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Role of ICH Q2/Q14 and ICH Q6 on establishment of control strategy

Hiroko Shibata, PhD.
Division of Biological Chemistry and Biologicals,
National Institute of Health Sciences

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Outline

- **Overview of Q2/Q14 Analytical Procedure Development and Validation of Analytical Procedure**
- **Role of ICH Q2/Q14 and ICH Q6 on Establishment of Control Strategy**
- **Future Prospects**

Overview of Q2/Q14
Analytical Procedure Development and Validation of Analytical Procedure

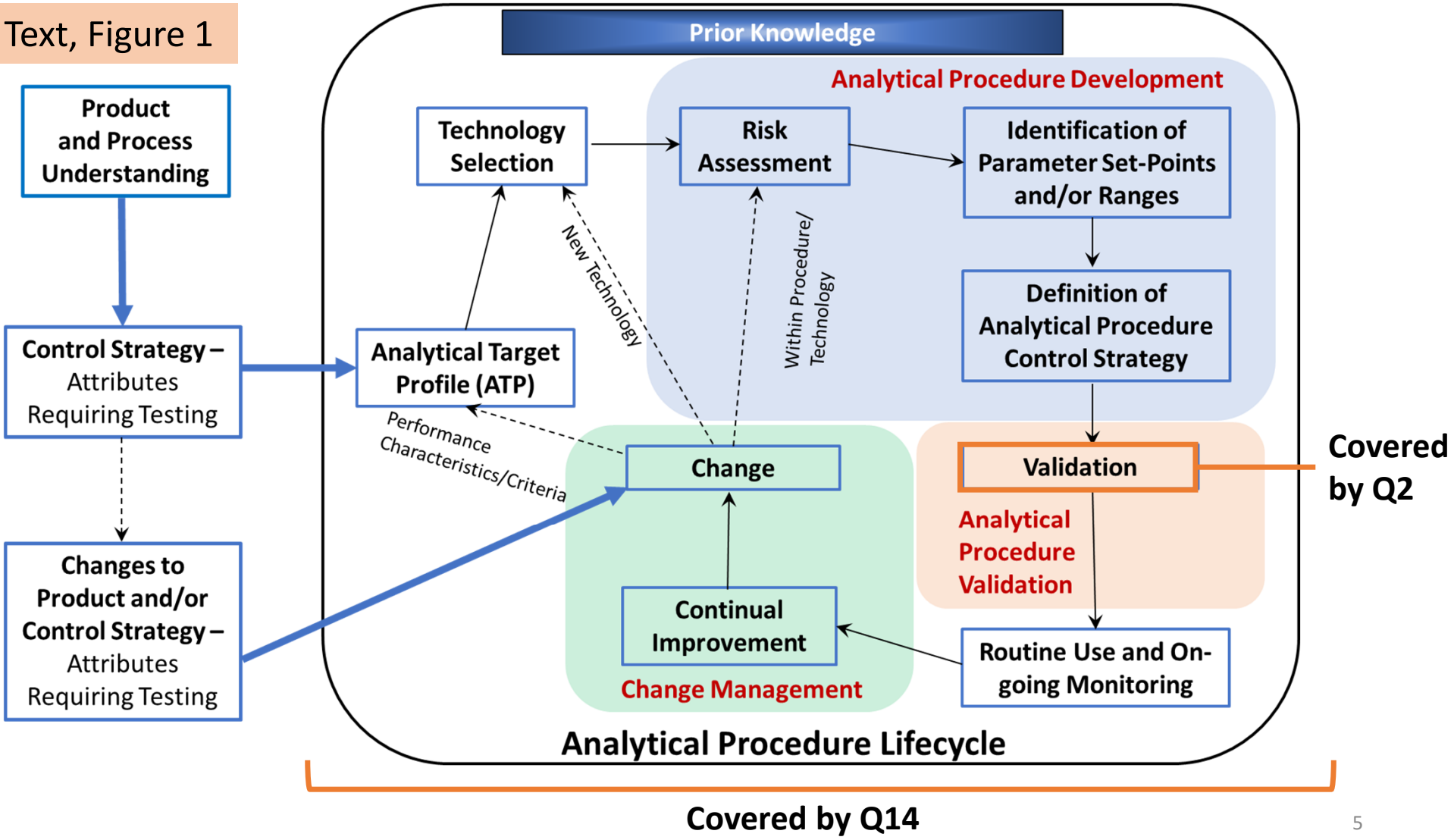
Overview of ICH Q2/14: Scope

- This guideline applies to analytical procedures used for **release and stability testing** of commercial drug substances and products.
- The guideline 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.**
- The scientific principles described in this guideline can be applied in a phase-appropriate manner to analytical procedures used during clinical development.

