Q14: Analytical Procedure Development

Q2 (R2): Validation of Analytical Procedures

Step 2

Step 2 document – to be released for comments

24 March 2022

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

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Background

- The documents have been signed off as *Step 2* documents (24 March 2022) to be issued by the ICH Regulatory Members for public consultation
- The documents were developed based on a Concept Paper (15 November 2018) and a Business Plan (15 November 2018)
- Targeting finalization as *Step 4* documents to be implemented in the local regional regulatory system: May 2023

Key Principles

- Together ICH Q14 and ICH Q2(R2) describe the development and validation activities suggested during the lifecycle of an analytical procedure used for the assessment of the quality of drug substances and drug products.
- ICH Q14 describes the scientific principles for development, change management and submission requirement of analytical procedures for the minimal and enhanced approach.
- ICH Q2(R2) provides guidance for establishing, submitting and maintaining evidence that an analytical procedure is fit for purpose (assuring drug quality).

Guideline Objectives – Q14

- Describes science and risk-based approaches for developing and maintaining analytical procedures fit for intended use, in line with the systematic approach suggested in ICH Q8 and using principles of ICH Q9.
- Specifies a minimal approach and elements of an enhanced approach for analytical procedure development.
- Describes considerations for the development of multivariate analytical procedures and for real time release testing (RTRT).
- Provides principles to support change management of analytical procedures based on risk management, comprehensive understanding of the analytical procedure and adherence to predefined criteria for performance characteristics.
- Includes submission considerations of analytical procedure development and related lifecycle information in the Common Technical Document (CTD) format.

Expected Benefits – Q 14

- Harmonization of scientific approaches, key factors and terminology for analytical procedure development
- Increased understanding of analytical procedure
- Employing predefined performance characteristics guides development and facilitates regulatory change management of analytical procedures
- Enabling preventative measures and facilitating continual improvement by using more analytical procedure knowledge.
- Reducing the amount of effort across the analytical procedure lifecycle.
- Guidance on demonstration of suitability for real time release testing.

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Table of Contents - Q14 Annex

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  - Measurement of Potency for an anti-TNF-alpha Monoclonal Antibody
- Annex B: Validation Strategies for MODRs
- Annex C: Example of Multivariate Model Lifecycle Components

Chapter 2: Scope

- Applies to new or revised analytical procedures used for release and stability testing of commercial drug substances and products (chemical and biological/biotechnological).
- Can also be applied to other analytical procedures used as part of the control strategy (ICH Q10, Pharmaceutical Quality System) following a risk-based approach.
- Scientific principles can be applied in a phase-appropriate manner during clinical development.
- May also be applicable to other types of products, with appropriate regulatory authority consultation as needed
- Development of pharmacopoeial analytical procedures is out of scope

Chapter 2.2: Minimal versus Enhanced Approaches to Analytical Procedure Development

