EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH Q2(R2)/Q14:
Analytical Procedure Validation and Development – Status Update

CASSS CMC Forum Europe 2020

Presented by Robert Bream on 12th May 2020
Quality Specialist, European Medicines Agency

An agency of the European Union

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.

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Overview

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

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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

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Objectives ICH Q2(R1) Revision

- Provide a general framework for the principles of analytical procedure validation applicable to products mostly in the scope of Q6A and Q6B.
- 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

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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.

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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.
- Not intended to introduce additional regulatory requirements.
- Complement existing and prospective ICH guidance.

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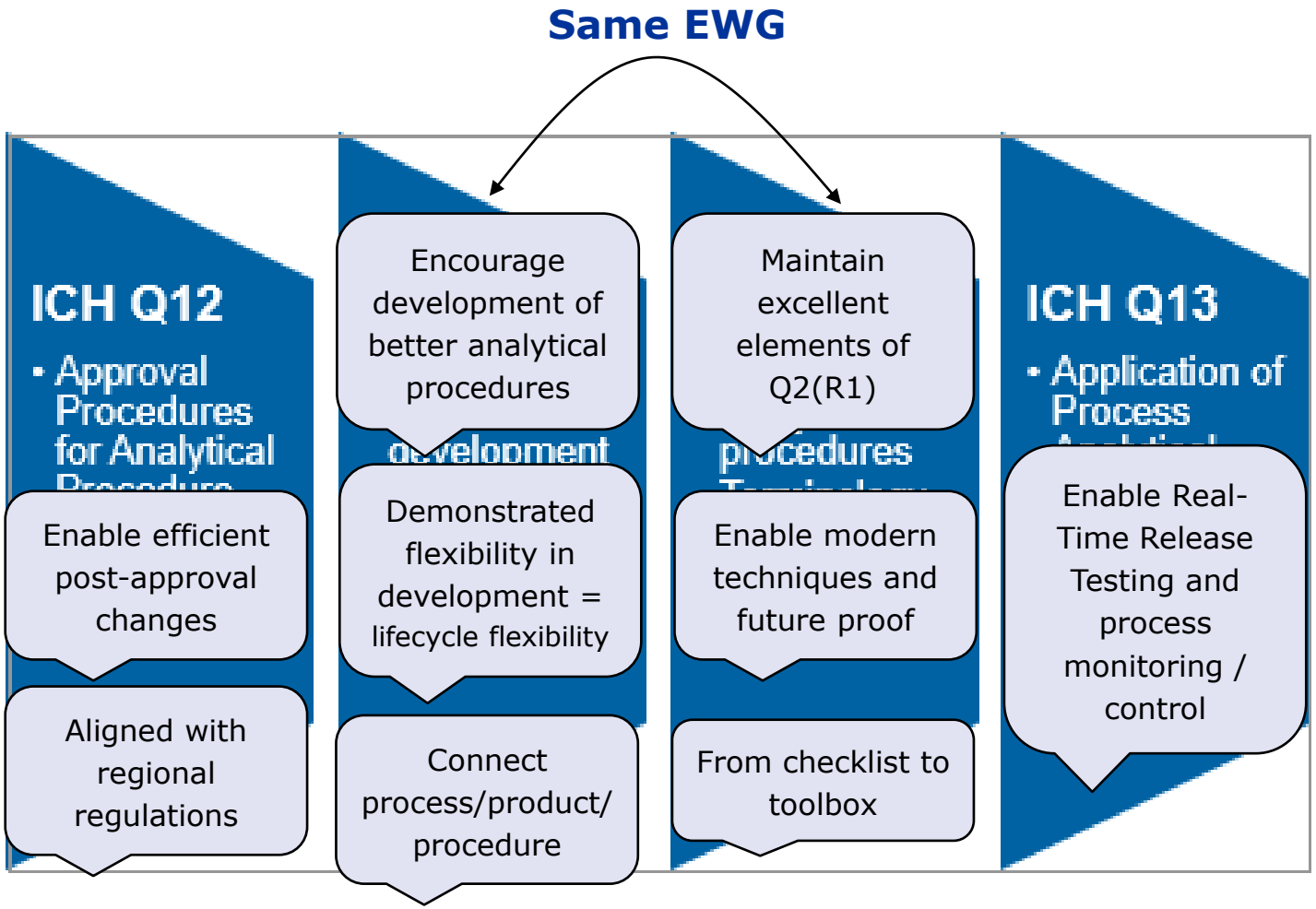
Multiple Related Guidelines



