A Review on Revision of ICH Q2 (R1) and New ICH Q14 Guidance

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ABSTRACT

The ICH stands for “international council on harmonization of technical requirements for registration of pharmaceutical for human use” it’s an initiative which brings together regulatory bodies and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. ICH guidelines include ‘Q’ series quality guidelines for harmonization. The amendment in analytical procedure development and the changes in validation of analytical procedure ICH Q2 (R1) is proposed to develop a new quality guideline and providing principles relating to analytical development procedures. Applying this guideline will improve regulatory communication between industry and regulators and Q2(R1) will include validation principles that cover analytical use of spectrometric data (e.g, NIR, NMR, Raman OR MS).

Keywords: ICH guidelines, Regulatory bodies, Harmonization, Q-series, Validation.

INTRODUCTION

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is an initiative that brings together regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceutical product development and registration. The mission of the ICH is to promote public health by achieving greater harmonisation through the development of technical Guidelines and requirements for pharmaceutical product registration.

Harmonisation leads to a more rational use of human, animal and other resources, the elimination of unnecessary delay in the global development, and availability of new medicines while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.

The ICH comprises the following bodies

1. ICH Assembly
2. ICH Management Committee
3. Med DRA Management Committee
4. ICH Secretariat

The ICH guidelines are classified into four categories and their topic codes are assigned according to these categories:

- Q : Quality Guidelines
- S : Safety Guidelines
- E : Efficacy Guidelines
- M : Multidisciplinary Guidelines

Quality guidelines:

Harmonisation achievements in the quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on GMP risk management.

It consists of Q1A-Q1F, Q2, Q3A-Q3D, Q4-Q4B, Q5A-Q5E, Q6-Q6B, Q7, Q8, Q9, Q10, Q11, & Q12.

There is revision in ICH Q2(R1) and ICH Q14 guidelines are described.

Type of Harmonisation action proposed

The new guideline is proposed for harmonizing the scientific approaches of analytical procedure development and providing the principles relating to the description of
analytical procedure development process. Applying this guideline will 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 procedure.

The scope of Q2(R1) revision will include validation principles that cover analytical use of spectroscopic or spectrometry data (e.g., NIR, Raman, NMR or MS) some of which often require multivariate statistical analysis.

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

These Q2 and Q14 proposed guidelines are intended to complement with ICH Q8 to Q12 guidelines, as well as on going ICH Q13 for continuous manufacturing.

Q14 Analytical Procedure Development guideline

As there is no ICH guide to Analytical Procedure Development, applicants often report individual validation results and are less likely to present performance tests with analytical results. This makes control communication ineffective especially if unfamiliar (e.g., real-time discharge tests) analytical procedures are used. In addition, the absence of guidelines prevents the applicant from the opportunity to provide a scientific basis for flexible control modes of change after the Analysis process after approval.

Q2(R1) Revision

Current Q2 (R1) “Guide to Verifying Analysis Procedures: Text and Method” does not cover the most recent use of analytical procedures, (e.g., Near Infrared (NIR) Spectroscopy or Raman Spectroscopy). Lack of guidance on these analytical data sets could lead to the delivery of insufficient verification data for these analytical processes, which has led to duplication of information requests and responses, which could delay application approval. This is mainly due to processes based on multivariate models, a category that does not have an ICH verification guide. Spectroscopy tools such as NIR or Raman are widely used in process control and real-time testing of pharmaceutical products using many analytical methods. Considering the differences between multivariate and traditional methods, the current Q2 (R1) method is not sufficient to establish the suitability of multivariate methods. For example, where traditional methods use indexing, analysis and anonymous samples, the effectiveness of these methods is verified and validated during each test. In contrast, the model-based approaches of various models generally do not apply the reference standards during the analysis. This makes strong development, validation and proper maintenance of such systems essential for reliable predictions throughout life.

Issues to be Resolved

Q14 Analytical Procedure Development guideline

Analysis processes are required to improve products and production process, to measure critical quality attributes and to ensure the quality of end products. These figures will be changed or improved throughout the product life cycle as a result of continuous improvement activities. Therefore, the new guide will provide an opportunity to present the impact of Analytical Procedure Development on traditional and improved approaches and simplify the management of effective and science-based change by improving communication between industry and regulators.

