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SCIENCE MEDICINES HEALTH

ICH Q2(R2) (Validation of Analytical Procedures) and ICH Q14 (Analytical Procedure Development):

Status Update, Key Concepts and Regulatory Perspective

CASSS Summer CMC Strategy Forum

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Disclaimer

The opinions expressed are my own and not necessarily those of the EU regulatory network or other ICH Q2(R2)/Q14 Expert Working Group members.

Overview

- Background and objectives – Q2 and Q14
- Relationship to other guidelines
- Timelines
- Guidance contents
- Key concepts

Background (Q2)

- ICH Q2(R1) was developed a long time ago (came into force in 1995).
- Primary focus is chromatographic techniques.
- New techniques developed (or applied) in the meantime:
  - Methods for testing biological products (CBPAs, quant. PCR etc.)
  - Hyphenated techniques (GC-MS, LC-MS etc.)
  - Methods requiring multivariate statistical analyses (NIR, Raman etc.)
- Not always straightforward to apply Q2 principles

Objectives ICH Q2(R1) Revision

- Provide a general framework for the principles of analytical procedure validation applicable to a wider range of techniques.
- Validation principles that cover analytical use of spectroscopic or spectrometric data (e.g., NIR, Raman, NMR or MS) some of which often require multivariate statistical analyses.
- Validation principles for techniques for analysis of biological products.
- Generalise but maintain familiarity/continuity with Q2(R1)
- Include new concepts as appropriate

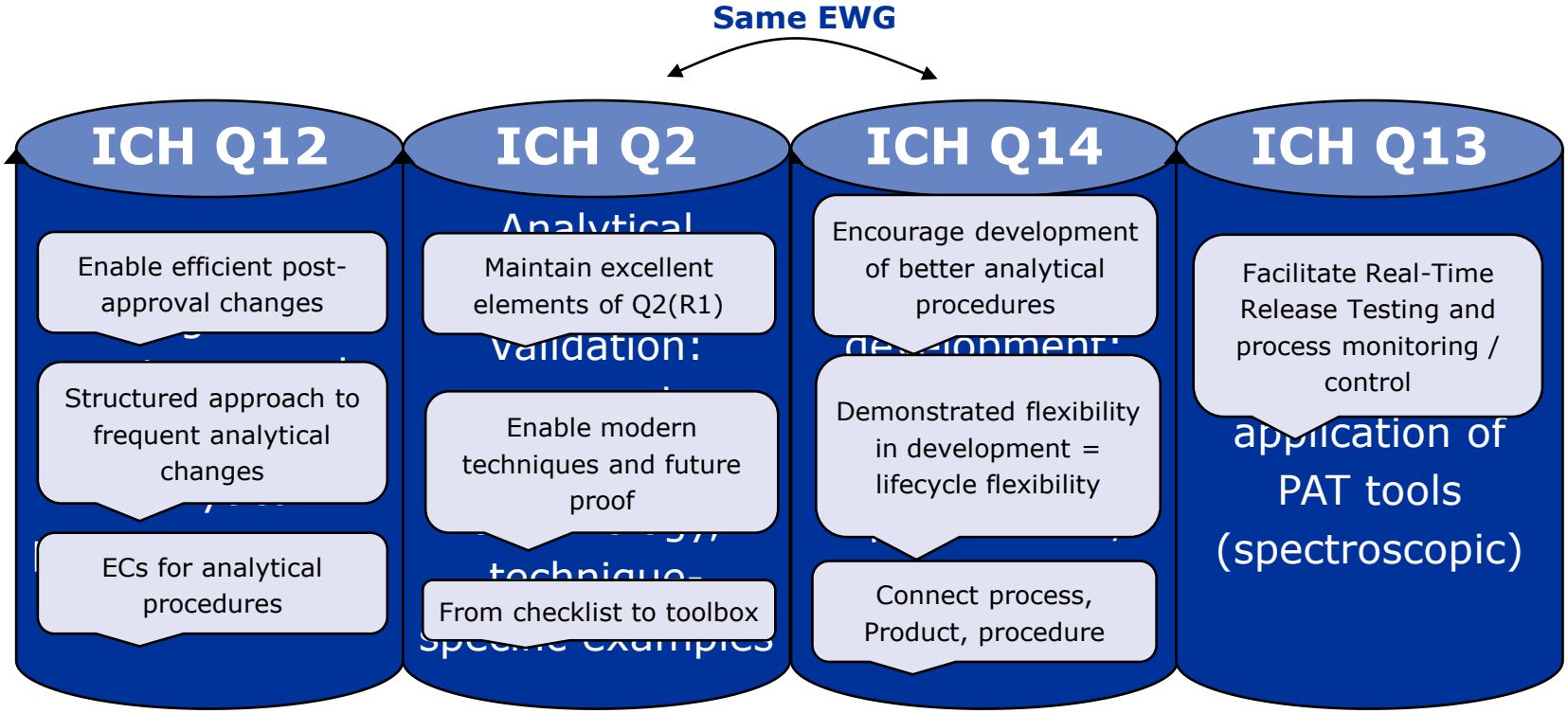
Background (Q14)

