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In-use Stability Study Design: A Regulatory Perspective

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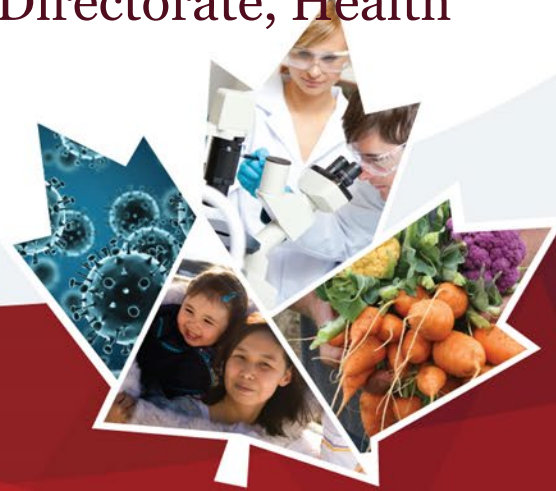

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Disclaimers

- 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

Presentation objectives

- Provide a regulatory perspective on in-use stability study design
- Core/basic elements of a foundational in-use stability study
- Risk-based approached to in-use stability study design

Current guidance on in-use stability studies

- In-use studies are not currently covered by the existing ICH Q1/Q5C stability guidelines
- Guidance on in-use studies largely exists in a collection of regional guidance documents
- WHO Guideline – Annex 10 – *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*
- ICH Q1/Q5C revision proposes to include guidance on in-use stability studies

What is in-use?

- In-use is generally defined as the conditions that mimic the **intended** use of the product following breach of the primary container closure system, as detailed in the instructions, and includes:
  - Preparation, handling, and administration after breaching
  - Proposed commercial components/materials demonstrated to be compatible with the drug product

- **In-use period** is defined as the duration and conditions under which product quality is maintained from breaching through preparation, handling, and administration

When are in-use studies required?

- In-use studies are generally required for:
  - Single-dose products requiring handling or preparation prior to administration
    - Dilution, reconstitution, co-mixing
    - E.g. Lyophilized products for injection or solutions for infusion
  - Multi-dose products
    - Containers or drug-device combinations
    - E.g. Multi-dose vials – container closure system can withstand repeated insertions and withdrawals

In-use study : Protocol design

- Protocol should mimic the intended use of the drug product, or a worst-case scenario, and should demonstrated product quality is maintained throughout the proposed in-use period

- Protocol should cover the conditions and duration of the in-use period and includes
  - Design elements
  - Selection of batches, attributes, and analytical procedures and acceptance criteria

In-use study design elements

- *Duration* : at minimum the study should cover the entire in-use period from breach of the primary container through to the end of administration
- *Withdrawal Frequency* : at minimum should mimic the intended use of the product
  - Nebulizer for twice daily administration : samples withdrawn twice daily
  - DDC for daily injection : samples withdrawn daily
- *Testing Frequency* : at minimum samples should be tested at the beginning and end of the proposed in-use period
- *Materials* : the proposed commercial container closure system/components previously demonstrated to be compatible

Selection of batches

- Generally, a minimum of two batches of commercial drug product is recommended based on the lower risk nature of in-use stability studies
- Generally, at least one batch should be ‘aged’
  - ‘Aged’ is defined as being within 25% of the proposed EOSL
    - 18 months for a shelf life of 24 months
  - This represents a worst-case scenario

- Batches should be provided in the intended commercial container closure system and prepared according the instructions-for-use
  - IV administration : drug product prepared in the proposed administration sets (e.g. bags, tubing, filter, catheter)
  - DDCs : drug product in the primary container closure should be integrated in the device (e.g. cartridge in an autoinjector)

Selection of Attributes

- Attributes should be selected to demonstrate the physical, chemical, and microbial stability of the product through the duration of the in-use period
- Attributes (CQAs) most likely to change over the in-use period should be consider for inclusion in the in-use study
- Selection of CQAs should be based on a risk-based approach
- The following attributes are typically included in an in-use study for a biologic:
  - Appearance, protein content, particles (visible/sub-visible), aggregates, impurities, and potency
  - PET/AET and a microbial enumeration method

Selection of analytical procedures and acceptance criteria

- Where applicable, analytical procedures should be the same as those used in the commercial stability specifications and should be validated
  - Exceptions to validated analytical procedures should be justified
    - E.g. monitoring polysorbate
- Potency is not always a stability-indicating parameter
    - May not be feasible at low concentrations/high dilutions
    - Justification for the use of a surrogate

- Acceptance criteria should be proposed, justified, and should not exceed the limits of the of the stability specification, where applicable

Risk-based approaches

- Risk-based approaches are well suited to a number of aspects of compatibility and in-use study designs
  - Leverage product and/or platform knowledge

- Strong justification will need to be provided to support a risk-based approach
  - What is the risk, how is it mitigated?

Risk-based approaches

- Selection of batches
  - General requirement for two batches of commercial drug product with one ‘aged’ sample
  - Risk-based approach:
    - Justification for not including an ‘aged’ batch
    - Justification for one batch
    - Justification for clinical/developmental batches
- Selection of analytical procedures and acceptance criteria
  - Risk-based approach
    - Justification for not including specific attributes (Potency, bioburden)

Conclusions

- In-use studies are needed to support an in-use period
- In-use studies should be designed to demonstrate physical, chemical, and microbial stability of the product over the proposed in-use period
- In-use studies should be designed to mimic the intended use of the product
- Risk-based approaches may be applied to in-use study design, where appropriately justified

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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Thank You

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