USP-MHLW/PMDA Joint Workshop

Sep 10-11, 2024 Virtual/Iino Conference Center Room B

Session 1: Advancing Harmonization of Standards
ICH-Q14 and ICH-Q2

Q2(R2)/Q14：Summary and JP perspective

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Outline

- Background of ICH Q2(R2)/Q14
- Overview of ICH Q2(R2)
- Overview of ICH Q14
- Perspective on the Japanese Pharmacopoeia (JP)

Background of ICH Q2(R2)

Validation of Analytical Procedures

Issues on Q2(R1)

- Q2(R1) not covering more recent application of analytical procedures (e.g., Near Infrared (NIR) Spectroscopy or Raman Spectroscopy).
- Lack of common understanding between applicants and reviewers regarding adequate validation data for submission

Recursive information requests and responses delay application approval

Purpose of Q2(R2)

- Additional information on validation of analytical procedures using **multivariate analysis**
- Presenting a guide to achieve robust development, validation and proper maintenance of various analytical procedures throughout the analytical procedure lifecycle.

History of Q2(R2)

Year	ICH Event
1994	Q2A ; Text
1996	Q2B ; Methodology
2005	Q2(R1) ; Q2A and Q2B combined
2017	**Revision of Q2(R1) was proposed by US FDA**
2018.06	ICH Assembly approved Q2(R2)/Q14 as new topic in Kobe meeting.
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2023.11	Step 3 sign-off, Step 4

Background of ICH Q14

Analytical Procedure Development

Lack of ICH guideline for analytical procedure development

- Applicants often report analytical validation results alone and rarely present performance evaluation with analytical development outcomes.
- Ineffective regulatory communication especially when non-conventional (for example, real time release testing) analytical procedures are employed
- Loss of opportunities for applicants to present scientific basis for flexible regulatory approaches to post-approval changes of analytical procedures

Purpose of Q14

- Presenting **science and risk-based approaches** for developing and maintaining analytical procedures
- Describes considerations for the development of **multivariate analytical procedures and for real time release testing (RTRT)**
- Provides guidance on how principles described in ICH Q12 can support **change management of analytical procedures based on risk management**
- Providing submission considerations of analytical procedure development and related lifecycle information in the **Common Technical Document (CTD) format**.

Background of ICH Q14

Analytical Procedure Development

Year	ICH Event
2014	**Enhanced Approaches for Analytical Procedure** is listed at Informal Quality Discussion Workshop .
2017	**Analytical Procedure Development was proposed by MHLW.**
2017/ 2018	One Expert Working Group for revision of Q2(R1) and Analytical Procedure Development was proposed jointly by US FDA and MHLW.
2018.06	ICH Assembly approved Q2(R2)/Q14 as new topic in Kobe meeting.
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2023.11	Step 3 sign-off, Step 4

USP publications

Pharm. Forum (2013)
Stimuli to the revision process:

- Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification

Pharm. Forum (2016)
Stimuli to the revision process:

- Analytical Target Profile: Structure and Application Throughout the Analytical Lifecycle
- Analytical Control Strategy