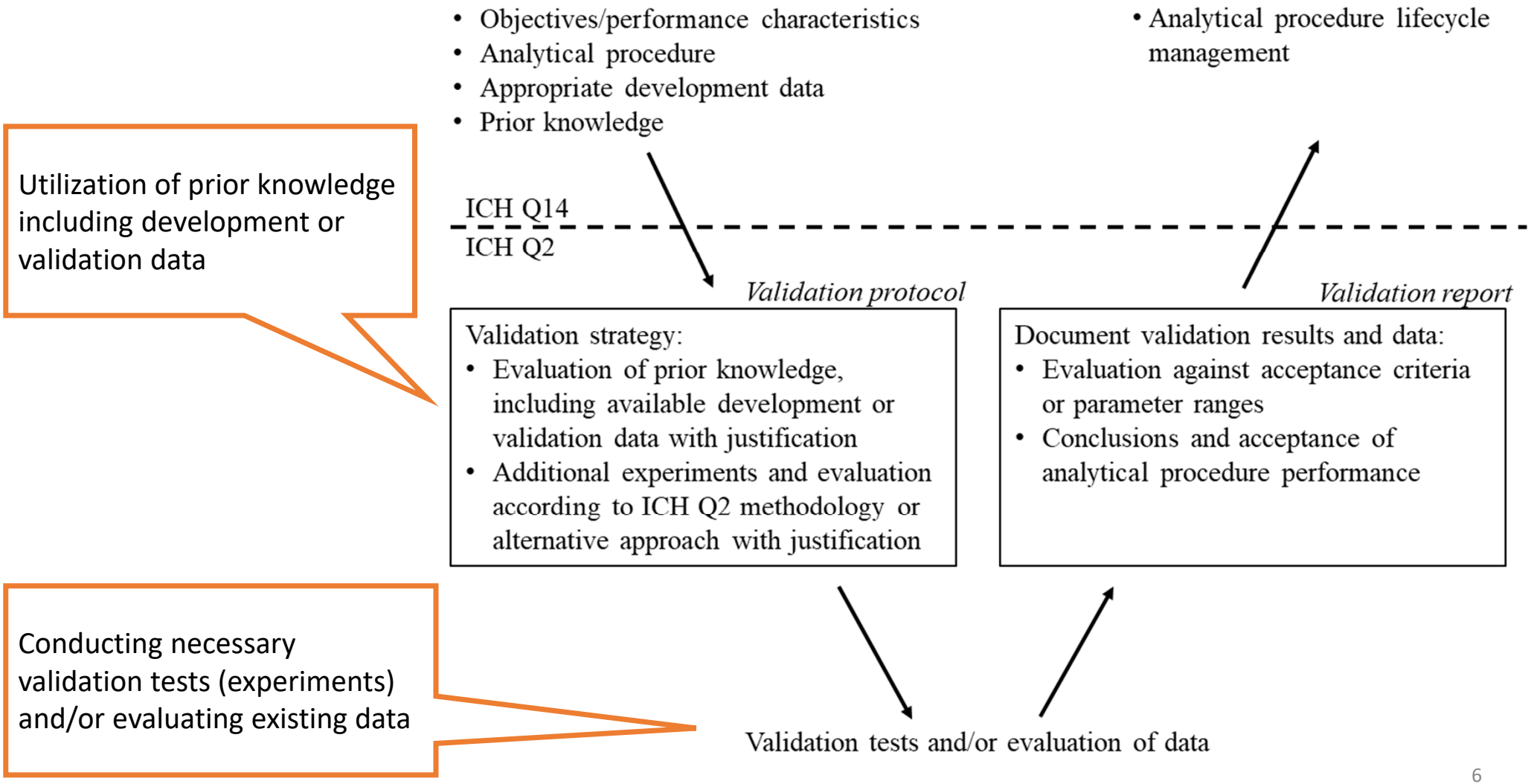
- Test procedures in a specification are within the scope.
- There are no limitations on the types of drugs covered by the scope.

