other degradation products, which were determined to be a promising candidate for modeling (FY25-OPQR-D5-026-S). Our team is drafting two additional technical reports documenting the entire 6-month stability studies for both trastuzumab products, and insulin lispro products. Our team has presented the updates for Aim 2 in several formal presentations which include internal meetings with regulatory staff. We plan to present an update on September 18th at the BsUFA interim public forum.

Specific Aim(s)	Progress	Outcomes	Communication Timeline
3. Create predictive models from the data collected using a frequentist and Bayesian approaches.	Most promising data from the 6-month stability study was provided to our modeling team, and models based on the charge profile changes of Trastuzumab are available for the 25°C and 45°C stability data. Model fitting and evaluation for other analytical data are currently in progress. We plan to use the pilot data provided to the modeling team as priors for Bayesian model development.	Models at 25°C and 45°C based on the loss of main charge peaks and an increase of acidic Trastuzumab charge variants are available, and our modeling team is working on long-term predictions based on these models.	The final statistical models will be published in 2027.

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 March of 2025. The findings of the early database search results were communicated in an internal presentation to regulatory staff in the Office of Pharmaceutical Quality Assessment III (OPQA III) in late spring of 2024, and a manuscript summarizing the results of the survey are undergoing internal review and will be submitted for publication late Summer 2025.

Aim 2: Produce kinetic stability data for kinetic modeling.

Pilot stability studies were conducted at real-time, and stressed conditions from November 2023-May 2024 using trastuzumab and insulin lispro to optimize the conditions for size exclusion chromatography (SEC-UPLC), reducing and non-reducing capillary electrophoresis, sodium dodecyl sulfate (rCE-SDS and nrCE-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, 45°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, and to optimize analytical conditions to detect protein degradants. Further optimization of other analytical assays was performed from Spring to Summer in 2024. These analytics include Fc-binding by Bio-layer interferometry (BLI), and dynamic light scattering (DLS) to monitor protein aggregation. Additionally, a new Ultra-High-Performance Liquid Chromatography High Resolution Mass Spectrometry (UHPLC-UV-HRMS) method was developed for analysis of insulin lispro and degradation products throughout the project. Based on the optimized conditions from the pilot studies, we moved forward with 6-month accelerated and stressed stability studies. Two-year long-term stability studies for trastuzumab, insulin lispro and their biosimilars are currently in progress, and will be finished in October 2026. Six month accelerated and stressed stability studies were conducted from October 2024-March 2025. Timepoints consistent with ICH Q5C were used for both the real-time (0, 1, 3, 6, 12 and 24 months), accelerated and stress stability studies (sample collection weekly for 1 month and monthly for 6 months). Throughout the study, CDER staff employed a panel of analytics to generate kinetic data of stability indicating attributes which include measurement of purity, potency, protein aggregation and degradation profiles to track specific degradation pathways to enable the development of improved kinetic models.

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

We plan to use kinetic stability data generated from aim 2 to determine the ability and accuracy of kinetic stability models to predict long term stability of trastuzumab and insulin lispro with minimal data, and to assess the suitability and criticality of using minimal accelerated and stress stability data to estimate the shelf-life of biosimilars. Preliminary model fitting based on the icIEF charge variant data for trastuzumab obtained in the 2023-2024 pilot studies was performed, and our modeling team has created the first models based on changes in the charge profiles of trastuzumabs throughout the 6-month accelerated and stressed stability studies. Other data have been provided to our modeling team, and work is ongoing to fit and develop models for other stability indicating attributes for insulin lispro and trastuzumab.

Research Outcomes

Research Outcomes Aim 1:

Additional database searches for stability modeling used in INDs, EUAs and BLAs were conducted. Thirty examples in which kinetic modeling, or extrapolation of limited stability data were used to support stability of biotechnology drug products were identified in INDs, EUAs and BLAs. Stability modeling was used in various contexts, including in-use stability, in process control strategies, specification setting, new manufacturing site comparability and others. Stability modeling was utilized during various stages of the manufacturing process. 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.

Research Outcomes Aim 2:

Six-month stability studies were performed at accelerated and stressed conditions to generate kinetic data of stability indicating attributes of Insulin lispro and trastuzumab products which may be used for model development, and validation. We have identified promising candidates for use in model development. For insulin lispro, candidate attributes include charge variants, high molecular weight impurities, A21-deamidation, and hydrodynamic radius. The potency of these insulin products at 6 months was significantly affected at 45°C, however, mildly affected at 40°C. Additionally, the hydrodynamic diameter changes of insulin lispro are temperature and time dependent indicating potential for modeling approaches. In contrast, the particle formation seems to follow non-linear kinetics indicating a more complex process behind the aggregation and particle formation. For trastuzumab products, several candidates that are promising for modeling included a shift to acidic charge variants and an increase in low molecular weight fragments occurring in a time and temperature-dependent manner.

Research Outcomes Aim 3: Most promising data from the 6-month stressed and accelerated stability studies were provided to the kinetics modeling team, and preliminary model assessment

is in progress. Models based on the loss of main charge peaks and an increase of acidic trastuzumab charge variants at 25°C and 45°C are available, and our modeling team is working on long-term predictions based on these models.

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 BsUFA Research Priority B: *"Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes."* 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 estimation of shelf-life from limited stability data at the time of submission 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.