- No ICH guidance on Analytical Procedure Development:
  - Validation results presented in the absence of development data.
  - Makes regulatory communication ineffective especially when non-conventional (e.g. RTRT) analytical procedures are employed.
  - Reduced opportunity to present scientific basis for *flexible regulatory approaches* to post-approval changes to APs.
- Current traditional/minimal should still be acceptable:
  - No need to submit or assess data for analytical procedures developed using "minimal approach."
- However, any flexibility needs to be justified by demonstrated understanding – CTD section for such data should it be submitted.
- Ensure compatibility with existing regional regulatory frameworks.

Objectives ICH Q14

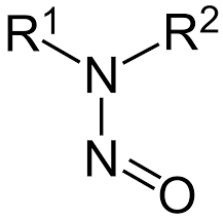
- Harmonise the scientific approaches to analytical procedure development, and provide the principles relating to the dossier description.
- Improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures.
- Complement (and compatibility with) existing and prospective ICH guidance.

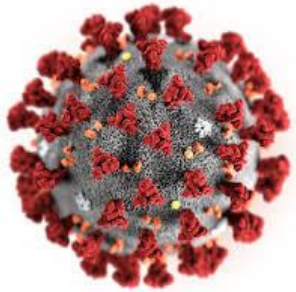
Multiple Related Guidelines for Analytical Procedures



Timelines

- Original Plan:
  - Start – November 2018
  - May 2020 – step 2, public comments
- Revised plan: December 2021 – step 2





ICH Q2 Revision - Contents

Main guideline text:

- Updated and generalised compared to original – similar structure
- Some topics moved to Q14 (system suitability test and robustness testing)
- Table from original Q2 (performance characteristics) retained and updated
- Included text on validating multi-variate procedures
- Included guidance on combined approaches for accuracy/precision
  - Total analytical error
  - Target measurement uncertainty

ICH Q2 Revision – Annex 2

Illustrative examples of validation approaches for various techniques:

- Quanititative separation techniques (HPLC, GC, CE)
- Separation techniques with relative area quantitation (e.g. charge variants)
- Elemental impurities (ICP-OES or ICP-MS)
- Dissolution
- Quantitative NMR
- Binding assay for potency (e.g. ELISA)
- Cell-based assay for potency
- Quantitative PCR (impurities)
- Particle size measurement
- NIRS
- Quantitative LCMS

Biological techniques included following survey of constituents - BWP members in EU

ICH Q12 Tools and Enablers – Applicable to ICH Q14

Applicability to analytical methods (to be expanded in Q14):

- Risk-based variations framework
- Established conditions (ECs)
  - Chapter 3.2.3.2 and Annex 1C
- Post-approval change management protocols (PACMPs)
- Product lifecycle management document (PLCM)
- Structured approach for frequent CMC changes
  - Annex II – frequent analytical procedure changes
  - Not applicable to multivariate and some biological methods
- Examples in annexes and future training material

Development Approach and Lifecycle Opportunities

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Development Approach	Outcome
Univariate investigation of parameters and other factors. Robustness study looks at likely variability during routine use.	Extensive analytical procedure description including set-points.

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Structured (enhanced) approach to development - prior knowledge, risk assessment, demonstrated understanding of impact of parameters and other factors on procedure performance.	Identification of more appropriate set of ECs to ensure procedure performance. Reporting category linked to risk and hazard – could be fewer ECs.

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Performance criteria fixed: requirements for performance characteristics fixed prospectively to provide an "anchor" for lifecycle changes.	Potentially reduced reporting categories, e.g. by inclusion of requirements in a PACMP.

