ICH Q14 & Related Regulatory Aspects

M. Nahid Parvin, Ph.D.
Biologist
Laboratory of Biochemistry, Virology and Immunochemistry
Division of Biological Standards and Quality Control
Office of Compliance and Biologics Quality
CBER, FDA

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Key Principles

- **ICH Q14 describes the scientific principles for development, change management and submission requirement of analytical procedures for the minimal (current) and enhanced approach**
- **ICH Q2 provides guidance for establishing, submitting and maintaining evidence that an analytical procedure is fit for purpose**
- **Together ICH Q14 and ICH Q2(R2) describe the development and validation activities recommended during the lifecycle of an analytical procedure**

Learning Objectives

- **Provide an update on the development of ICH Guidelines Q14 and Q2(R2)**
- **Describe main topics addressed in Q14**
- **Principles of the development of analytical procedure**
- **Regulatory expectations**

Why Q14?

- No ICH Guideline for analytical procedure development
- No guidance on data supporting analytical development outcomes
- Inefficient communication during review
- Applicant has no opportunity to present basis for post-approval changes within the assay design

Why Revise Q2(R1)?

- **Developed in 1995 based on only chromatographic techniques**
- **Since then, newer combination techniques are available**
- **Multivariate tools have been applied as Process Analytical Technology (PAT) tools**

Guidance is needed to address validation of these techniques

Current Status of Q14 and Q2(R2)

- **The documents were developed based on a Concept Paper and a Business Plan created in November 2018**
- **The draft Q14 and Q2(R2) documents were signed off as *Step 2* documents on March 24, 2022**
- **Issued by the ICH Regulatory Members for public consultation and public comments are under review by expert working group**
- **Draft documents are available on ICH Website**
- **Targeting finalization as *Step 4* in May 2023**

Objective of Q2(R2)

- 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
- Bridges 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 of Q2(R2)

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

Content Highlights of Q14-- (1)

- 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
- Introduces concept of Analytical Target Profile (ATP). A prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement
- Evaluation of Robustness and Parameter Ranges

Content Highlights of Q14-- (2)

- Knowledge and Risk Management
- Analytical Procedure Control Strategy
- Established Conditions (ECs) for analytical procedure
- Lifecycle management and Post-approval Changes
- Describes considerations for the development of multivariate analytical procedures and for real time release testing (RTRT).

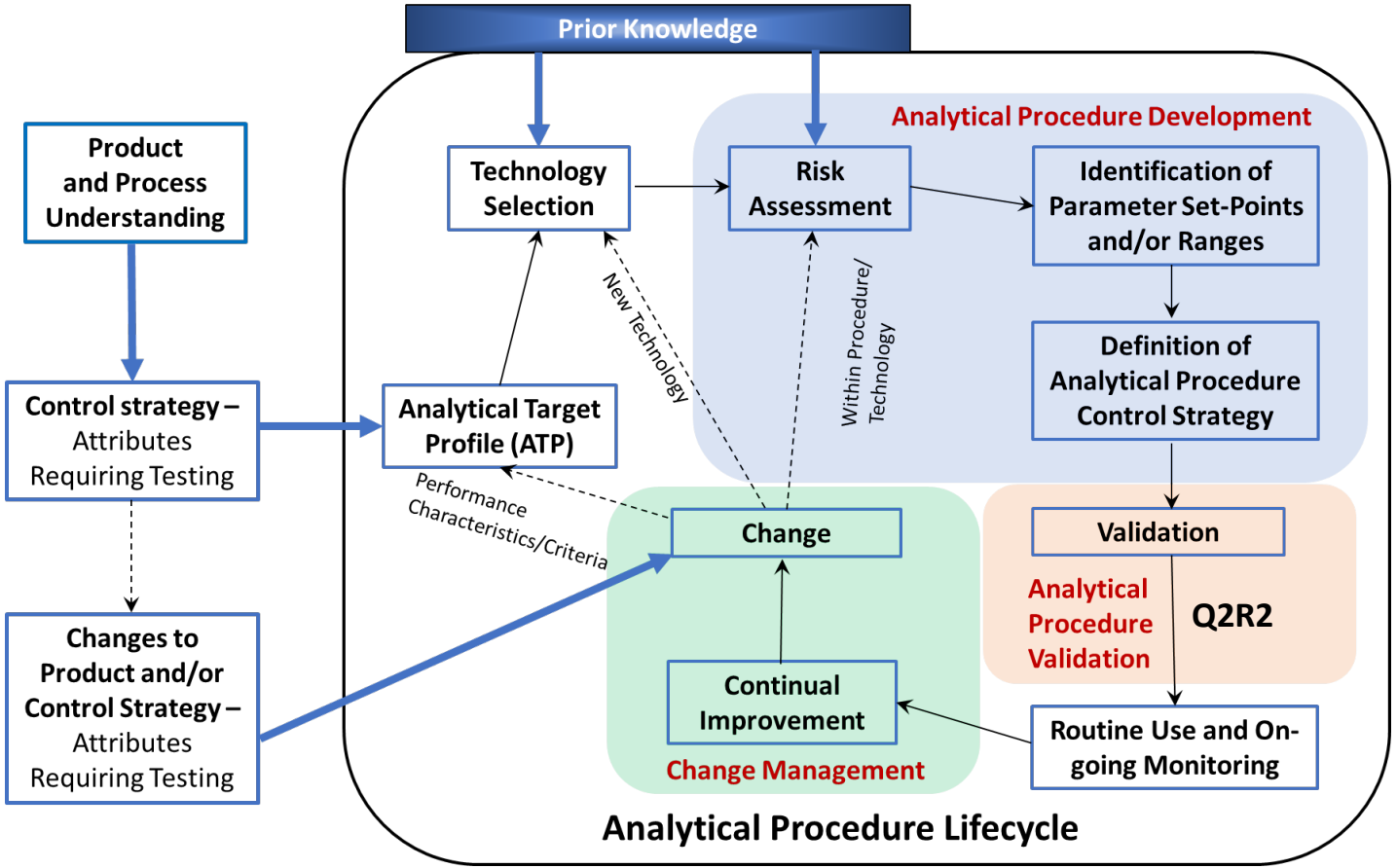
Content Highlights of Q14-- (3)