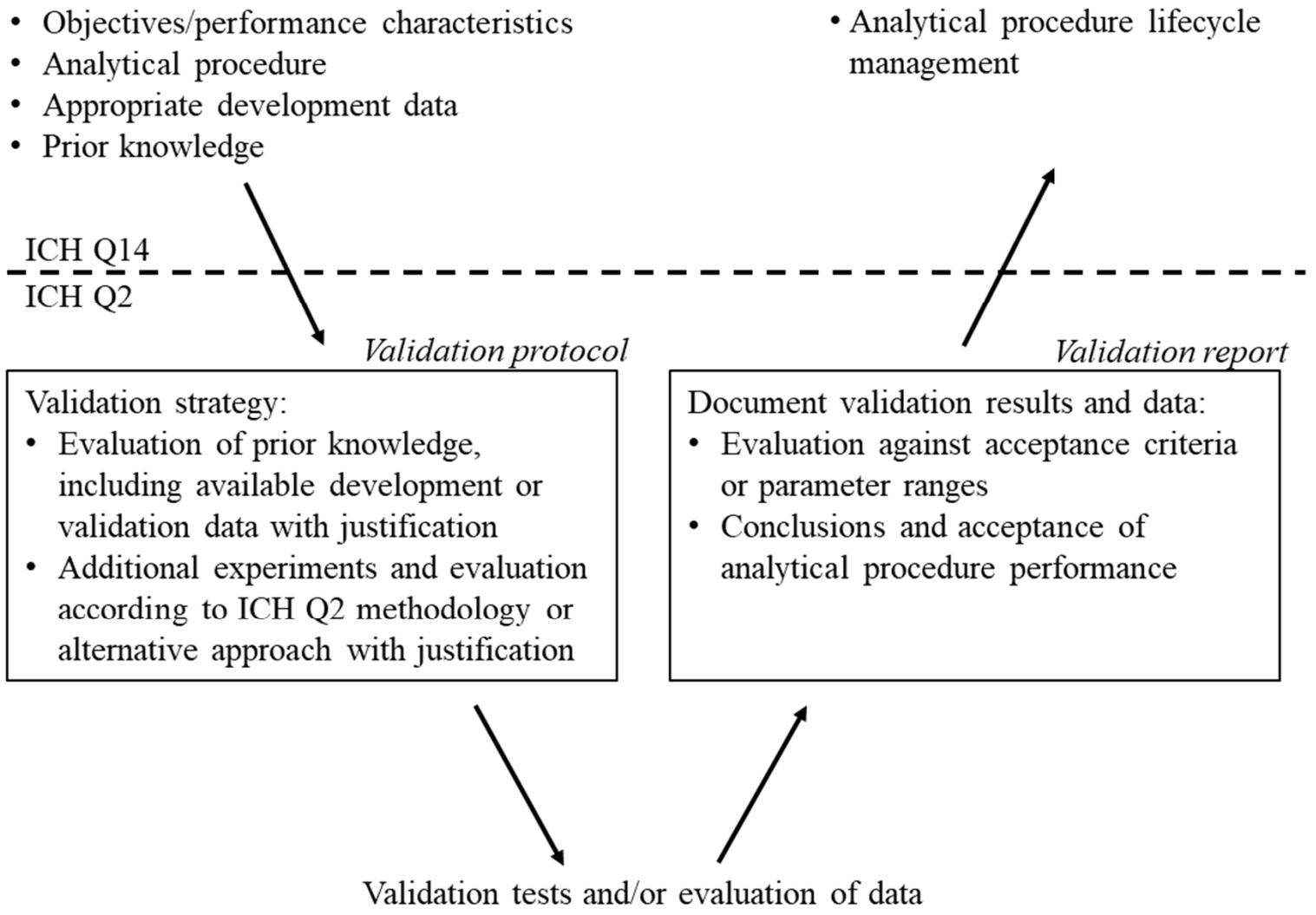
Pharm Forum (2017)

- Proposed new USP general chapter: the analytical procedure lifecycle <1220>

Overview of ICH Q2(R2) : Comparison with Q2(R1)

Previous version Q2(R1)	Q2(R2) ※New contents in red
PART Ⅰ : Text on validation of analytical procedures 1. Introduction 2. Types of analytical procedures to be validated Table Glossary PART Ⅱ : Validation of analytical procedures: Methodology Introduction 1. Specificity 2. Linearity 3. Range 4. Accuracy 5. Precision 6. Detection limit 7. Quantitation limit 8. Robustness 9. System suitability testing Q14	1. Introduction 1.1 Objective 1.2 Scope 2. General considerations for analytical procedure validation 2.1 Analytical procedure validation study 2.2 Validation during the lifecycle of an analytical procedure 2.3 Reportable range 2.4 Demonstration of stability-indicating properties 2.5 Considerations for multivariate analytical procedures 3. Validation tests, methodology and evaluation 3.1 Specificity/Selectivity 3.2 Range 3.3 Accuracy and Precision 3.4 Robustness 4. Glossary 5. References 6. Annex 1: Selection of validation tests 7. Annex 2: Illustrative examples for analytical techniques • Linear response • Non-linear response • Multivariate calibration Combined approaches for accuracy and precision

