ICH Q1 Guideline Revisions: Risk Frameworks and Regulatory Readiness

Paula Russell, PhD
Sr. Quality Reviewer
BQD, BRDD, Health Canada

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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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Background on the Q1 Revision

- 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

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
  - Introduces tools to address modern challenges (e.g., drug shortages)
  - Provides a framework for standard and alternative 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 modeling for shelf life setting and extension
    - Limited regulatory experience and understanding of risk

Risk Framework with the Q1 Guideline

- Risk framework includes the following elements:
  - Proposal for an alternative approach
  - Justification of approach
  - Assessment of risk
  - Risk mitigation strategy
- The rigour of the framework is proportional to risk
  - In-use stability: justifying alternative approach (1 batch) v. standard approach (2 batches)
  - Stability model to set a shelf life beyond available real-time data

Risk Framework for Stability Modeling

- Justification for application of stability modeling
- Elements to consider
  - Model choice
  - Selection of quality attributes for inclusion
  - Selection of data and parameters
  - Evaluation of data
  - Output
  - Model verification
  - Risk management

Stability Modeling Case Study – AKM

- Phase 2 CTA application for a standard mAb with a binding mechanism of action
- Advanced Kinetic Modeling (AKM) used to set shelf life for drug product
- Proposed drug product shelf life of **18 months** when stored at 2-8°C
- No additional factors or considerations

Stability Modeling Case Study – AKM (cont'd)

- The following information was provided in the submission
  - Drug product stability data
    - Toxicology batch: 3 months under long-term (2-8°C) and 3 months under accelerated conditions
    - Clinical batch: t(0) under long-term (2-8°C)
  - Drug substance stability data
    - Clinical batch: 3 months under long-term (-60°C) and 3 months under accelerated conditions (2-8°C)
- Accelerated Predictive Stability - AKM

Stability Modeling Case Study – AKM (cont'd)

- AKM package included the following elements:
  - Model description
  - Assessment approach
    - AKM training/evaluation, validation, prediction, verification
  - Selection of attributes
    - Purity (CE-SDS and SEC), Charge heterogeneity, and Potency
    - Risk assessment provided to support attributes not included in the model (e.g., colour, sterility…)
  - Model parameters (e.g., temperatures, time period, and goodness of fit assessment)
  - All parameters within specification >60 months
  - Proposed a shelf life of 18 months

Stability Modeling 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 modeled and non-modeled parameters
  - Proposed shelf life extension protocol

Stability Modeling Case Study – AKM (cont'd)

- Outcome
  - Comprehensive request for additional information
  - Indicated that the 30 day review period for CTAs did not provide adequate time to review the model
  - Proposed drug product shelf life of 18 months was established based on 9 months of data

Stability Modeling 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

Regulatory Readiness at Health Canada

Regulatory Readiness

- The goal is to build internal harmonization and establish consensus expectations
  - Delivering sessions with more planned as the guideline advances
    - Internal training, ICH training
  - Engaging in-house Biostats unit to provide direction on stability modeling
    - Preparing internal guidance for Quality reviewers
  - Engaging other relevant parties within Health Canada
    - ROEB (GMP Inspections), Veterinary Drugs, Natural Health Products
- Building international harmonization through our partners
  - Training opportunities with ACCESS partners

Regulatory Readiness, for Industry

- Some things to consider:
  - For alternative 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 re-test period for a biological or a predictive stability approach, provide a comprehensive justification
  - Consider scheduling a pre-submission meeting to discuss and receive advanced feedback on new strategies

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**

Thank you