THE CASE FOR REVISION TO THE ICH STABILITY GUIDELINES:
AN INDUSTRY PERSPECTIVE

CASSS-AT Europe
Regulatory Trends Session; 24 May 2022

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A proposal to update and modernise the Stability guidelines has been accepted by the ICH Management Committee and recommended to the Assembly (ICH SOP section 2.3, Revision Procedure):

- **June 2021**: The Assembly endorsed the proposal on *Stability Testing Guideline (ICH Q1)* – Targeted revisions and additional issues in the ICH Q1 series/Q5C, with an informal WG to be established with a delayed start ..... A Concept Paper outline will be provided for Assembly endorsement electronically in the June 2021 timeframe

- **November 2021**: Targeted revisions and additional issues in the ICH Q1 series/Q5C: start date in June 2022, when the ICH Secretariat will send the call to ICH Members and Observers for nominations of experts.

- **24-25 May 2022**: .....
PROPOSED MODERNISATION OF THE ICH QUALITY GUIDELINES

There are 7 separate ICH Stability guidelines:

- Q1A as a parent guideline, from 1993 with 2 revisions and multiple supplements
- Q1A has elements for biologics and refers to Q5C for “further guidance”
- ICH Q1 is a tier 1 guideline: implementation as a condition for ICH.

Common Technical Document (CTD)
(ICH M4Q, eCTD: ICH M8)

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Updates in progress: Updates to come

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- M4Q Q-CTD Structure of the Quality Submission
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System
- Q12 Life Cycle Management
- Q13 Continuous Manufacturing

Paradigms

- Biologics
  - Q5B Cellular Expression of Recombinant Protein
  - Q5D Cell Substrates
  - Q5E Comparability
- Impurities
  - Q3A Drug Substance
  - Q3B Drug Product
  - Q3C Residual Solvents
  - Q3D Elemental Impurities
  - Q5A Viral Safety
  - Q3E Extractables & Leachables
  - M7 Mutagenic Impurities
- Analytics
  - Q6A Specification for Drug Substance & Drug Product
  - Q6B Specification Biological / Biotech
  - Q1A New Drug Substances and Products
  - Q14 Analytical Life Cycle Management
  - Q2 Validation of Analytical Procedures
  - M9 Biowaivers Classification
  - Q4B Pharmaceutical Harmonisation
- Stability
  - Q1C New Dosage Forms
  - Q1B Photostability Testing
  - Q1D Bracketing & Matricing Designs
  - Q1F Climatic Zones III and IV (WHO)
- GMP
  - Q7 GMP for APIs

There are 7 separate ICH Stability guidelines
FIVE STEP ICH PROCESS TO ACHIEVE A HARMONISED GUIDELINE
(APPLIES TO NEW GUIDELINES AND REVISIONS)

Step 1: Concept Paper
- Consensus Building
- Develop draft guidance
- Sign-off by Industry & Regulators

Step 2: Draft guideline adopted

Step 3: Public Consultation
- Endorsement by ICH assembly and Topic leads
- Sign-off by Regulators

Step 4: Adoption of final guideline (or revision)
- Adopted by Regulators
- Sign-off by Regulatory Topic leads

Step 5: Implementation by Regulators

ABOUT THE EFPIA STABILITY ICH SUPPORT TEAM

- **30** Members
- **18** Companies
- **11** Small molecule SMEs
- **16** Biologic SMEs
- **4** ATMP / ADC SMEs
PROBLEM STATEMENT

- Update to align with more recent QbD and risk management ICH guidelines: Q8 (pharma dev), Q9 (risk management), Q10 (PQS) and Q11 (DS development & manufacture)

- Risk-based approaches to accelerate CMC are not described, e.g. modelling, prior knowledge

- Guidance considered as too prescriptive and interpretations too narrow - e.g. batches, protocol

- Confusion on elements of the Q1 series that apply to biologicals

- Guidance for newer therapeutic modalities is lacking

- Identified gaps in current guidance, include:
  - In-use stability
  - Short-term end user stability
  - Integral drug-device combination (iDDC) products
  - Integrated, end-to-end stability
SOME PROPOSALS FROM INDUSTRY
Transfer most content from Q1A - E, Q5C, and potentially Q1F & WHO guideline into a single Q1 guideline with addenda / annexes

- Experience in manufacturing biologicals, our scientific understanding of the products and analytical technology has increased vastly over the past 20 years
- **Guideline of stability concepts and principles** that emphasises the ‘What’ and ‘When’ rather than on the ‘How’ – *aligns to more recent guidelines*
- Remove ambiguity & uncertainty related to interpretation & application – *see Problem Statement*
- Harmonise between therapeutic modalities - small molecules, biologic, vaccines, oligonucleotides, cell-based therapies, gene therapy – *general principles and concepts for Stability testing & evaluation should apply to all.*
- **Annexes** for specific aspects relating to a particular modality and **Appendices** for examples – *see ICH Q8*

There is now less need to distinguish between therapeutic Modalities
PROPOSED SCOPE

• small, chemically synthesised active pharmaceutical ingredient (API).
• well-characterised proteins and polypeptides, which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology,
• well-characterised proteins and polypeptides conjugated to a chemically synthesised moiety,
• well-characterised cell-based substances isolated from body tissues and may be modified,
• viral vectors, for example oncolytic viruses and vectors used for gene therapy and vaccines,
• Integral drug-device combination (iDDC) products and the medicinal product component of co-packaged drug-device products,
• and their associated drug products.

may apply to conventional vaccines, antibiotics, vitamins and newer pharmaceutical modalities.
Enhanced product and process understanding (QbD):

- **Stability profile modelling tools:**
  - Kinetic modelling
    - ASAP
    - Arrhenius
    - Advanced kinetic analysis
  - Prior knowledge

- **Science & risk-based approach to:**
  - Number of batches – proportionate to risk, representative
  - Stability tests – focus on stability-indicating tests; shelf-life limiting
  - Testing frequency – lean/smart approach to testing

- **Greater use of prior knowledge**
  - Earlier representative development batches
  - Stability knowledge from ‘like-molecules’ (structure, stability profile etc)
• An integrated (end-to-end), holistic, approach to stability from drug substance to finished drug product including end-user storage and handling

• Ensure guidance is suitable for anticipated developments in:
  o Digitalisation & automation
  o Analytical tools (e.g. multi-attribute methods)
  o Statistical analyses
  o CTD content changes (ongoing ICH M4Q revision)

• Harmonisation of expectations for lifecycle changes
SUMMARY OF BENEFITS TO STAKEHOLDERS

- Products to patients faster with adequate assurance of stability and reduced ‘scrap’
- Supports innovation and use of new stability testing tools including modelling
- Increased harmonisation of expectation and efficiency of review
  - Better structured dossiers, easier to review by agency
  - Less jurisdiction-specific requirements
  - Better understanding of agency/inspection expectations
- Consistent expectation and incorporation of modern science & risk-based approaches that reduce redundancy and non-value-added stability testing
ACKNOWLEDGEMENTS

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