Overview of ICH Q2/14: The Analytical Procedure Lifecycle

Q14 Main Text, Figure 1



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



Overview of ICH Q14: Minimal vs Enhanced Approach

Minimal approach (Traditional 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: Minimal vs Enhanced Approach

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.

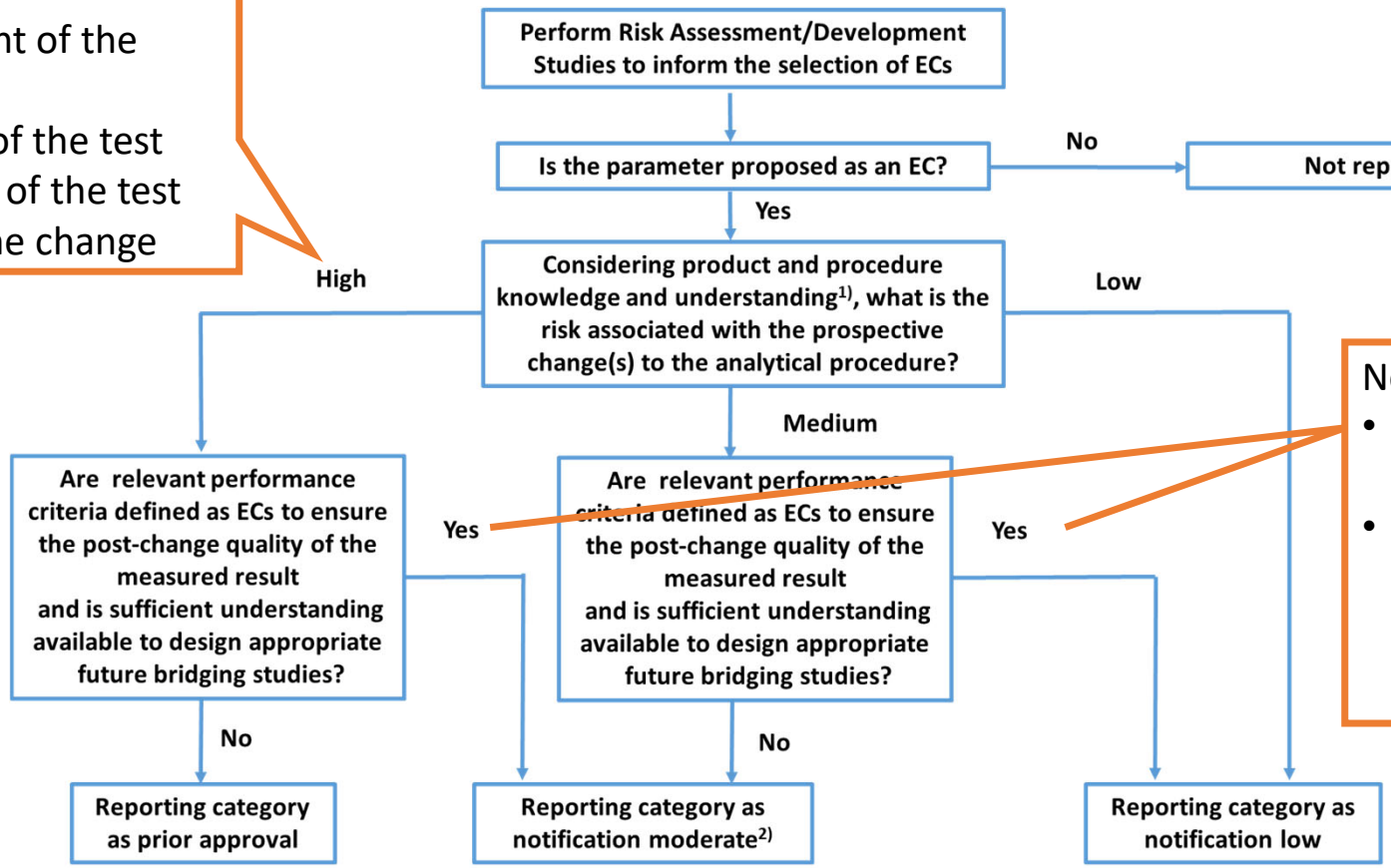
ATP is a **technology-independent** element.