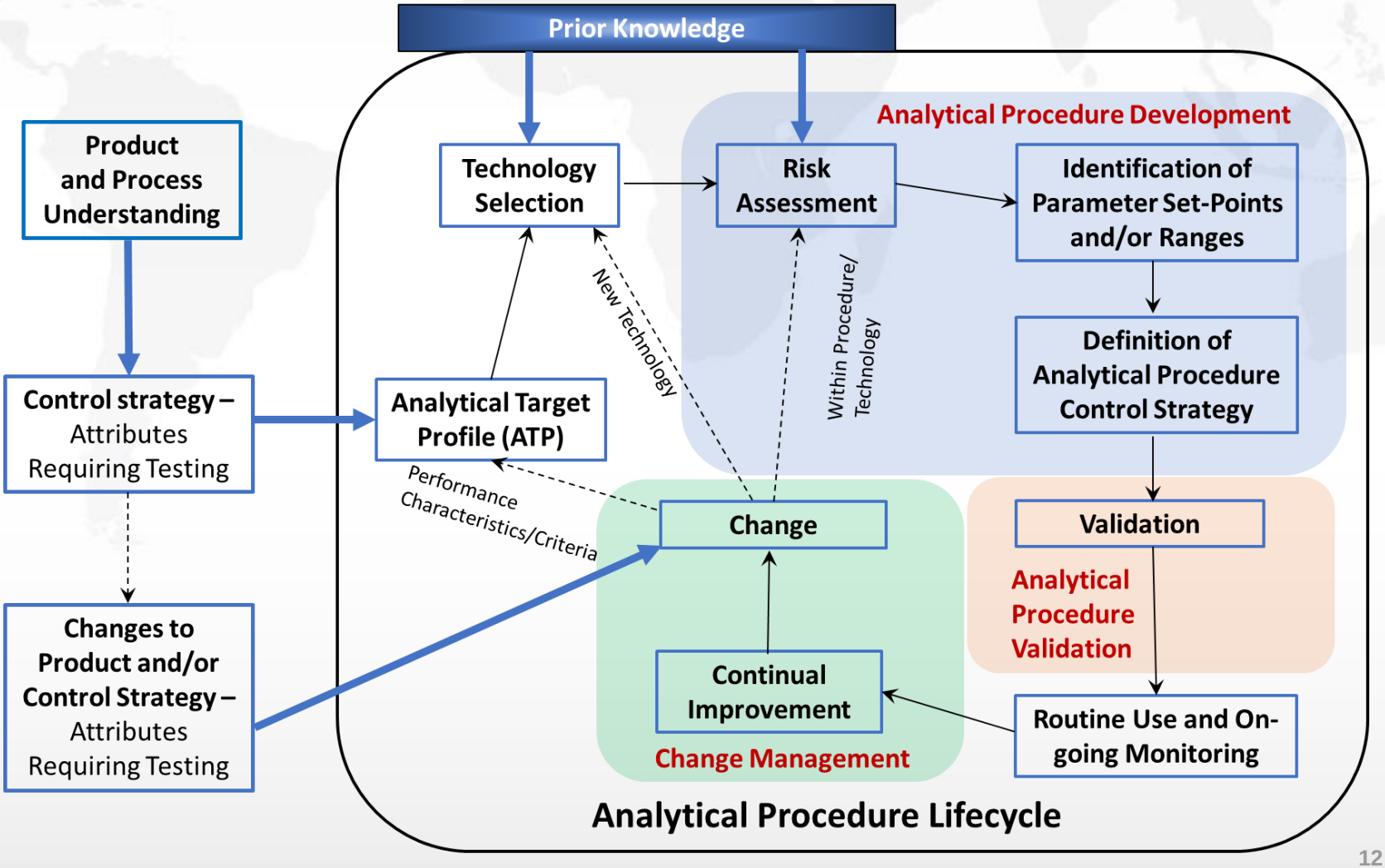
Minimal approach

- Identifying attributes need to be tested
- Selecting appropriate technology and related instruments
- Conducting appropriate development studies
- Defining analytical procedure description

Enhanced approach

- Evaluation of the sample properties
- Defining the analytical target profile (ATP)
- Conducting risk assessment and evaluating prior knowledge
- Conducting uni- or multi-variate experiments
- Defining an analytical procedure control strategy
- Defining a lifecycle change management plan

Chapter 2.2: Analytical Procedure Lifecycle



Chapter 3: Analytical Target Profile (ATP)

ATP is an element of the enhanced approach

- A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement.
- Facilitates the selection of the technology, the procedure design and development as well as the subsequent performance monitoring and continual improvement of the analytical procedure.
- Multiple available analytical techniques may meet the performance requirements.
- Maintained over the lifecycle and can be used as basis for lifecycle management
- Examples described in Annex A

Chapter 4: Knowledge and Risk Management in Analytical Procedure Development and Continual Improvement

Knowledge Management

- Prior knowledge is explicitly or implicitly used for informing decisions during analytical procedure development and lifecycle management.
- Prior product knowledge plays an important role in identifying the appropriate analytical technique.
- Knowledge of best practices and current state-of-the-art technologies as well as current regulatory expectations contributes to the selection of the most suitable technology for a given purpose.
- Platform analytical procedures can be leveraged to evaluate the attributes of a specific product without conducting additional procedure development.
- Knowledge related to analytical procedures should be actively managed throughout the product lifecycle.