Overview of ICH Q2(R2) : Validation Study Design and Evaluation



Overview of Q2(R2) : Annex 2

Illustrative examples for analytical techniques

★Not mandatory, non-binding examples. Alternative approaches may also be acceptable.

- Separation techniques (e.g., 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
- Dissolution with HPLC as product performance test for an immediate release dosage form
- Quantitative ^{1}H-NMR (internal standard method) for the assay of a drug substance
- 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 a property test
- NIR analytical procedure for core tablet assay
- Quantitative LC/MS analysis of trace impurities in product

Overview of ICH Q14: Minimal vs Enhanced approach

Minimal approach

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

Including the analytical procedure control strategy

Elements of the enhanced approach

- Evaluating the sample properties
- Defining the **analytical target profile (ATP)**
- Conducting risk assessment and evaluating prior knowledge
- Conducting uni- or multi-variate experiments

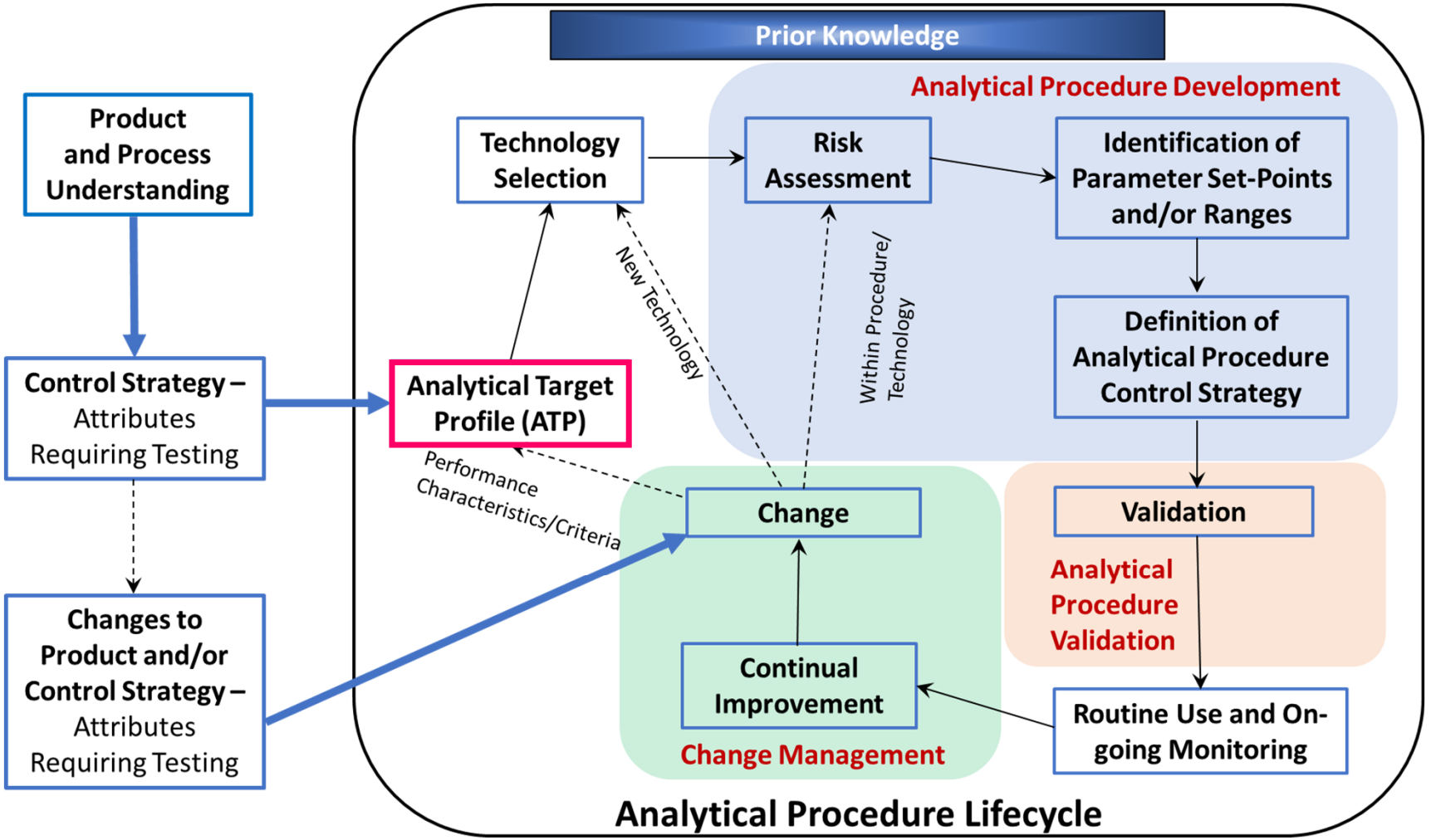
To explore ranges and interactions between identified analytical procedure parameters