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

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

Example:
Risk assessment of the change
- Relevance of the test
- Complexity of the test
- Extent of the change



Note:
- Performance criteria should be defined as ECs.
- Sufficient understanding should be available to design appropriate future bridging studies.

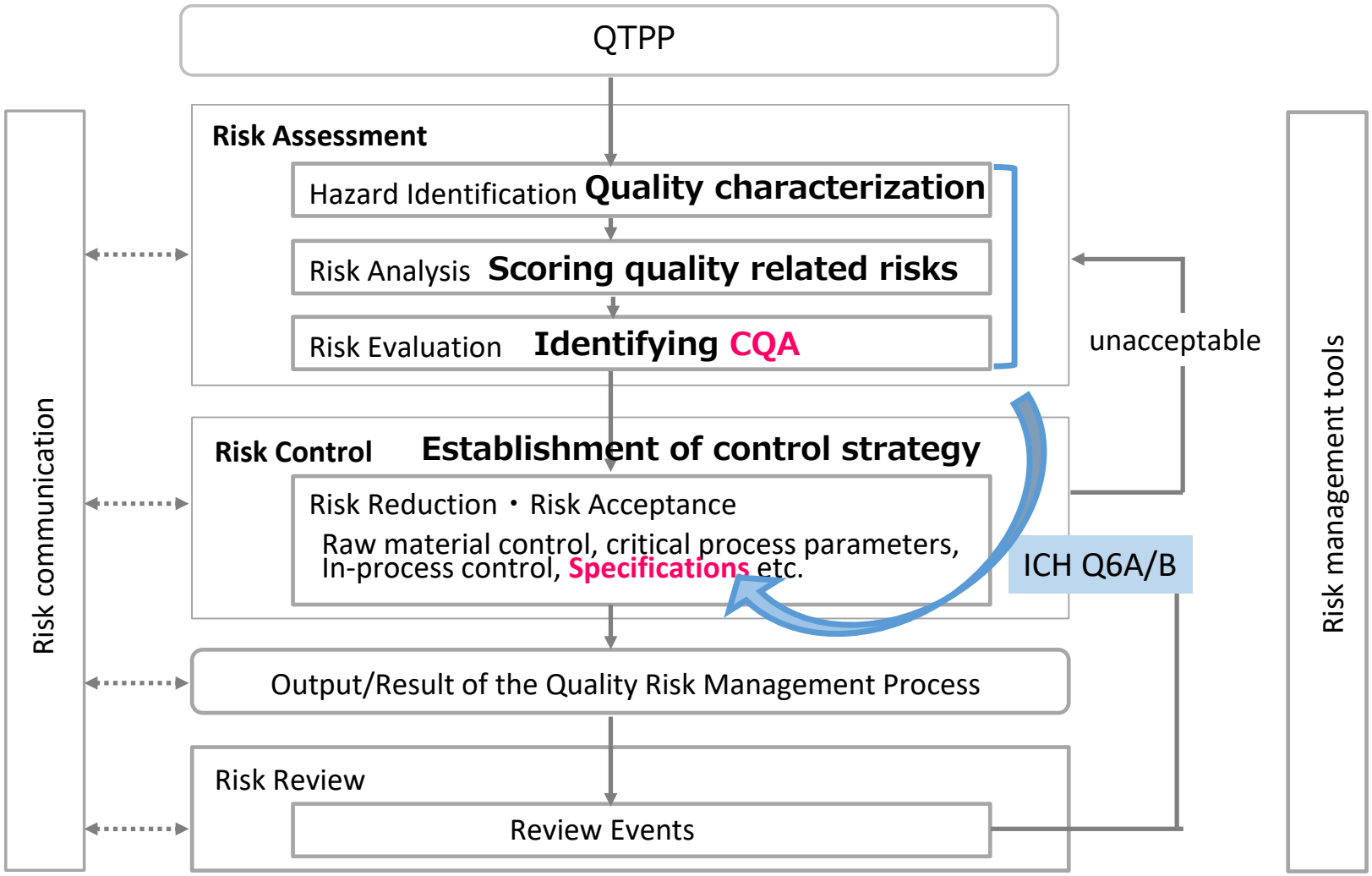
1) Including analytical procedure control strategy