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)
Use of modeling to support stability in biotechnology regulatory submissions	Formal Presentation	Office of Pharmaceutical Quality Assessment III (OPQA III) all hands meeting on April 2nd, 2024, Silver Spring MD.	N/A
Use of modeling to support stability in biotechnology regulatory submissions	Formal Presentation	Office of Pharmaceutical Quality Research Division IV all hands meeting, August 28th, 2024	N/A
Use of modeling to support stability in biotechnology regulatory submissions	Formal Presentation	Office of Pharmaceutical Quality Research (OPQR) Lab Advance, Sept 11th, 2024, Saint Louis, MO	N/A
FY25-OPQR-D4-002-T Research update for BsUFA project: Model development and verification to evaluate minimum stability data required for biosimilar submissions.	Internal Technical Report	Report documenting the status of the accelerated and stressed stability studies at 1 month	N/A
FY25-OPQR-D5-026-S Development of an UHPLC-UV-HRMS analytical procedure for the simultaneous evaluation of identity, assay, preservative(s), and degradation products in insulin lispro and its biosimilar for a BsUFA III stability study	Internal Technical Report	Report documenting the development of a novel method for analysis of insulin lispro degradation products for the BsUFA stability modeling project	N/A

Communication and Dissemination Aim 1:

Dr. Uriel Ortega-Rodriguez presented findings from the regulatory database search 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 Aim 1 results to assessors and regulatory leadership. The discussion included specific examples of biotechnology product classes, modeling strategies, stability modeling contexts, and regulatory outcomes.

Planned Communication and Timeline Aim 1:

Dr. Uriel Ortega-Rodriguez and Dr. Mari Lehtimaki have drafted a manuscript titled "Current landscape of predictive stability modeling in well characterized biotechnology regulatory submissions," focusing on regulatory database search findings for stability modeling in biotechnology drug products. The manuscript is currently undergoing internal CDER clearance and will be submitted for peer review by Fall 2025. Aim 1 has been completed.

Communication and Dissemination Aim 2:

Dr. Uriel Ortega-Rodriguez gave a formal presentation at the Office of Pharmaceutical Quality Research (OPQR) Division IV all hands meeting on the progress of the project, with emphasis on the research activities from Aim 2 of the project.

Dr. Uriel Ortega-Rodriguez gave a formal presentation at the OPQR lab advance in Saint Louis, MO on September 11th, 2024. The presentation highlighted the highly collaborative nature of the project, with emphasis on the research activities from Aim 2, which encompasses groups from OPQR divisions III, IV, V and VI.

Two technical reports have been published documenting Aim 2 analytical data:

• FY25-OPQR-D4-002-T: Dr. Uriel Ortega-Rodriguez and Dr. Mari Lehtimaki documented analytical data from 1-month timepoint accelerated and stressed stability studies for the BsUFA project focused on model development and verification to evaluate minimum stability data required for biosimilar submissions.

• FY25-OPQR-D5-026-S: Dr. Jinhui Zhang described development of a new Ultra-High-Performance Liquid Chromatography High Resolution Mass Spectrometry (UHPLC-UV-HRMS)-based method for analyzing insulin lispro and degradation products during stability studies.

Planned Communication and Timeline Aim 2

Two additional technical reports documenting the 6-month stability studies conducted for Aim 2 are undergoing internal review, and will be available to CDER, and the BsUFA III committee by August 2025. One technical report will document the analytical data for trastuzumab products, and the other will document the data from the insulin lispro products.

Dr. Uriel Ortega-Rodriguez, and Dr. Mari Lehtimaki will present at the September 18th BsUFA interim public forum. The focus of the presentation will be the collaborative scientific and regulatory-related activities completed towards Aims 1-3 of the project. Drs. Uriel Ortega-Rodriguez, Mari Lehtimaki, Michelle Stafford and Ashutosh Rao will participate in the discussion panel for the September 18th BsUFA interim public forum.

Planned Communication and Dissemination Aim 3:

Models based on Aim 2 analytical data will be available by the end of 2027. These will be communicated through formal presentations to research and regulatory staff after final model validation with 2-year long-term stability data. A manuscript describing model evaluation and validation is planned for late 2027, led by collaborators in the Office of Translational Sciences (OTS).

Scientific and Technical Challenges

No scientific or technical challenges were reported for this past year.

Next Steps

A manuscript related to aim 1, focused on the survey of modeling approaches used in biotechnology regulatory applications is undergoing internal review and will be submitted for publication in late Summer 2025, once formal CDER clearance has been obtained.

We are preparing for the analytical testing of the 12-month long-term stability samples in mid-October 2025 and the 24-month long-term stability samples in mid-October 2026. Both trastuzumab and insulin lispro product samples will be distributed to the analytical teams and the long-term stability dataset will be updated for preliminary use in modeling and model validation.

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 mid-year 2026. We are on schedule to finish the real time stability study in mid-September 2026.

The statistical plan outlining the production of frequentist models on the most promising analytical outcomes has been established. The frequentist models will be used to develop the Bayesian approaches. The analytical data will be processed into formats compatible with use of R programming and packages. The reaction kinetics of specific degradation pathways are being explored to capture degradation pathways observed by the individual analytics in preparation of applying differential equations to the modeling.

References

1. Food and Drug Administration. (2015, April). Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product: Guidance for industry. U.S. Department of Health and Human Services. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-demonstrating-biosimilarity-therapeutic-protein-product-reference-product
2. Campa, C., Pronce, T., Paludi, M., Weusten, J., Conway, L., Savery, J., Richards, C., & Clénet, D. (2021). Use of Stability Modeling to Support Accelerated Vaccine Development and Supply. Vaccines (Basel), 9(10). https://doi.org/10.3390/vaccines9101114