Robustness vs. Method Operable Design Region (MODR)

- Robustness: evaluation of the analytical procedure's suitability within the intended operational environment - should be considered during development
  - Consider noise and variable parameters
  - Investigate within likely range of inherent operational variability
- MODR: a combination of analytical procedure parameter ranges within which the analytical procedure performance criteria are fulfilled and the quality of the measured result is assured.
  - Deliberate investigation of parameters wider than operational variability (*cf* PARs)
  - Intent is operational flexibility – changes within approved ranges managed in PQS
  - Validation requirements can vary on a case by case basis

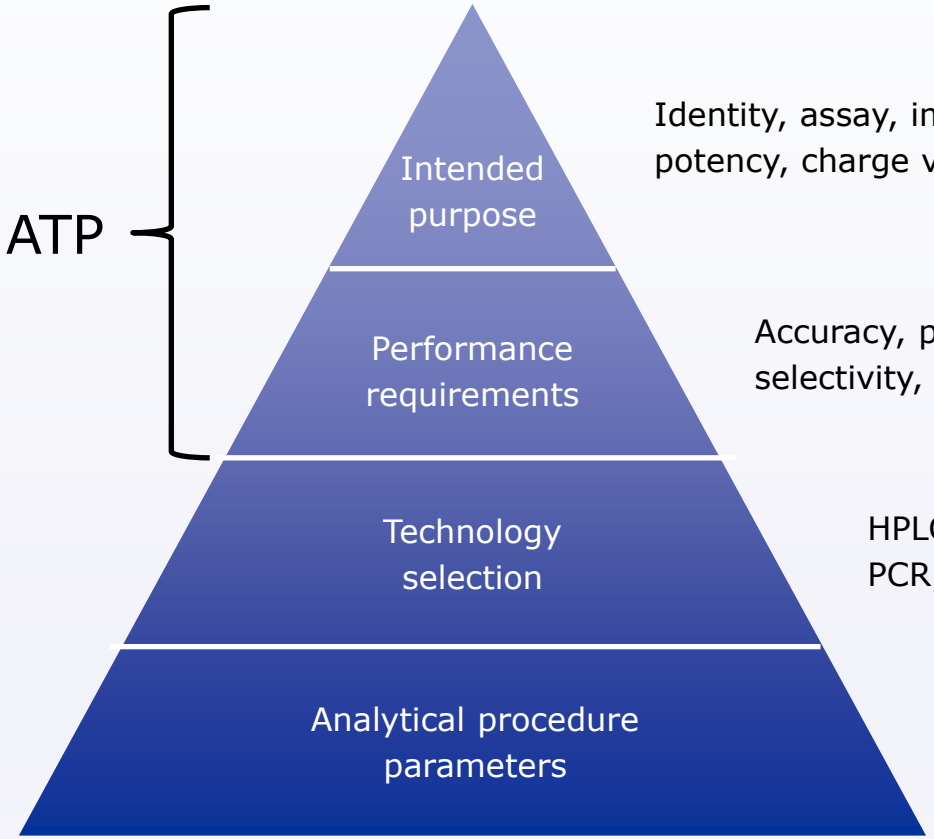
Q14 – Analytical Procedure Control Strategy

- Ensures that the analytical procedure performs as expected throughout its lifecycle.
- Procedure description:
  - Sample, reference materials and the reagents, sample and control preparations, use of the apparatus, generation of the calibration curve, use of formulae for calculations, etc.
- Sufficient detail that skilled analyst can perform analysis
  - ECs AND supportive information
- System suitability test
- Sample suitability assessment (where relevant)

Identification of ECs for Analytical Procedures

- Industry constituents desire more detailed guidance on how to identify ECs
- Limited high level guidance in ICH Q12
  - Chapter 3.2.3.2
  - Annex IC (minimal approach – based on WHO change classification)
- More detailed proposals under consideration + examples

Analytical Target Profile (ATP) - Basic Concept



Identity, assay, impurities, potency, charge variants etc.

Measure product CQAs
Link to QTPP

Accuracy, precision, selectivity, LoQ etc.

Performance characteristics + associated performance criteria

HPLC, (N)IR, CE, KF, PCR, ELISA etc.

Column type, flow rate, temperature, ampholyte, gradient, etc.

Analytical Target Profile - Utility

- Analogy with QTPP - tool to facilitate a structured approach to development
- Facilitates communication of procedure understanding to authorities
- Could facilitate identification and justification of ECs and associated reporting categories
- Could form the basis of a PACMP to allow implementation of AP changes at a lower reporting category

Q14 – Thoughts on implementation

- Some concepts in Q14 already implementable (without new guidance)
- Align with Q12 which has been adopted by all ICH regulatory members
  - Exploit existing lifecycle concepts for Analytical Procedures
- Q12 will take time to implement in some regions (inc. EU)
  - Updates to legislative framework to accommodate Q12 concepts
  - Allow for Q14 proposals

Any questions?

Further information

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