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

Role of ICH Q2/Q14 and ICH Q6B on Establishment of Control Strategy

Overall Flow of Control Strategy Establishment

ICH Q8-Q11



Example: Control of CQAs in a Control Strategy

T-mab: human IgG1, Inhibition of target cell proliferation, effector activity via Fc domain

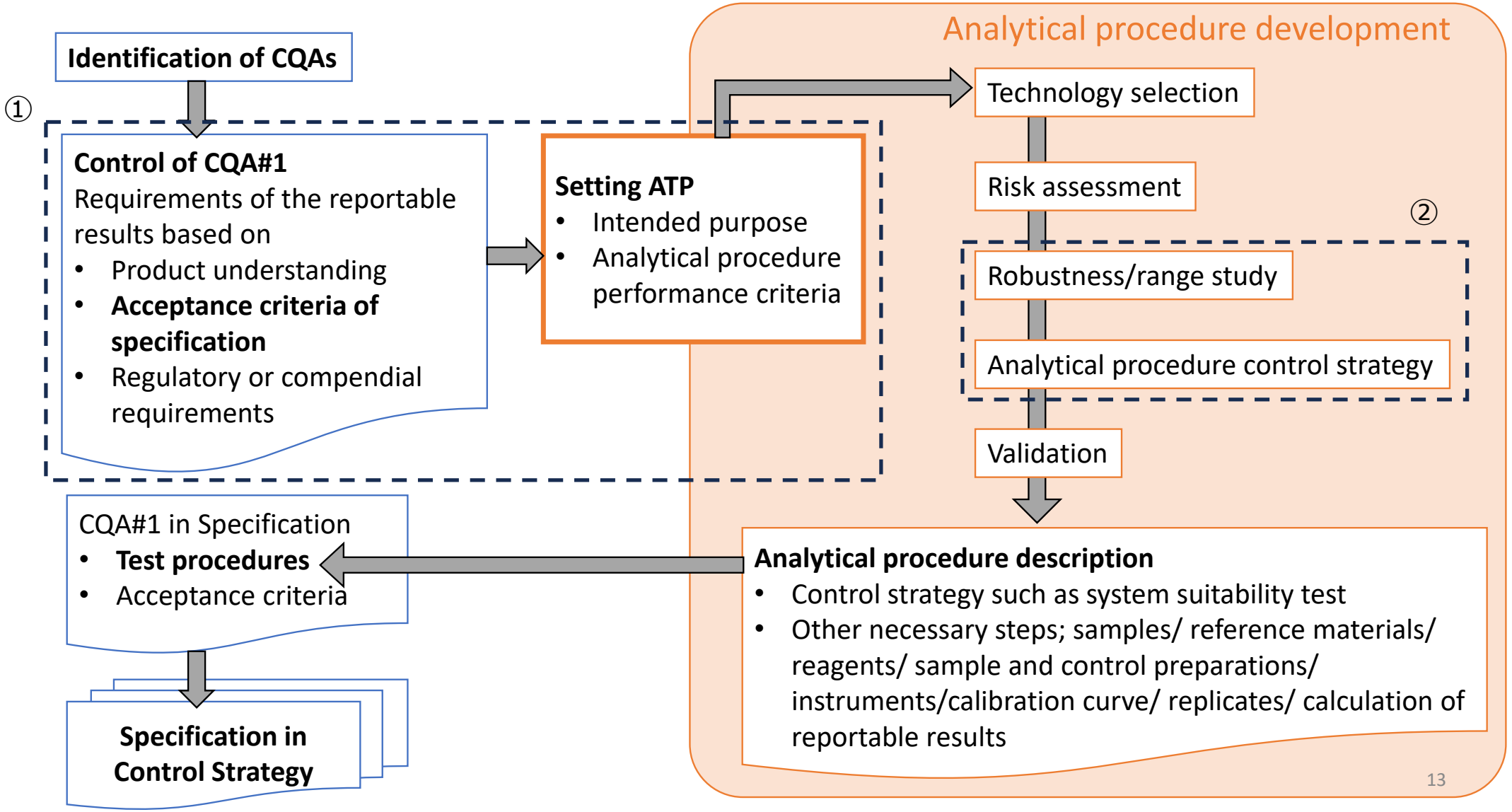
ICH Q6A/B

ICH Q1/Q5C

CQA **Drug substance**	**Raw material Control**	**≈**	**Process Evaluation**	**Process Control**	**In-process Test**	**Process Monitoring**	**Specification**	**Stability**
Potency				✓			✓	✓
Aggregation			✓	✓			✓	✓
Deamidation				✓			✓	✓
Oxidation				✓			✓	✓
Afucosylation	✓			✓			✓	
Galactosylation	✓			✓			✓	
High mannose	✓			✓			✓	
≈								
HCP	✓		✓	✓				
DNA	✓		✓	✓				
Microorganisms	✓			✓	✓	✓	✓	✓
Virus	✓		✓	✓	✓			