Chapter 4: Knowledge and Risk Management in Analytical Procedure Development and Continual Improvement

Quality Risk Management (QRM)

- Risk assessment tools as described in ICHQ9 can be used to identify and assess analytical procedure parameters (factors and operational steps) with potential impact on performance and prioritize them for experimental investigation
- Analytical procedure control strategy can be established following risk control principles
- Continual improvement of analytical procedure performance should be supported by risk communication

Chapter 5: Evaluation of Robustness and Parameter Ranges of Analytical Procedures

- The robustness of an analytical procedure is a measure of its capacity to meet the expected performance requirements during normal use.
- Robustness is typically conducted during development and does not necessarily need to be repeated during validation.
- Depending on the design and outcome of the development studies Proven Acceptable Range (PAR) or Method Operable Design Range (MODR) may be established for a single or multiple parameters.
- Moving within an established parameter range (once approved) does not require regulatory notification.
- The part of a PAR or an MODR intended for routine use in the analytical procedure must be covered by validation data (example in Annex B).

Chapter 6: Analytical Procedure Control Strategy

- Ensures that the analytical procedure performs as expected during routine use throughout its lifecycle
- Consists of a set of controls (i.e., analytical procedure parameters needing control and system suitability test (SST))

Chapter 6: Analytical Procedure Control Strategy

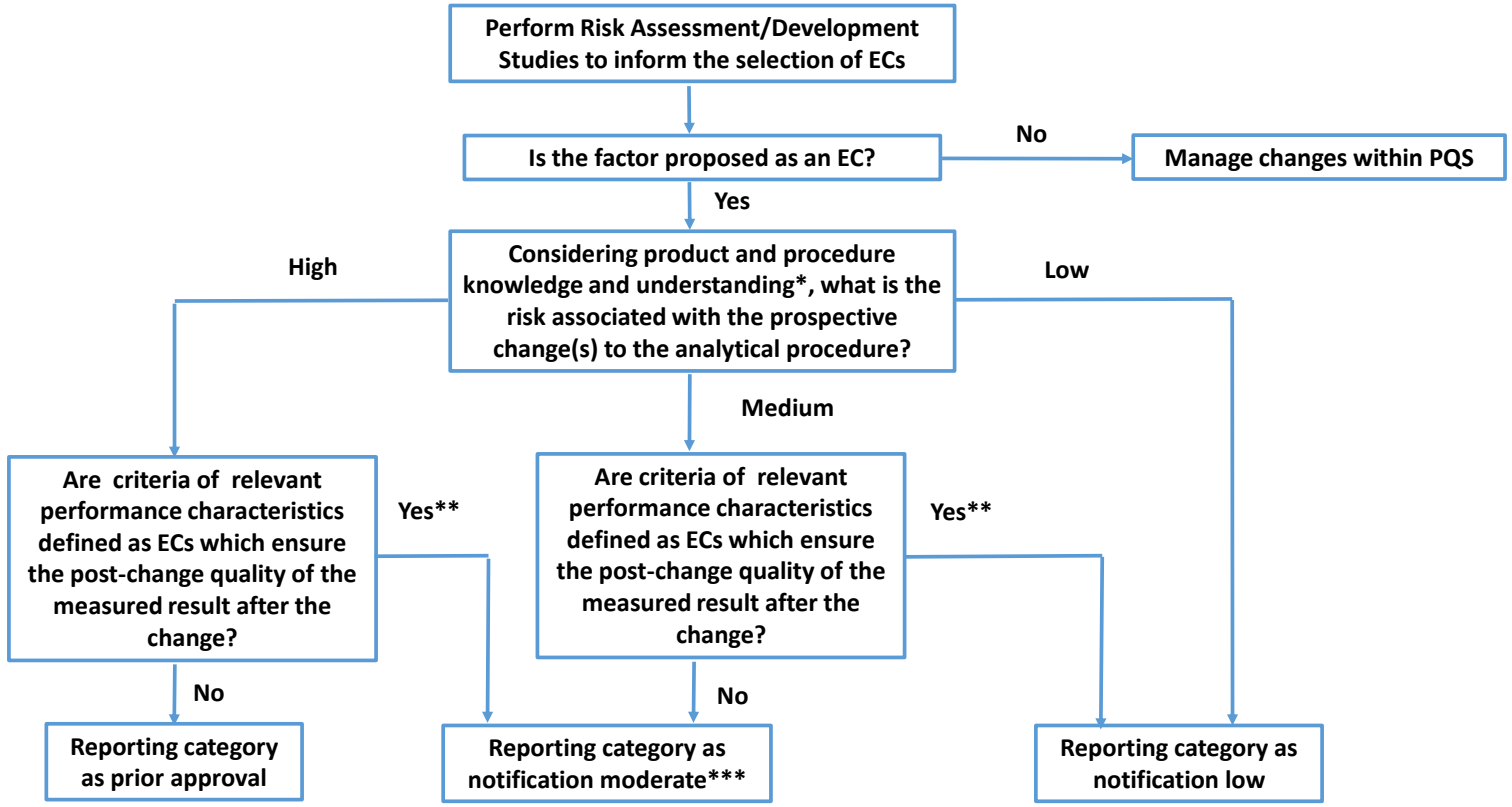
Established Conditions (ECs) for analytical procedures

