Modeling for Product-specific Stability: A Regulatory Perspective

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Disclaimers

• The views expressed in this presentation are those of the presenter and do not convey official Health Canada policy.

• The views expressed in this presentation are those of the presenter and are not intended to represent the ICH Q1/Q5C EWG.

• The information in this talk relates to biotherapeutics, specifically monoclonal antibodies.
My background

- Sr. Biologist/Evaluator in the Biotherapeutics Quality Division of the Biologic and Radiopharmaceutical Drugs Directorate (BRDD), 2017

- Heavily involved in the review of COVID biotherapeutics

- As a reviewer, my focus is on adoption and integration of innovative practices and lessons learned from review during the pandemic
Presentation objectives

• Share the regulatory thinking applied to the use of models in product-specific stability predictions

• Detail regulatory concerns and challenges with respect to stability modeling

• Case study with a focus on the regulatory questions and responses

• Outline aspects to consider to work toward adoption and integration of stability models
Why modeling within the stability space?

- Stability studies are routinely cited as a major rate-limiting step in biologic product development
- Support accelerated product development
- Support shelf-life setting in situations with seriously truncated development timelines
- Broader use in setting of specifications, temperature excursions, formulation, comparability assessments
- Ultimate goal – approval of a proposed shelf life that exceeds available product-specific real-time data (D. Kuzman, 2021)
Current landscape for stability modeling

• Generally, not an established practice for biologic products
  – Perception that it is difficult to model biologics owing to their complexity, structure/function relationship, and temperature response
  – ICH guidelines are not understood to facilitate the use of modeling, especially for biologics

• Limited experience with modeling as a component of the stability package

• Extrapolation more common in clinical trial applications (CTAs)
Current landscape for stability modeling - Regulatory

• General and specific lack of familiarity with modeling
  – Types of models
  – Understanding of risk

• Rely on broader regulatory approaches, questions, and critical thinking
  – Approach models like an analytical method
    • Demonstration suitability for the intended purpose
    • Validation and/or verification
Case study – Random slope model

• IgG1 monoclonal antibody with a binding mechanism of action
• Product was granted priority review status based on unmet need
• Random slope model used to predict shelf life in excess of available real-time data
• What was included in the submission:
  – Description of the model
  – Parameters modeled included purity and charge species
  – Predicted a shelf life of 36 months at 2-8 C
  – 15 months of real-time data for drug product stored under long-term conditions
Case study – Random slope model

- What was not included in the submission:
  - Updated stability data was requested and included an OOS for fill volume at 18 months
  - Clear description of model components
  - Goodness of fit assessment was requested
    - 2 parameters had an $R^2 > 0.9$ while 1 parameter had an $R^2 < 0.49$
  - Ongoing verification or validation of the model was requested and not provided
Case study – Random slope model

• Outcome
  – Recommendation regarding shelf life was made based on real-time data and not based on model output
  – *Encouraged sponsor to continue to develop and submit models*

• Lessons learned
  – A pre-submission meeting to discuss the proposed model would have helped to build understanding ahead of the review and would have provided the sponsor with some valuable advanced feedback
  – Goodness of fit and ongoing verification are essential and should be addressed in the initial submission
Regulatory concerns

• Model is not suitable for the intended purpose
• Inaccurate predictions
• OOS results within predicted shelf-life
  – Significant regulatory implications
• OOS for parameter not included in the model
  – Fill volume/weight, particles (V and SV), appearance, protein content
• Appropriateness of the data included in the model
  – Justification needs to be provided and support the selection of input data
Prior knowledge

- Product-specific prior knowledge
  - Use of product-specific knowledge is well established
  - Development data
  - Advanced kinetic modeling (Huelsmeyer, 2023; Kuzman, 2021)

- Prior knowledge from analogous molecules
  - Less well established
  - Justifications to support use of prior knowledge from analogous molecules
    - Demonstration of suitability
How much prior knowledge is needed?

• Product-specific prior knowledge
  – Demonstration of comparability throughout development
• Prior knowledge from analogous-molecules
  – Justification of suitability
    • Structure/function
    • Mechanism
    • Stability data – degradation profile and kinetics
  – Confirmation that sufficient data has been included but not so much that your product is swamped
• Too early to provide any definitive guidance on how much is enough and how much is too much
Going Forward
Things to consider

- For modeling to be fully embraced in a regulatory context:
  - Develop understanding and build confidence
  - Logical progression
  - Risk-mitigation strategies
- Continue to file submissions that include a modeling component
- Meet with regulators before filing
- Workshops/Training Sessions
  - Joint industry and regulatory training sessions
- Publish papers
- Establish best practices for modeling for biologics
Best practices for modeling

- Purpose of model
- Selection of model
- Parameters to be modeled
- Input data
- Output result
- Goodness of fit
- Ongoing verification
Building model capacity through development

• Introduce model with clinical material and in CTAs
  – Setting stability specifications
  – Setting product shelf-life
  – Meet with regulators
• Build model as product progresses through clinical trials and into market authorization application
• Continue to verify model as more data becomes available
• Use model as supporting stability
• Discuss at a pre-submission meeting prior to filing for market authorization
Health Canada

• We welcome regulatory questions via pre-CTA meetings or pre-NDS meetings in-person or via teleconference
• Contact Office of Regulatory Affairs

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