- Includes submission considerations of analytical procedure development and related lifecycle information in the Common Technical Document (CTD) format
- Annex A includes examples describing lifecycle management of analytical procedures

Expected Benefits of Q14

- Harmonization of scientific approaches, key factors and terminology for analytical procedure development
- Increased understanding of analytical procedures
- Employing predefined performance characteristics guides development and facilitates regulatory change management of analytical procedures
- Enabling preventative measures and facilitating continual improvement by using analytical procedure knowledge
- Efficient post-approval changes and regulatory communication
- Guidance on demonstration of suitability for real time release testing

Concept of Analytical Procedure Lifecycle



Analytical Procedure Development-Minimal Approach

Analytical procedure development should include the following elements as appropriate:

- Identifying which attributes of the drug substance or drug product need to be tested by the analytical procedure
- Selecting an appropriate analytical procedure technology and related instruments or suitable apparatus
- Conducting appropriate development studies to evaluate analytical procedure performance characteristics such as specificity, accuracy and precision over the reportable range (including the calibration model, limits at lower and/or higher range ends) and robustness
- Defining an appropriate analytical procedure description including the analytical procedure control strategy (e.g., parameter settings and system suitability)

Analytical Procedure Development-Enhanced Approach

An enhanced approach should include one or more of the following elements in addition to those already described for the minimal approach:

- An evaluation of the sample properties and the expected variability of the sample based on manufacturing process understanding
- Defining the analytical target profile (ATP)
- Conducting risk assessment and evaluating prior knowledge to identify the analytical procedure parameters that can impact performance of the procedure
- Conducting uni- or multi-variate experiments to explore ranges and interactions between identified analytical procedure parameters
- Defining an analytical procedure control strategy based on enhanced procedure understanding including appropriate set-points and/or ranges for relevant analytical procedure parameters ensuring adherence to performance criteria
- Defining a lifecycle change management plan with clear definitions and reporting categories of established conditions (ECs), proven acceptable ranges (PARs) or method operational design regions (MODRs) as appropriate

Advantages of Enhanced Approach

- Provides an understanding of analytical procedure attributes essential to procedure performance (i.e., ECs)
- Employs predefined performance characteristics (e.g., in the ATP) linked to critical quality attributes (CQAs) and their acceptance criteria to provide purpose driven protocols for validation of analytical procedures and for future comparisons between current and new analytical procedures/technologies
- Improves analytical procedure control resulting in more reliable operation
- Enables preventative measures and facilitates continual improvement using analytical procedure knowledge
- Reduces effort to make changes across the analytical procedure lifecycle

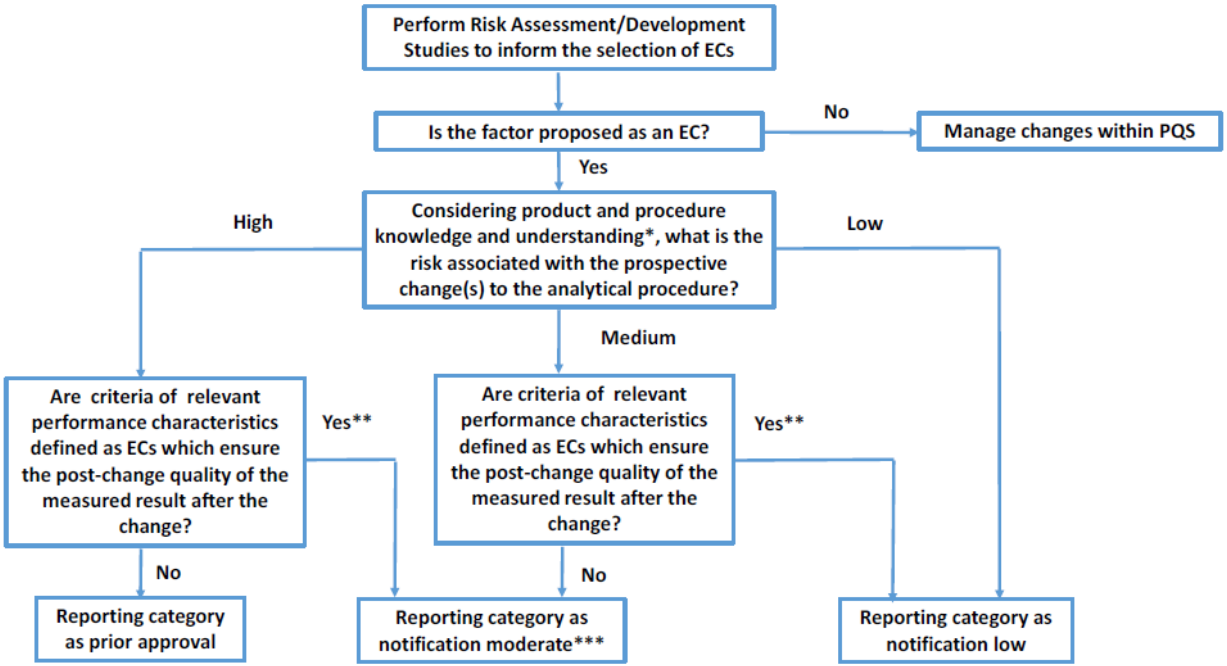
Established Conditions for Analytical Procedures-- (1)