Some of main technical and scientific elements, which require harmonization, include:

- Submission of Analytical Procedure Development and related information in CTD format
- The concept and strategy of enhanced approaches for Analytical Procedures
- Performance criteria of Analytical Procedures.
- In line with ICH Q8 and ICH Q11, greater understanding of Analytical Procedure can create the basis for more efficient, sound science and risk-based change management (e.g., using analytical Quality by Design principles).
- Key elements and terminology
- Demonstration of suitability for Real Time Release testing.

Q2(R1) Revision

In addition to the current guideline, the revised guide will clarify common process validation features, such as NIR, nuclear magnetic resonance spectroscopy (NMR), and hyphenated techniques, for example CE-MS, CE-ICP-MS, LC-NMR, GC-MS, LC-MS. Although these methods use very different equipment, the output of the data is robust in frequency range or weight to charge the average distance. If necessary, data analysis can be facilitated by the appropriate use of multivariate statistical analysis to compare ratings between test and reference samples.

Procedures reliant on multivariate methods below will be also addressed:

- Definition of validation characteristics applicable to multivariate methods which may differ with the area of application (e.g., identification vs. quantitation, batch vs. continuous process, dosage form assay vs. blending monitoring)
- Important method parameters (e.g., the number of latent variables) established during method development
- Robustness which is well understood, however does not have a quantitative measure.

Background to the Proposal

The new Analytical Procedure Development guideline (Q14) will be for S4, P4 and P5 of CTD and will complement with Q8(R2) and Q11.
The purpose of this proposal is to provide an opportunity to present information obtained through improved analytical methods. The proposed guide will assist in selecting or identifying developmental approaches that will address post-approval change and facilitate effective, sound - and risk-based change management. Applying an improved method of analytical processes can contribute to the development of resource-saving drugs and the post-CMC approval.

The revised Q2 (R1) guide will be for S4, P4 and P5 for CTD with an emphasis on systematic Analytical Development.

The expected result will be an extended Q2 that will directly address validation of some of the new analytical processes, and include a discussion of mathematical features in validation.

The Q2 (R1) review will include verification methods based on instrumentation that provides a spectra in frequency range (e.g., Raman, NIR or NMR) or beyond the weight of the billing range (e.g., mass spectrometry). The review will include the introduction of appropriate mathematical methods with consideration of sample size and validation of continuous performance.

As Analytical Development activities are followed by Analytical Validation activities, the above two activities will be systematically performed by one EWG. Two separate documents will be produced.

**Type of Expert Working Group and Resources**

Because activities are strongly interrelated, one Expert Working Group will be designated to establish the new Analytical Procedure Development and revise ICH Q2(R1). An Expert Working Group composed of experts with expertise in the area of analytical chemistry and pharmaceutical control is needed.

**Opportunities for revision of Q2(R1)**

It defines the common validation characteristics for more recent procedures. Eg. NIR, NMR and hyphenated techniques.

Clarification of procedures based on multiple methods:

- Most important parameters is to be investigated during method development.
- Requirements for validation data sets.
- It defines validation characteristics which vary with area of application (batch vs Continuous process)
- Demonstration of robustness
- Inclusion of post-approval verification and maintenance considerations as a part of validation.

**Goals of ICH Q14:**

- Providing the principles relating to the description of analytical procedure development process in line with ICH Q8 and Q11 and improvement of regulatory communication between industry and regulators.
- Facilitation of more efficient, sound scientific and risk based approval as well as post approval change management of analytical procedures.
- Alignment on key elements and terminology.
- Guidance on demonstration of suitability for real time release testing.

![Figure 1: Expectations on Analytical methods](image1)

**Applying QBD to analytical procedures:**

QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way.

![Figure 2: QBD to analytical procedures](image2)

![Figure 3: From QTPP to ATP](image3)
**Analytical target profile:**

The combination of all performance criteria required to ensure the measurement of a quality attribute is fit for the intended purpose and produces data which can be used with the required confidence to support for example:

- Specification pass/fail decisions
- Other quality decisions during development and across the lifecycle.

An ATP would be developed for each of the attributes defined in the control strategy.