- In line with ICH Q12
- Nature and extent of ECs depends on development approach, complexity of the analytical procedure and demonstrated understanding
- With a minimal approach, the number of ECs may be extensive with fixed analytical procedure parameters and set points.
- In the enhanced approach an increased understanding of analytical procedure parameters and impact on performance facilitates identification of which factors require control and thus enable a more appropriate set of ECs (examples in Annex A).
  - ECs can be focused on performance characteristics (e.g., specificity, accuracy, precision)

Chapter 7: Lifecycle Management and Post-Approval Changes of Analytical Procedures

- If a minimal approach to development is taken, then any changes should be reported according to existing regional reporting requirements.
- The use of different elements of the enhanced approach can facilitate management and regulatory communication of post-approval changes.
- In cases where ECs are proposed, the risk associated with prospective changes should be assessed up front to define the appropriate reporting category. The reporting category should be commensurate with the risk.
- During implementation QRM can be used to re-confirm that the originally agreed reporting category is still appropriate. The outcome of this risk assessment informs the design and extent of the studies needed to support the change including an appropriate bridging strategy.

Chapter 7: Lifecycle Management and Post-Approval Changes of Analytical Procedures



* Including analytical procedure control strategy

** Sufficient information or prior knowledge should be available to design appropriate future bridging studies

*** In some cases, moderate risk changes proposed by the company may require prior approval based on health authority feedback

Chapter 8: Development of Multivariate Analytical Procedures

- Expectations for the development of multivariate analytical procedures are provided by describing the following important aspects:
  - Sample and sample population
  - Variable selection
  - Data transformation
  - Robustness
  - Recalibration and model maintenance
- The multivariate model lifecycle is iterative and can be broken down into 3 major components: (1) model establishment, (2) routine production and (3) model maintenance.
- Example of Multivariate Model Lifecycle Components is provided in Annex C

Chapter 9: Development of Analytical Procedures for Real Time Release Testing: Special Considerations

- Real time release testing (RTRT) can be based on an appropriate combination of one or more process measurements and/or material attributes to provide a prediction of one or more product Critical Quality Attributes (CQAs) and needs to be specific for that CQA.
- The relationship between the RTRT approach and the product CQAs, as well as acceptance criteria, should be fully justified.
- As appropriate, an RTRT procedure should be validated as recommended in ICH Q2.
- Consideration for sample and sample interface are provided.
- The impact on specifications if an RTRT approach is used is described.

