Norwegian Medical
Products Agency

ICH Q1 Annex 3

Stability of Advanced Therapy Medicinal Products

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Although the ICH Q1 stability testing consensus technical document has been published, it should be noted that the guideline is still in Draft status and is expected to change based on comments received during the ICH public consultation process.

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Draft ICH Q1 Document

Structured to support stability considerations across product development and the product lifecycle, covering core elements of stability assessment. It introduces additional topics (e.g. in-use stability, short-term stability, processing and holding times) while enabling science- and risk-based approaches where justified.

- Outlines a standard approach to stability study design by describing general principles and strategies for assessing stability-related topics
    - Establishes common stability principles for drug substances and drug products, including biological products, reflecting current experience
- Supports global harmonisation while providing flexible tools and frameworks to address standard, alternative, and emerging challenges
    - Enables science- and risk-based approaches where justified
    - Encourages use of enhanced product and process knowledge

Annex 3

- Annex 3 provides ATMP-specific stability recommendations in support of core ICH Q1
  - It is not a stand-alone guideline, where core ICH Q1 remains the basis for general stability principles
- Where Annex 3 is silent, relevant core guideline principles apply
- ATMP stability strategy should be product- and process-specific

Scope

- Applies, as appropriate, to stability considerations for:
  - drug substance
  - intermediates
  - drug product
  - relevant starting materials

Stability study design: general principles

- Study design should be based on product and process knowledge
- Identify stability-indicating CQAs for the specific product type and manufacturing process
- Consider the full pathway: starting materials → processing → storage → shipping → in-use
- Risk-based approaches may be used where appropriate
  - Where used, risk assessment and justification should be provided
- For limited material / patient-specific ATMPs, justified adaptation of testing frequency may be acceptable

Analytical strategy

- Analytical procedures should support stability-indicating CQAs
  - Potency is a critical stability CQA, may require multiple complementary assays
- Assay ability to detect degraded / subpotent product should be confirmed
- Product-related impurities should be assessed, as relevant
- Acceptance criteria should be justified using preclinical and clinical batch data
  - Shelf-life specifications may differ from release specifications, where justified

Study conditions

- Real-time studies under intended storage conditions are expected
- In-use stability should be addressed where relevant
- Accelerated and stress studies are recommended
  - Used to understand degradation profile, temperature deviations, and assay performance
  - May not directly support shelf-life assignment
- Conditions should reflect product/process knowledge, risk, and worst-case handling/storage
- For cell-based ATMPs, shipping studies should assess physical forces

Batches

- Three primary stability batches for the primary stability study generally recommended
  - Alternative numbers may be justified based on risk
  - Clinical batches may be acceptable if comparable to production batches
  - Patient-derived material is preferred for patient-specific cellular ATMPs
- Bracketing may be used where material is limited
- Consider cumulative storage time, hold times, and frozen intermediates, as relevant
- Starting materials and vectors may affect stability and should be considered within the overall stability programme

Shelf life

- Shelf life should generally be based on long-term stability data
- Developmental data, prior knowledge, and analogous-product information may support an initial claim
  - These do not replace product-specific real-time evidence
- Use of prior knowledge should be discussed with regulators, as appropriate
- At least 6 months of stability data should be included at submission
  - If proposed shelf life is <6 months, data should cover the intended shelf life

Summary

- A scientifically justified adaptation of the standard ICH Q1 stability approach may be acceptable, provided the alternative approach gives adequate assurance of stability
- Any such adaptation should be supported by product and process knowledge, risk assessment, and relevant data
- This is particularly important for ATMPs with limited material availability, patient-specific manufacturing, or other product-specific constraints

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