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Timelines - Planned

- January 2020 – draft documents for constituent review
- 24-28th May – step 1 adoption for public comments

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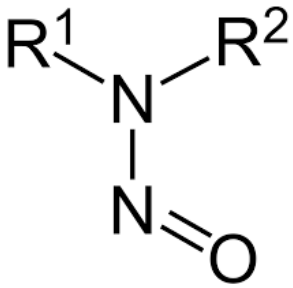

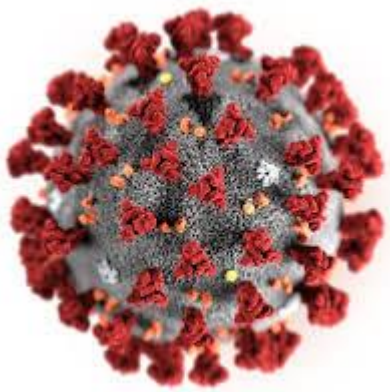

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Timelines - Revised

- 27th April – documents available for ***high level*** constituent review – QWP and BWP.
- 25-29th May – virtual ICH meeting. Adapt the guidelines based on constituent comments.
- June – finalise document for ***in depth*** constituent review
- September – collated constituent comments (WP review)
- 15-19th November – ICH meeting, amend, edit, step 1 sign-off

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ICH Q2 Revision - Contents

Main guideline text: Updated and generalised compared to original. Some topics moved to Q14 (system suitability test and robustness testing)

- Table from original Q2 (performance characteristics) retained and updated
- Chapters structure:
  - Selectivity/specificity
  - Range
  - Accuracy
  - Precision
  - Total analytical error
  - Operational environment

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ICH Q2 Revision - Contents

Appendix 1: A flow-sheet aimed as universal guidance on which validation tests to perform to demonstrate that performance criteria are met

Appendix 2: Adapted examples for common techniques

- Quanititative separation techniques (HPLC, GC, CE)
- Dissolution (UV or separation)
- Elemental impurities (ICP-OES or ICP-MS)
- Quantitative NMR
- Bioassay for potency/identity (cell-based or ELISA)
- Bioassay for impurity quantitation
- Quantitative LCMS
- Quantitative PCR
- Particle size assay
- NIRS

Some techniques included following survey of BWP members and NCAs

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ICH Q14 Contents

Main guideline text based on structure of ICH Q8 with some additions

- Analytical procedure development
- Enhanced approach to analytical procedure development
- Change management of analytical procedures
- Lifecycle management
- Submission of data in the dossier
- Development of multivariate analytical procedures
- Real time release testing

Also preparing glossary common to both GLs and appendices with examples

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Some Concepts (Link to Q8)

Difficult to define enhanced approach in absence of currently undefined minimal approach – ideally no additional regulatory requirements

Product	Analytical Procedure
Quality Target Product Profile	Analytical Target Profile (ATP)
Risk Assessment	Risk Assessment
Critical Quality Attribute	Critical Method Attribute
Design Space	Method Operable Design Region (MODR)
Control Strategy	Analytical Procedure Control Strategy
Ongoing Process Verification	Ongoing Method Verification