ICH Q2(R2)/Q14

How Q14 Elements can be used for Specification Setting



ATP and Specification Acceptance Criteria

Example of ATP

Q14 Annex A, 13.1.2 : Measurement of Potency for an anti-TNF-alpha Monoclonal Antibody

Intended Purpose

Measurement of the **potency** of an anti-TNF-alpha monoclonal antibody in drug substance and in drug product at **release and for stability testing**

Link to CQA (biological activity)

The mode of action of the drug is the neutralization of the biological activity of soluble TNF-alpha by preventing TNF-alpha from binding to the TNF-alpha receptor.

Target acceptance criteria: 80% to 125% relative potency.

Generally, performance criteria will be defined considering risks to make incorrect decisions.

Intended Purpose

Measurement of the potency of an anti-TNF-alpha monoclonal antibody in drug substance and in drug product at release and for stability testing.

Link to CQA

neutralisation of the biological activity of soluble TNF-alpha by preventing TNF-alpha from binding to the TNF-alpha receptor. Target acceptance criteria: 80% to 125% relative potency[1)]

Characteristics of the reportable result

Performance Characteristics	Acceptance Criteria for Performance Characteristics	Rationale
Accuracy	overs the reportable range. No bias is observed over the tested relative potency range The 95% confidence interval of the slope of the fitted regression line between theoretical and measured potency falls within a range of 0.8 to 1.25 The upper and lower 90% confidence interval for the relative bias calculated at each potency level is not more than 20%[1)]	Parameters are assessed based on compendial guidance The acceptance criteria are determined considering the intended purpose of the measurement Selected performance characteristic ensures that the intended analytical procedure delivers the quality of the reportable result
Precision	Upper 95% confidence interval for the average intermediate precision across levels across the reportable range (95% CI % geometric coefficient of variation) is not more than 20%[1)]	
Specificity	Analytical procedure is specific for the intended mechanism of action of the active ingredient	Critical characteristic of a bioassay to ensure specificity towards the targeted biological activity
	No interference from relevant process related impurities or matrix components	For example, process related and matrix components do not significantly affect the characteristics of the dose response curve
	Assay is stability indicating *i.e.*, capable of detecting a change in potency and/or a change in the shape of the dose response curve, confirmed using forced degraded samples	To ensure that the product remains within specification over its shelf-life
Reportable Range	The potency range is the range that meets accuracy and precision. It should include the specification range (80% to 120% of the specification range in this case corresponding to 64% to 150% for a specification of 80% to 125% relative potency[1)])	Stated range for which the required accuracy and precision characteristics are demonstrated

1) Individual values are just an example and can be different from product to product.

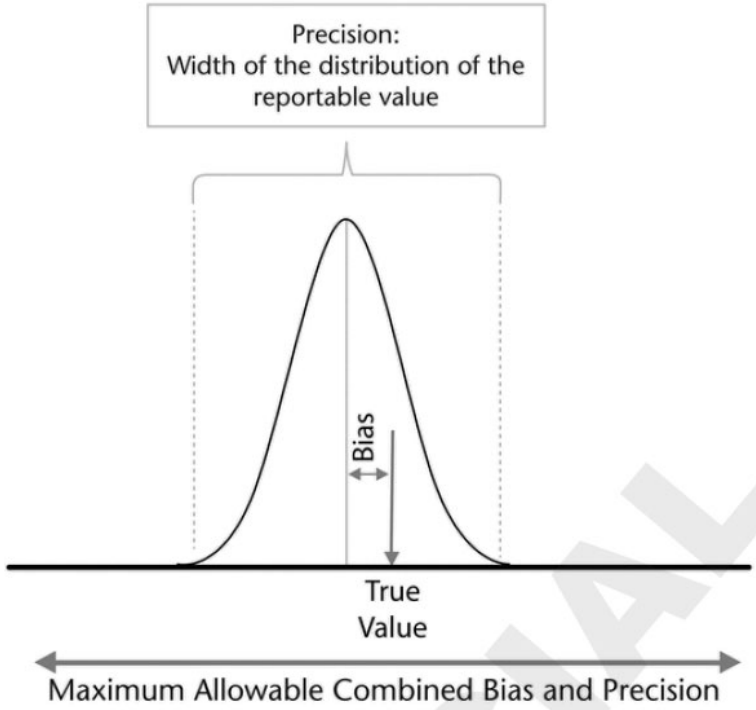
ATP and Specification Acceptance Criteria