Chapter 10: Submission of Analytical Procedure Related Information

- Information to be included in the CTD section 3.2.S.4.2 and 3.2.P.5.2.
  - The analytical procedure description
  - In the enhanced approach: Performance characteristics and acceptance criteria and other elements of the enhanced approach (e.g. MODRs, PARs)
- Other analytical procedures used as part of the control strategy can be included in relevant CTD sections (e.g., 3.2.S.2, 3.2.P.3 and 3.2.P.4).
- Information to be included in the CTD section 3.2.S.4.3 and section 3.2.P.5.3
  - Validation data
  - Additional development and additional information needed to justify control strategy, ECs and their reporting categories to support the proposed lifecycle management strategy
- Specific guidance for submission of multivariate procedures and their validation is provided

Annex A: Analytical Procedure Lifecycle Management

Provides examples describing how

- analytical procedure performance characteristics derived from the product context and knowledge could be summarized in an ATP
- ECs for analytical procedures can be identified (enhanced approach)
- QRM and the adherence to associated criteria for relevant performance characteristics can
  - help to justify the respective reporting categories for ECs
  - ensure the post-change quality of the measured result during post approval change management of analytical procedures
- Example 1: Measurement of Stereoisomers as Specific Process Related Impurities in a Small Molecule Drug Substance (DS)
- Example 2: Measurement of Potency for an anti-TNF-alpha Monoclonal Antibody

Guideline Objectives – Q2

- Presents a discussion of elements for consideration during the validation of analytical procedures included as part of registration applications submitted within the ICH member regulatory authorities
- Guidance and recommendations on how to derive and evaluate the various validation tests for each analytical procedure
- Serves as a collection of terms, and their definitions
- Bridge the differences that often exist between various compendia and documents of the ICH member regulatory agencies
- Provides an indication of the data which should be presented in a regulatory submission

Expected Benefits – Q2(R2)

- Encouragement of the use of more advanced analytical procedures leading to more robust quality oversight by pharmaceutical drug manufacturers
- Adequate validation data, resulting in reduction of information requests and responses, which can delay application approval
- Modernisation of general methodology to include analytical procedures and data evaluation for biotechnological products and statistical/multivariate data evaluations
- Incorporation of the principles described in ICHQ8-Q10 which did not exist when Q2 (R1) was issued

Table of Contents

Chapter 2 – Scope

- Applies to new or revised analytical procedures used for release and stability testing of commercial drug substances and products (chemical and biological/biotechnological).
- Can also be applied to other analytical procedures used as part of the control strategy (ICH Q10, Pharmaceutical Quality System) following a risk-based approach.
- Scientific principles can be applied in a phase-appropriate manner during clinical development.
- May also be applicable to other types of products, with appropriate regulatory authority consultation as needed
- Aligned with ICH Q14

Chapter 3 – Analytical Procedure Validation Study

- Design of an analytical validation study based on analytical procedure performance characteristics and technology selected
- Guidance on how prior knowledge can be incorporated into the validation study design
- Validation approaches during the analytical procedure lifecycle (partial, cross- and co-validation)
- Expected reportable ranges for common uses of analytical procedures
- Contains Table 1 : "Typical performance characteristics and related validation tests for measured product attributes"