- Defining the analytical procedure control strategy

Set-points and/or ranges for relevant analytical procedure parameters (e.g. PARs and MODRs)

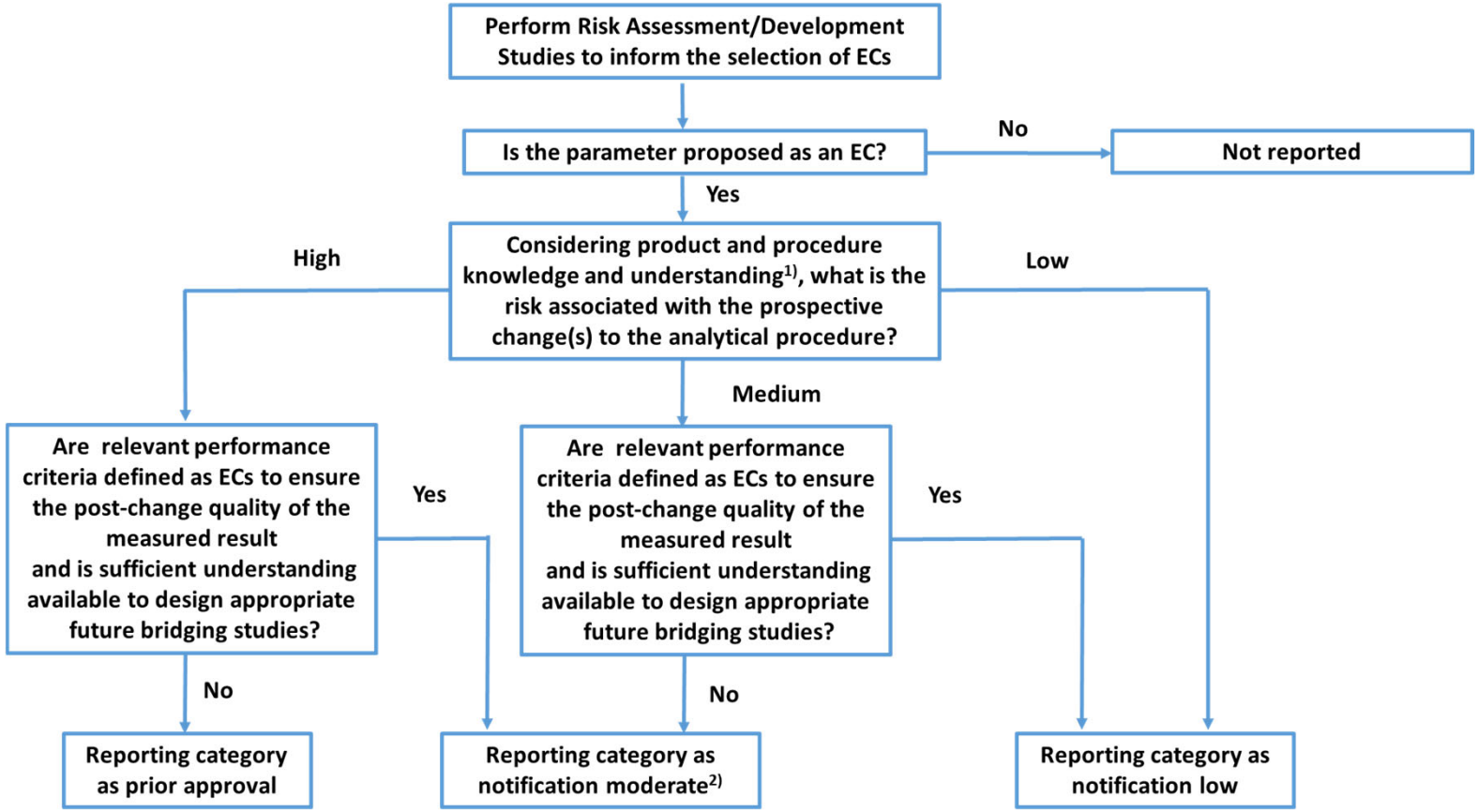
Copy from Q2(R2)/Q14 step 4 presentation with some modifications