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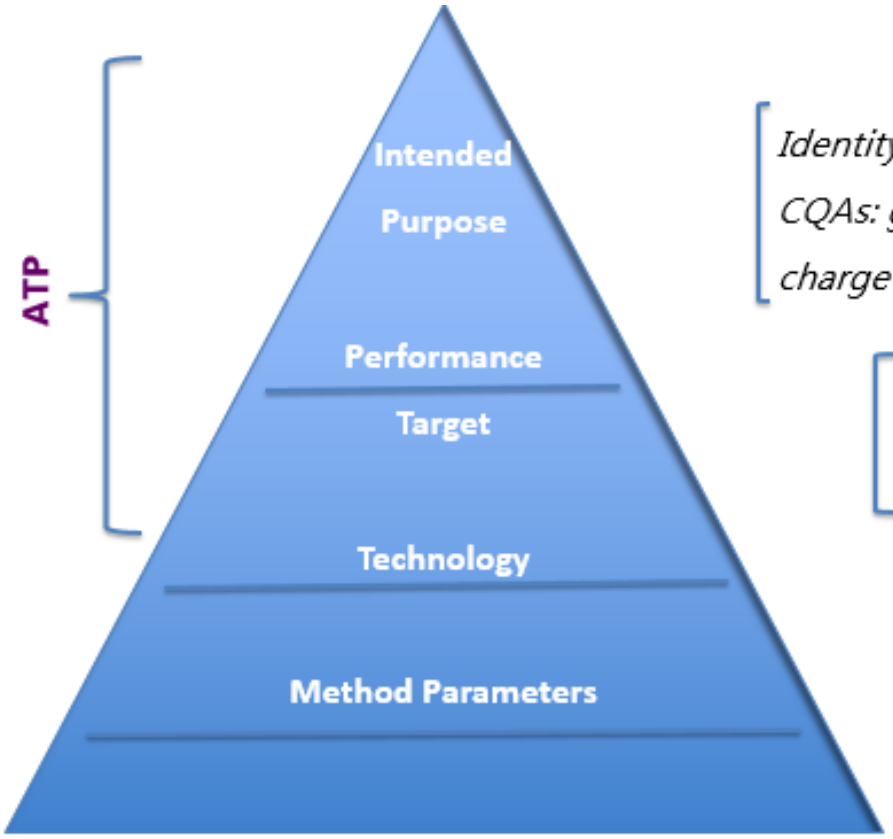
ATP Concept – Technology Independent



Identity, Purity , Assay, Potency
CQAs: glycosylation, size variants
charge variants, oxidation, etc

Product CQAs

Accuracy, precision, specificity, (QL, calibration model...)

Performance characteristics

IEC, CIEF, iCIEF, CZE,
SEC, CE-SDS etc

Column, flow rate,
Gradient, ampholyte etc

"A prospective summary of the performance characteristics of the analytical procedure with anticipated performance criteria to ensure the results are appropriate for the intended purpose."

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Robustness - MODR

- Multivariate experimental design (DoE) allows investigation of parameter interactions, inter-dependencies and ranges.
- Outcome may vary between parameters:
  - Set-points
  - Ranges (*cf* PARs)
  - MODR - a multidimensional (n≥2) region of numerical operating parameters which ensures that the responses of the analytical procedure (outputs) fulfil the ATP criteria and by this providing assurance of quality at an acceptable level of probability.
  - May cover some aspects of validation

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Q14 - Change Management

- Aim should be to reduce the burden of variations where justified by development – presentation of documentation that could be the basis for allowing flexibility.
- The documented knowledge and understanding would also demonstrate robustness of methods, and the guideline could act as a stimulus to develop more robust methods.
- However, need to avoid overlap or contradiction with ICH Q12 and bear in mind that changes need to follow the EU variations classification guidance - changes already subject to risk assessment indicated by established variation class. Q12 tools could be applied to analytical procedures (e.g. PACMPs).

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Acknowledgements

- Tone Agasøster (NOMA) – EU topic lead

- Any questions?

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