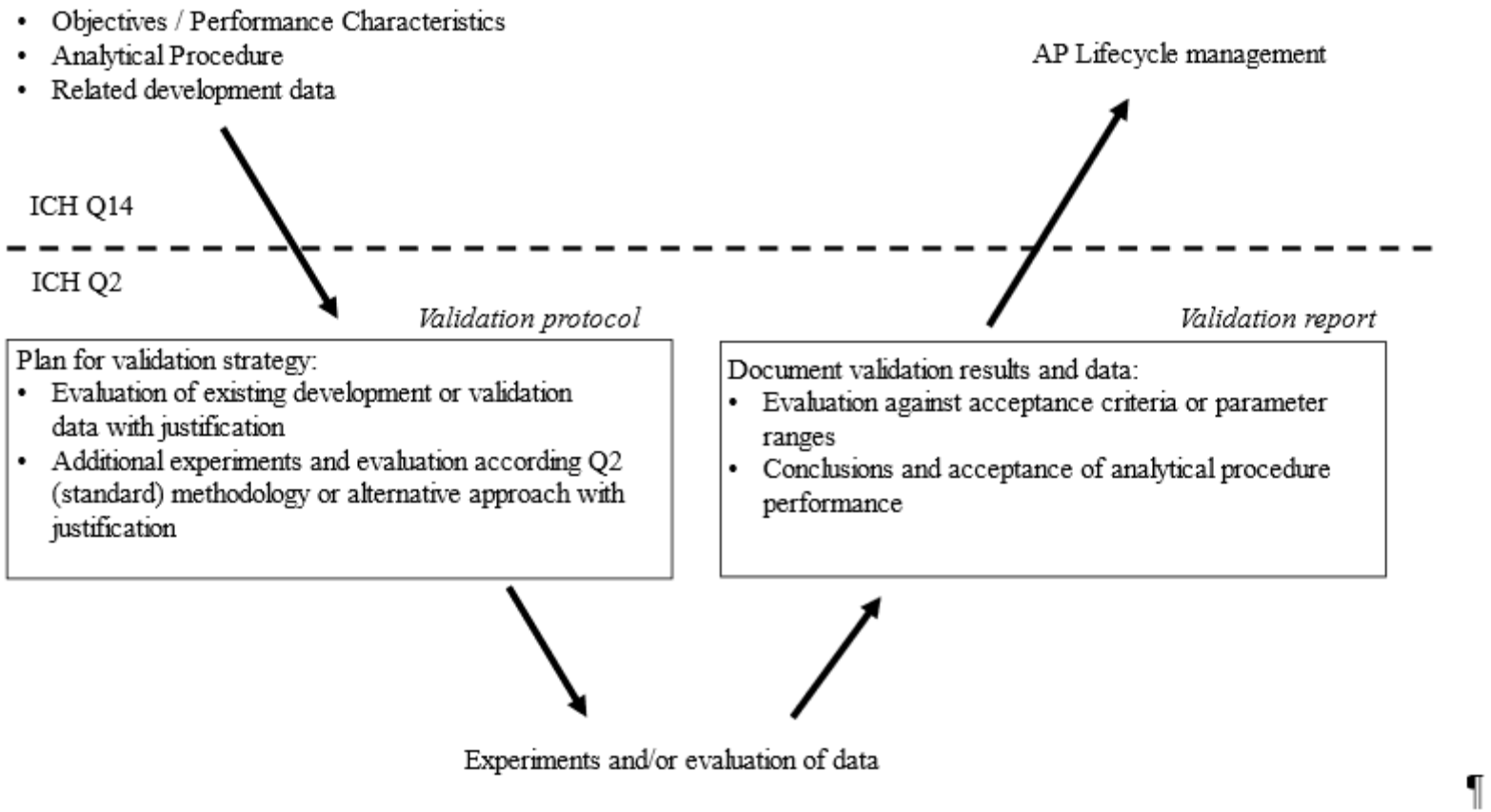
Chapter 3 – Table 1

Table 1: Typical performance characteristics and related validation tests for measured product attributes

Type of measured product attribute / Analytical Procedure Performance Characteristics to be demonstrated (2)	IDENTITY	IMPURITY (PURITY) Other quantitative measurements (1)		ASSAY content/potency Other quantitative measurements (1)
		Quantitative	Limit	
Specificity (3) Specificity Test	+	+	+	+
Working Range Suitability of Calibration model	-	+	-	+
Lower Range Limit verification	-	QL (DL)	DL	-
Accuracy (4) Accuracy Test	-	+	-	+
Precision (4) Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

