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Modeling for Product-specific Stability : A Regulatory Perspective

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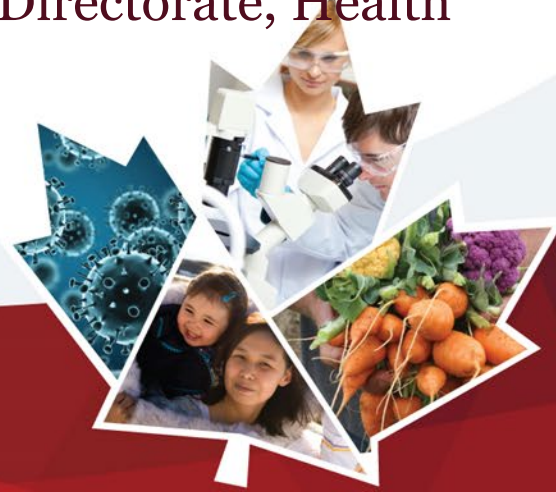

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Disclaimers

- 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

Office of Regulatory Affairs
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