Predictive Stability Modelling : Health Canada's Risk Framework and Regulatory Readiness

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

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Overview

- ICH Q1 Draft Guideline
  - Objective
  - Reflections
  - Risk Frameworks
- Predictive Stability Modelling within a Risk Framework
  - Overview
  - Case Study
- Regulatory Readiness – Predictive Stability Modelling Goes Mainstream
  - Regulators and Industry

Objectives of the revisions to ICH Q1

- Revision of the ICH Stability Guidelines Q1A-F, Q5C was recommended to:
  - Streamline the series by combining the various guidelines into a single guideline focused on core stability principles
  - Promote harmonised interpretation
  - Inclusion of new topics, tools, products
  - Address additional technical issues, stability strategies, and innovative tools that strengthen the application of risk management
  - Provide guidance on enhanced approaches (e.g., stability modelling)

Reflections on the Q1 Revisions

- What the revisions accomplish:
  - Establishes core stability principles across product types
    - Committed to embracing the sameness where it exists and the difference where it is necessary
  - Reflects the current state of biologicals
  - Leverages experience gained since the drafting of Q5C
  - Contributes to global harmonization on stability expectations
  - Provides a framework for ***standard***, ***alternative***, and ***enhanced*** approaches

Risk Frameworks in the Q1 Guideline

Risk Frameworks with the Q1 Guideline

'Alternative science- and risk-based approaches where justified'

- Varying degree of risk with some of the new concepts, tools, approaches
  - In-use stability
    - well established practice where sponsors and reviewers have significant experience with the expectations for setting an in-use period and storage conditions
  - Extrapolation for frozen drug substance
    - Significant experience with extrapolation for clinical material
  - Re-test period for frozen drug substance
    - Unfamiliar concept for biologicals
  - **Stability modelling** (shelf life setting, comparability/similarity assessments, temperature excursions, formulation studies)
    - Limited regulatory experience and understanding of risk

Risk Framework with the Q1 Guideline

- Risk framework includes the following elements:
  - Proposal for an alternative or enhanced approach
  - Justification of approach
  - Assessment of risk
  - Risk mitigation strategy
- The rigour of the framework is proportional to risk and understanding
  - Stability modelling as supportive data
  - Stability modelling to set a shelf life beyond available real-time data
  - Application to of stability modelling to drug substance v. drug product

Risk Framework for Stability Modelling

- Justification for application of stability modelling
- Elements to consider
  - Model choice
  - Justification for selection of quality attributes for inclusion/exclusion
  - Selection of data and parameters
  - Evaluation of data
  - Model validation
  - Output and Proposal
    - Model prediction for duration within specifications v. proposed shelf-life
  - Model verification (e.g., ongoing verification with real-time data)
  - Risk management (e.g., managing OOS)

Stability Modelling Case Study – AKM

- Phase 2 CTA application for a standard mAb with a binding mechanism of action
- Stability data provided: 3 months long-term, 3 months accelerated for DS and DP
- Advanced Kinetic Modeling (AKM) used to set shelf life for drug product
  - Model description and justificaiton for the selection of attributes were provided
  - Model parameters (e.g., temperatures, time period, and goodness of fit assessment) were identified
  - All parameters within specification >60 months
- Proposed drug product shelf life of **18 months** when stored at 2-8°C

Stability Modelling Case Study – AKM (cont'd)

- AKM package did not included the following elements:
  - Justification of the model parameters (e.g., temperatures, time period, and goodness of fit)
  - Justification for the appropriateness of the model selection
  - Proposal for continuous verification with long-term data
  - Proposal for handling OOS for modelled and non-modelled parameters
  - Proposed shelf life extension protocol

- Outcome
  - Updated stability data was provided and was used to set shelf life of 18 months

Stability Modelling Case Study – AKM (cont'd)

- Main highlights
  - Provide a justification for using an alternative approach
  - Provide all available stability data in the initial submission
  - Provide a comprehensive package to support the application of stability modeling
  - Models when used as supportive data are inherently lower risk
  - Need for comprehensive training to build understanding and to establish consistent expectations

Predictive Stability Modeling and Regulatory Readiness

How modeling moves into the mainstream

Regulatory Readiness

- The goal is to build internal harmonization and establish consensus expectations
  - Address potential application of predictive stability modelling for myriad uses
  - Cross-directorate team dedicated to increasing capacity predictive stability modelling
    - Shelf-life, comparability/similarity assessment, risk files
  - Delivering training and information sessions
    - Internal training, ICH training
  - Engaging in-house Biostats unit to provide direction on stability modeling
    - Preparing internal guidance for Quality reviewers
- Building international harmonization through our partners
  - Training opportunities with ACCESS partners
  - Building capacity together

Regulatory Readiness, for Industry

- Some things to consider:
  - For alternative and enhanced strategies to be successful, they need to be justified and they need to be understandable
  - Continue to file submissions that include a modeling component
  - Coordinate through your industry group to publish papers and establish best practices
  - Participate in joint Industry/Regulator training sessions and workshops
  - When you are introducing something novel, like a predictive stability modelling approach, provide a comprehensive justification
  - Consider scheduling a pre-submission meeting to discuss and receive advanced feedback on new strategies

Thank you

Pre-submission Meetings

- We welcome regulatory questions via pre-CTA meetings or pre-NDS/SNDS meetings
  - Written feedback can be provided on a meeting package
  - Meetings are offered in-person or via teleconference
- To request a pre-submission meeting, contact Office of Regulatory Affairs

  Email: **BRDD.ORA@hc-sc.gc.ca**