Chapter 3 – Figure 1

Figure 1: Validation study design and evaluation



Chapter 4 - Validation Tests, Methodology and Evaluation

Chapter 4.1 - Specificity / Selectivity

- The *specificity* or *selectivity* of an analytical procedure can be demonstrated through
  - absence of interference
  - comparison of results to an orthogonal procedure
  - inherently given by the underlying scientific principles of the analytical procedure.
- Selectivity could be demonstrated when the analytical procedure is not specific.
- For identification tests, a critical aspect is to demonstrate the capability to identify the analyte of interest based on unique aspects of its molecular structure and/or other specific properties.
- The specificity/selectivity of an analytical procedure should be demonstrated to fulfil the accuracy requirements for the content or potency of an analyte in the sample.

Chapter 4.2 - Working Range

- Depending on the sample preparation (e.g., dilutions) and the analytical procedure selected, the reportable range will lead to a specific working range.
- Linear response : A linear relationship between analyte concentration and response should be evaluated across the working range of the analytical procedure
- Non-linear Response: The suitability of the model should be assessed by means of non-linear regression analysis (*e.g.*, coefficient of determination).
- Multivariate response: Algorithms used for construction of multivariate calibration models can be linear or non-linear, as long as the model is appropriate for establishing the relationship between the signal and the quality attribute of interest
- Validation of lower range limits: Detection and Quantitation Limit can be validated through signal-to-noise, Standard Deviation of a Linear Response and a Slope or through Accuracy and Precision at lower range limits

Chapter 4.3 - Accuracy and Precision

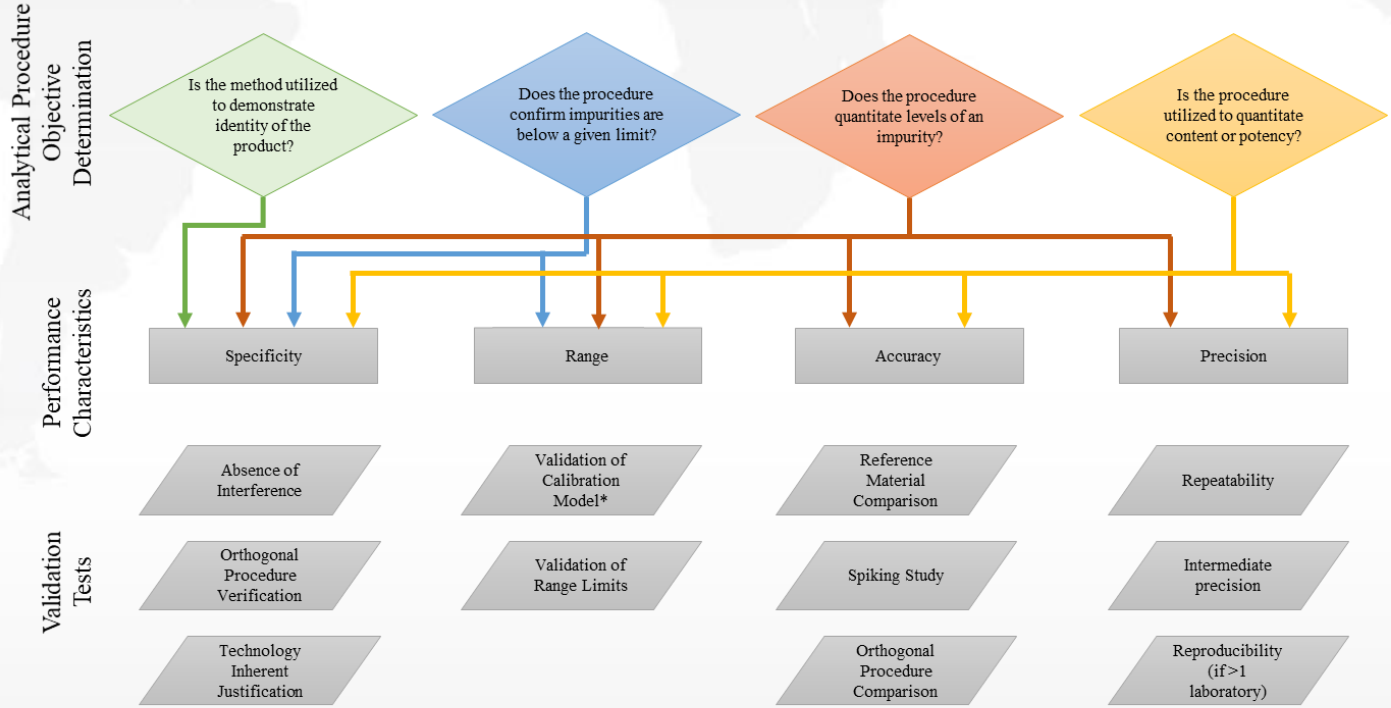
- Accuracy and precision can be evaluated independently, each with a predefined acceptance criterion.
- Accuracy should be established across the reportable range of an analytical procedure and is typically verified through Reference material comparison, a spiking study or an orthogonal procedure comparison.
- Precision: Validation of tests for assay and for quantitative determination of impurities or purity includes an investigation of precision. Repeatability and Intermediate precision are typically determined. Investigation of reproducibility is usually not required for regulatory submission.
- An alternative to a separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion.