USP <1220> Analytical Procedure Life Cycle

Points to consider for performance criteria settings

Appropriate limits for bias and precision in the ATP can be determined based on several factors, including:

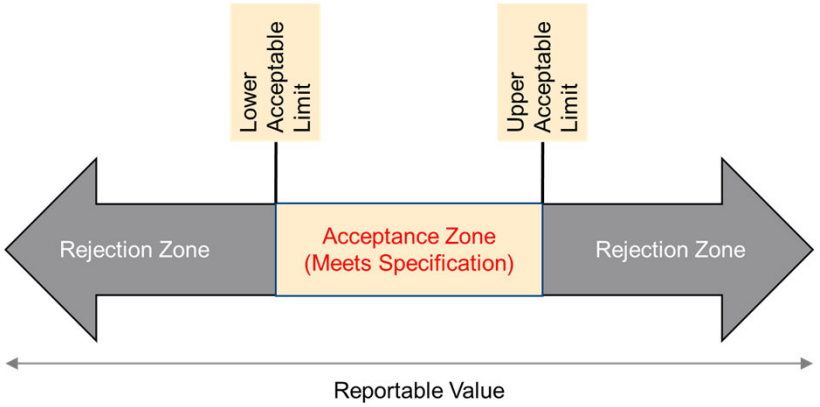
- The criticality of the quality attribute being measured
- The risk that an unacceptable error could occur
- The width of the **specification acceptance range for the quality attribute measured** by the procedure
- The potential clinical safety or efficacy impact (if known) that an analytical error can have



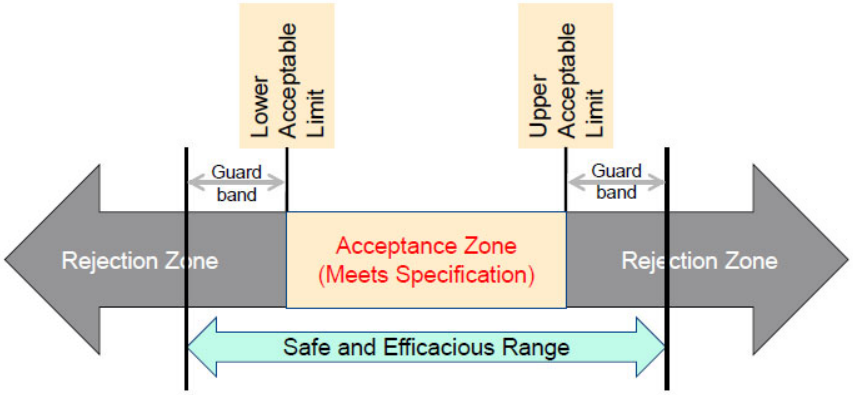
ATP and Specification Acceptance Criteria

