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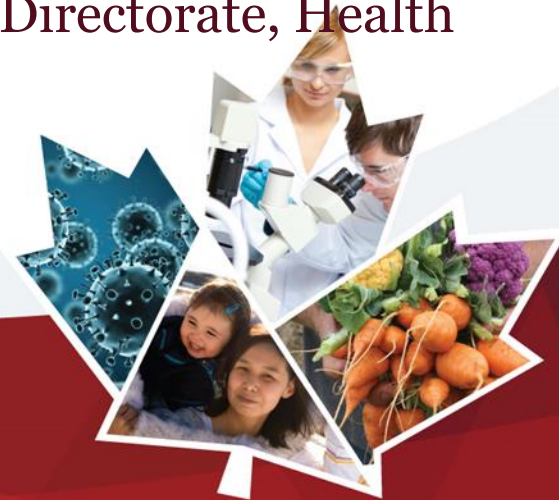
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Modeling for Product-specific Stability : A Regulatory Perspective

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My background

- Sr. Biologist/Evaluator in the Biotherapeutics Quality Division of the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) of Health Canada
- Health Canada's Topic Lead on the ICH Q1/Q5C EWG
- As a reviewer, my focus is on adoption and integration of innovative review practices and lessons learned from review during the pandemic
- Initially very skeptical about the utility of model for product stability

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

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

Current landscape for stability modeling

- Large gap between industry and regulatory experience
- 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
- 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 – Advanced Kinetic Model/Bayesian/Random Slope
 - 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
- Risk-assessment and Risk-mitigation
 - What are the risks and how best to mitigate those risk

Risk and stability modeling

- Often only stability indicating parameters are modeled
 - Purity, Charge Species, High Molecular Weight Species
 - Potency can be difficult to model given method variability
- What happens in the event of an Out-of-Specification (OOS)
 - For modeled parameter – model invalidated?
 - For non-modeled parameter – visible/sub-visible particles, sterility
- Mitigation strategies
 - Robust PQS to handle OOS/Deviations/Investigation
 - Ongoing verification with real-time data

Regulatory concerns

- Model is not suitable for the intended purpose
 - Understanding of why model parameters were selected
- Appropriateness of the data included in the model
 - Justification needs to be provided and support the selection of input data
 - Product-specific prior knowledge
 - Use of product-specific knowledge is well established
 - Development data
 - Advanced kinetic modeling (*Huelsmeyer, 2023; Kuzman, 2021*)
- Ongoing verification of the model

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

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
- Risk-assessment and risk mitigation strategies
- 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

Conclusions

- Growing evidence of the suitability of stability modeling for some biologics and may facilitate accelerated development under some circumstances
- More regulatory experience is needed to grow integration of modeling within a stability program
- Risks inherent to the application of stability modeling need to be identified and mitigation strategies need to be proposed
- Stability modeling is best applied as a component of a comprehensive stability program

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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Thank You

- Thank you to CASSS for supporting my participation
- Thank you to my colleagues for supporting the presentation



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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