Chapter 4.4 - Robustness

- The evaluation of the analytical procedure's suitability within the intended operational environment should be considered during the development phase and depends on the type of procedure under study.
- Robustness testing should show the reliability of an analytical procedure with respect to deliberate variations in parameters.
- The robustness evaluation can be submitted as part of development data for an analytical procedure on a case-by-case basis or should be made available upon request.
- ICH Q14 describes robustness methodology as part of analytical procedure development.

Annex 1 - Selection of validation tests based on the objective of the analytical procedure

- experimental methodologies to evaluate the performance of an analytical procedure
- grouped by the main performance characteristic



* May not be needed for limit test

Annex 2 - Illustrative Examples for Analytical Techniques

Specific non-binding examples for common techniques :

- Separation techniques (HPLC, GC, CE) for impurities or assay
- Separation techniques with Relative Area Quantitation, e.g., product-related substances such as charge variants
- Elemental Impurities by ICP-OES or ICP-MS as purity test
- Dissolution with HPLC as product performance test for an immediate release dosage form
- Quantitative 1H-NMR (internal standard method) for the Assay of an API
- Binding assay (e.g., ELISA, SPR) or Cell-based assay for determination of potency relative to a reference
- Quantitative PCR (quantitative analysis of impurities in drug substances or products)
- Particle size measurement (Dynamic light scattering; Laser diffraction measurement) as property test
- NIR method validation example for core tablet assay
- Quantitative LC/MS (quantitative analysis of impurities (e.g., genotoxic impurities) in drug substances or products)

Considerations

- The ICH Q14 and ICH Q2(R2) guidelines should be applied in conjunction with other existing and prospective ICH "Q" guidelines, including Q8–Q13.
- Analytical procedure development can be performed following a minimal or enhanced approach. Though not mandatory the use of individual elements of the enhanced approach is encouraged to be applied in an as needed basis.
- Tools and enablers discussed in ICH Q12 are applicable to analytical procedures, irrespective of the development approach.
- Examples in ICH Q2 Annex 2 describe common analytical technologies. The principles, however, can be applied in a similar fashion to other analytical technologies.

Conclusion

- The ICH Q14 and ICH Q2(R2) guidelines establishes harmonized scientific and technical principles for analytical procedure over the entire analytical procedure lifecycle.
- Applying principles described in ICH Q14 can 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.
- ICH Q2(R2) will continue to provide a general framework for the principles of analytical procedure validation and has been modernized to include newer technologies (e.g., for biological products or multivariate analytical procedures).

Contact

- **For any questions please contact the ICH Secretariat:**

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