- In line with ICH Q12, applicants may define established conditions (ECs) for an analytical procedure
- ECs are legally binding information considered necessary to assure product quality measured by analytical procedure. As a consequence, any change to ECs necessitates a submission to the regulatory authority
- ECs are proposed and justified by the applicant and approved by the regulatory authorities
- ECs can be identified using tools including risk assessment, prior knowledge, and learnings from uni- and/or multi-variate experimentation
- The nature and extent of ECs will depend on the development approach, the complexity of the analytical procedure and a demonstrated understanding of how parameters and other factors impact its performance

Established Conditions for Analytical Procedures-- (2)

- ECs could consist of performance criteria (e.g., in the ATP or as part of SST), the analytical procedure principle (i.e., the physicochemical basis or specific technology), and set points and/or ranges for one or more parameters
- Analytical procedure parameters which need to be controlled to ensure the performance of the procedure as well as those where the need for control cannot be reasonably excluded should be identified as ECs
- If a parameter is controlled through performance characteristics and criteria, that parameter may not necessarily need to be defined as an EC or may be assigned a lower reporting category

Risk-based approach to identification of ECs and reporting categories for associated changes in the enhanced approach



* 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

Regulatory requirement for Established Conditions-- (1)

- A suitably detailed description of the analytical procedures is expected to provide a clear understanding regardless of the approach used to identify ECs for analytical procedures
- Description of analytical procedures can include supportive information as well as identified ECs
- Use of the enhanced approach should not lead to providing a less detailed description of analytical procedures in a regulatory submission
- The risk associated with prospective changes should be assessed up front to define the appropriate reporting category. The level of risk (high, medium or low) should be assigned
- Submitting the outcomes of the risk assessments to regulatory agencies when ECs are identified can help justify reporting categories for future changes to analytical procedures
- Changes to parameters that are not ECs should be documented in the PQS but do not require regulatory reporting

Regulatory requirement for Established Conditions-- (2)

- When implementing changes to analytical procedures, QRM can be used to evaluate the impact of the changes and 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 to demonstrate that the revised or new procedure is fit for purpose
- The implementation of an already validated analytical procedure at a different location, including the concepts of the analytical procedure transfer, should follow the same verification and bridging strategies
- If an applicant proposes a new analytical procedure, a thorough risk assessment and evaluation should be conducted to determine any impact on the performance. The analytical procedure control strategy for the new procedure should be established. ECs associated with the new procedure should be justified when reporting the change

General Regulatory considerations and Documentation

- Analytical Procedure Descriptions should be included in CTD section 3.2.S.4.2 for drug substance or section 3.2.P.5.2 for drug product
- The analytical procedure should describe the steps in sufficient detail for a skilled analyst to perform the analytical test, analysis and interpret the result
- Submission of validation data should follow the recommendations in ICH Q2. The criteria used in the validation study should be included in the CTD section 3.2.S.4.3 for drug substance or section 3.2.P.5.3 for drug product
- Validation data and any supportive information needed to justify the analytical procedure control strategy should be included

Regulatory requirements for multivariate analytical procedures and RTRT

- Development information related to multivariate analytical procedures should be provided commensurate with the level of impact of the model (ICH Q8/Q9/Q10)
- The process development section of the submission (e.g., 3.2.S.2.6 or 3.2.P.2.6) should include the model development information for multivariate models used as part of manufacturing development studies or for in-process controls or tests
- Supportive development information for RTRT multivariate models can be included in either the appropriate analytical procedure validation or process development section
- Validation information on analytical procedures used as reference methods should be included in CTD section (e.g., 3.2.S.4.3 or 3.2.P.5.3). The model development, calibration and validation information can be included directly in the CTD section or be in an appended document

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 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 establish harmonized scientific and technical principles for analytical procedures 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)

Thank You!

Acknowledgement

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