Overview of ICH Q14: The Analytical Procedure Lifecycle



Overview of ICH Q14: Lifecycle Management and Post-Approval Changes

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



1) Including analytical procedure control strategy

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

Perspective on Japanese Pharmacopoeia (personal views)

Basic Principles for Preparation of JP19

"Five Principles for JP revision"

1. Enriching monographs by prioritizing inclusion of drugs which are important in healthcare
2. **Making qualitative improvement by introducing the latest science and technology**
3. **Promoting further internationalization** in response to globalization of drug market
4. Making prompt partial revision as necessary and facilitating smooth administrative operation
5. Ensuring of transparency regarding the revision, and disseminating the JP throughout Japan and the rest of the world

(Ministry of Health, Labour and Welfare, Administrative Notice, October 25, 2021)

The ICH guidelines are being actively incorporated.

Q. Is it possible to incorporate all of the elements described in ICH Q14 into the JP?

Q. Is it necessary to update the JP general information Validation of Analytical Procedure <*G1-1-130*> to reflect the revisions in ICH Q2 ?

Perspective on JP: Difference in Development Process

Development process in line with Q14

Manufacturer A

- Identifying attributes that need to be tested (Evaluating the sample properties)
- Defining the analytical target profile (ATP)
- Selecting technology
- Conducting risk assessment and uni- or multi-variate experiments
- Defining the analytical procedure control strategy (e.g. SST, set-pints, PARs, MODRs)
- Conducting analytical procedure **validation** following to ICH Q2
- **Implementation** of the analytical procedure

Process for newly listing of pharmacopoeia monograph

MHLW, JP Committee/PAFSC*
- Determination of Basic Principles
- Determination of Drugs to be listed in JP

*PAFSC: Pharmaceutical Affairs Food Sanitation Council

PMDA
- Requesting initial draft
- Initial modification of draft

Request / Draft submission

Company in Charge of Drafting

JP Expert Committees
- Expert Committees-Review
- Public Consultation
- Finalization of draft

Questions / Answers

Public Consultation

Pharmaceutical Industry & Other Stakeholders

MHLW, JP Committee/PAFSC*
- Adoption and Promulgation of JP
- Publication of JP

Public Consultation

- Conducting analytical procedure **verification**
- **Implementation** of analytical procedure

Multiple manufacturers

Manufacturer B　Manufacturer C　Manufacturer D . . .

Perspective on JP: Recent Trends in JP

Adoption and Implementation of G-20 Chromatography (JP18 first supplement)

General Tests 2.00 Chromatography

4. Adjustment of chromatographic conditions

The chromatographic conditions described have been validated during the elaboration of the monograph.