ATP can be used to direct the selection of an appropriate analytical technique, to develop a full understanding of how input parameters affect the reportable result and serve as focal point for continuous improvement and change control.

**Benefits using the ATP concept:**

- Facilitation of technology selection and guidance for method development.
- Correct use of ATP ensures that the method selected and developed is fit for required purpose.
- Clear link between method performance and CQAs and their acceptance criteria.

**Method validation**

- The ATP provides purpose driven criteria for validation.
ATP will drive value added validation above tick box generic validation.

Method lifecycle

- It ensures robust fit for purpose analytical procedures are used as part of the control strategy for marketed products throughout the lifecycle of a marketed product.
- ATP provides criteria for purpose driven comparison between current and new analytical procedures.

**Table 1: Analytical Target Profile Charge Heterogeneity for a MAb in Early Stage Development**

| ATP Performance Characteristic | ATP Performance Criteria |
|-------------------------------|--------------------------|
| Specificity                   | Determination of Acidic Region and Basic Region and Main Peak Stability indicating properties |
| Accuracy                      | Main Peak: 90.0-100.0 % of assumed true value (area%) |
| Precision of reportable result| Main Peak: ≤ 6.0 % RSD (consider extent of Main Peak) |
| Range                         | Main Peak: at least 80%-120% of nominal protein concentration Other components: QL- 120% of upper spec limit |

**STATUS Q2**

- Link to expected analytical procedure performance
- Updated glossary Q2/Q14 with additional elements in alignment with principles Q8,9,10
- Validation examples beyond Chromatography
- Methodology modernized to include newer technologies
- Streamlined structure by methodology

**STATUS Q14**

Emphasis on analytical procedure objectives to define “fit for purpose”
- In alignment with Q8,Q9,Q10
- Elements
- Risk management
- Robustness and operable ranges
- Analytical procedure control strategy
- Change management
- RTTR
- Guidance on how to present knowledge from analytical procedure development in CTD

**CONCLUSION**

The increased scope of analytical procedures to which Q2(R2) and Q14 ICH guidelines can be directly applied. The Q2(R2) and Q14 ICH guidelines are sustainable and can be applied to technologies to be developed in the future without recursive revision. The revision in guidelines increased the understanding on the following parts of applicants of requirements for development and validation of robust analytical methods, the information reviewers need to fully assess suitability analytical methods and how to communicate the development process and justification of analytical method development and validation. It provides the increased assurance on the part of regulators that applicants have developed and validated suitable analytical methods. It harmonized the definitions for enhanced analytical procedure development approaches and streamlined review processes and lifecycle management for analytical methods. The Revision of guidelines gives increased harmonization among global regulators of expectations for analytical methods.
REFERENCES

1. Bhavya K, Manisha Vishnumurthy K, Rambabu D and Sumakanth M. ICH guidelines – “Q” series (quality guidelines) - A review. GSC Biological and Pharmaceutical Sciences, 2019;6(3):89-106.

2. Rajesh Dumpala, Chirag Patil An Overview of Regulatory Affairs in Pharmaceutical Industry, International Journal of Universal Pharmacy and Bio Sciences, 2017; 9(4):18-24.

3. Gandhi A, Roy C; Quality by design (QbD) in pharmaceutical industry: tools, perspectives and challenges; pharmatutor; 2016;4(11):12-20.

4. https://www.ich.org/page/ich-guidelines

5. https://en.wikipedia.org/wiki/International_Council_for_Harmonisation_of_Technical_Requirements_for_Pharmaceuticals_for_Human_Use

6. Rajesh Dumpala, Jaini Bhavsar, Chirag Patil "Quality by Design: A Present to Future Perspective" Published in International Journal of Trend in Scientific Research and Development ISSN: 2456-6470, Volume-4 Issue-5, August 2020, pp.878-885,

7. “Douglas J. Pisano and David S. Mantus” “Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics’ Second Edition, August 2008.

8. ICH Q9: Quality Risk Management - an update 14 May 2014.

9. Anat IB (2013) QbD Strategy Leader, “Bud implementation in Generic Industry: Overview and Case-Study” IFPAC JAN.

10. Gillian Doherty and Jane Beach Martha Friendlyn “Quality by design: What do we know about quality in early learning and child care, and what do we think?” A literature review pp. 1-32.

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