The extent to which the various parameters of a chromatographic test may be adjusted without fundamentally modifying the pharmacopoeial analytical procedures are listed below. Changes other than those indicated require revalidation of the procedure.

Multiple adjustments can have a cumulative effect on the performance of the system and are to be properly evaluated by the users. This is particularly important in cases where the separation pattern is described as a profile. In those cases, a risk assessment has to be carried out.

Any adjustments must be made on the basis of the pharmacopoeial procedure.

If adjustments are made to a pharmacopoeial procedure, additional verification tests may be required. To verify the suitability of the adjusted pharmacopoeial procedure, assess the relevant analytical performance characteristics potentially affected by the change.

When a pharmacopoeial analytical procedure has been adjusted according to the requirements stated below, no further adjustments are allowed without appropriate revalidation.

Compliance with the system suitability criteria is required to verify that conditions for satisfactory performance of the test or assay are achieved.

Q14: Prior Knowledge

Appropriate control strategy at each stage of a chromatography lifecycle is important.

General Information

Control Strategies and Change Control Concepts at Each Stage of Chromatography Lifecycle (Change Control in Chromatography Lifecycle) <*G1-5-181*>

Objective

Describes the outline of the methodology for establishing control strategy at each stage of a chromatography lifecycle, aiming at the efficient control of analytical procedures, including changes of analytical methods

Table of contents

1. Analytical procedures that give test results suitable for the purpose of the test
2. Design and development of the draft procedure of chromatography
3. Preparatory stage for qualification
4. Qualification of analytical procedure performance
5. Continuous verification of Analytical Methods
   1) Routine monitoring
   2) Change of analytical procedures
      ① within acceptable range
      ② beyond the acceptable range
      ③ laboratory change
      ④ new analytical procedure or technology
      ⑤ target profile
6. References (USP <1220> etc.)

Q14:
Defining Analytical Target Profile (ATP)

Q14:
- Conducting risk assessment
- Conducting multivariate experiments
- Defining the analytical procedure control strategy

Q14:
On-going monitoring

Q14:
Change within/beyond PARs, MODRs

Q14:
- Evaluation of prior knowledge including development data
- Additional experiments

Comparison between ICH Q2(R2) and JP General Information <*G1-1-130*> Validation of Analytical Procedures

	ICH Q2(R2)	JP <*G1-1-130*>
Objective	To present elements for consideration during the validation of analytical procedures included as part of registration applications	To present required data for analytical procedures to be carried in the JP
Scope	Analytical procedures used for release and stability testing of commercial drug substances and products	• When an analytical procedure is to be newly carried in the JP • When a test carried in the JP is to be revised • When the test carried in the JP is to be replaced with a new test according to regulations in general notices.
Methodology	New items • Considerations for multivariate analytical procedures • Specificity : Technology inherent justification • Range: Non-linear response, Multivariate calibration • Combined approaches for accuracy and precision	(The contents of previous ICH Q2 and the JP <*G1-1-130*> are not the same.)

Summary

- ✓ ICH Q2(R2) and Q14 describe development and validation activities during the lifecycle of analytical procedures
- ✓ Many of the methodologies required to actually carry out what is described in ICH Q2(R2) and Q14 are supported by pharmacopoeias.
- ✓ The concepts or elements described in Q14 have already been partially incorporated in JP.
- ✓ The JP Validation of Analytical Procedure may not necessarily match ICH Q2(R2), considering each objective and expected role. However, some of new items could be incorporated into JP.

Future challenges and expectations

- ✓ When listing an analytical procedure developed using the enhanced approach of Q14, it may be necessary to discuss whether information on the analytical procedure performance should be described in the pharmacopoeia monograph.
- ✓ Look forward to seeing how the JP becomes the pharmacopoeia that can incorporate latest technologies and present ways to utilize the technologies, given the differences in the nature and role of the JP and ICH guidelines.