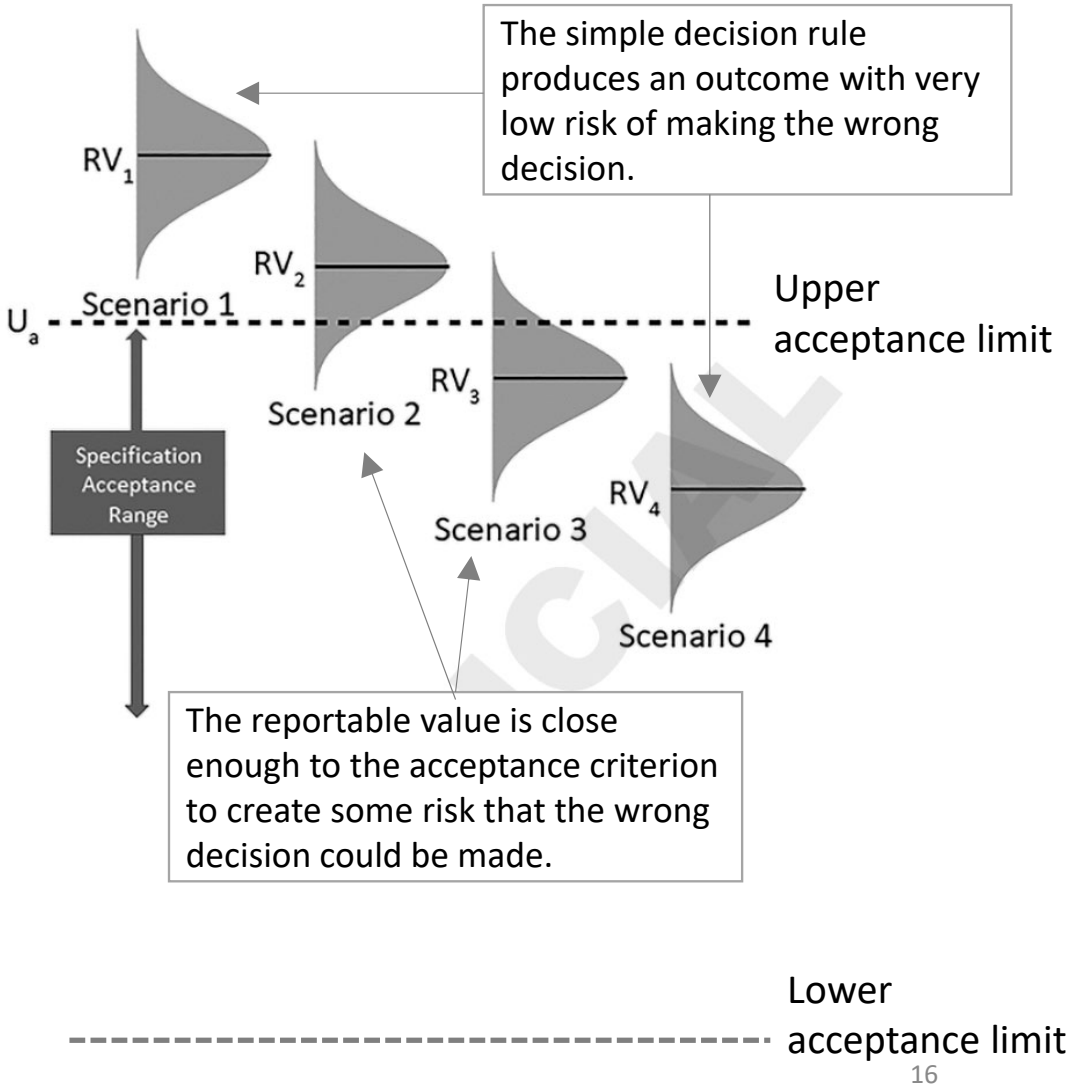
USP <1220> Analytical Procedure Life Cycle

Simple decision rule



Decision rule using guard bands





ATP and Specification Acceptance Criteria

Specification Acceptance Criteria

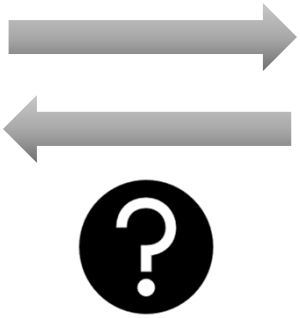
Control of CQA#1
Requirements of the reportable results based on

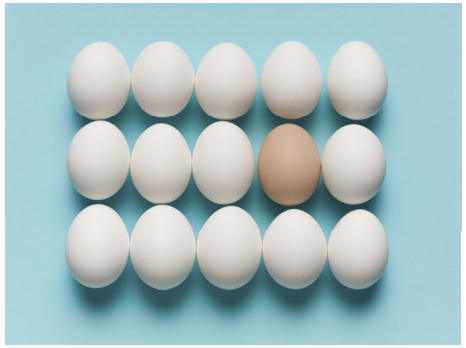
- Product understanding
- **Acceptance criteria of specification**
- Regulatory or compendial requirements

Performance criteria of analytical procedure

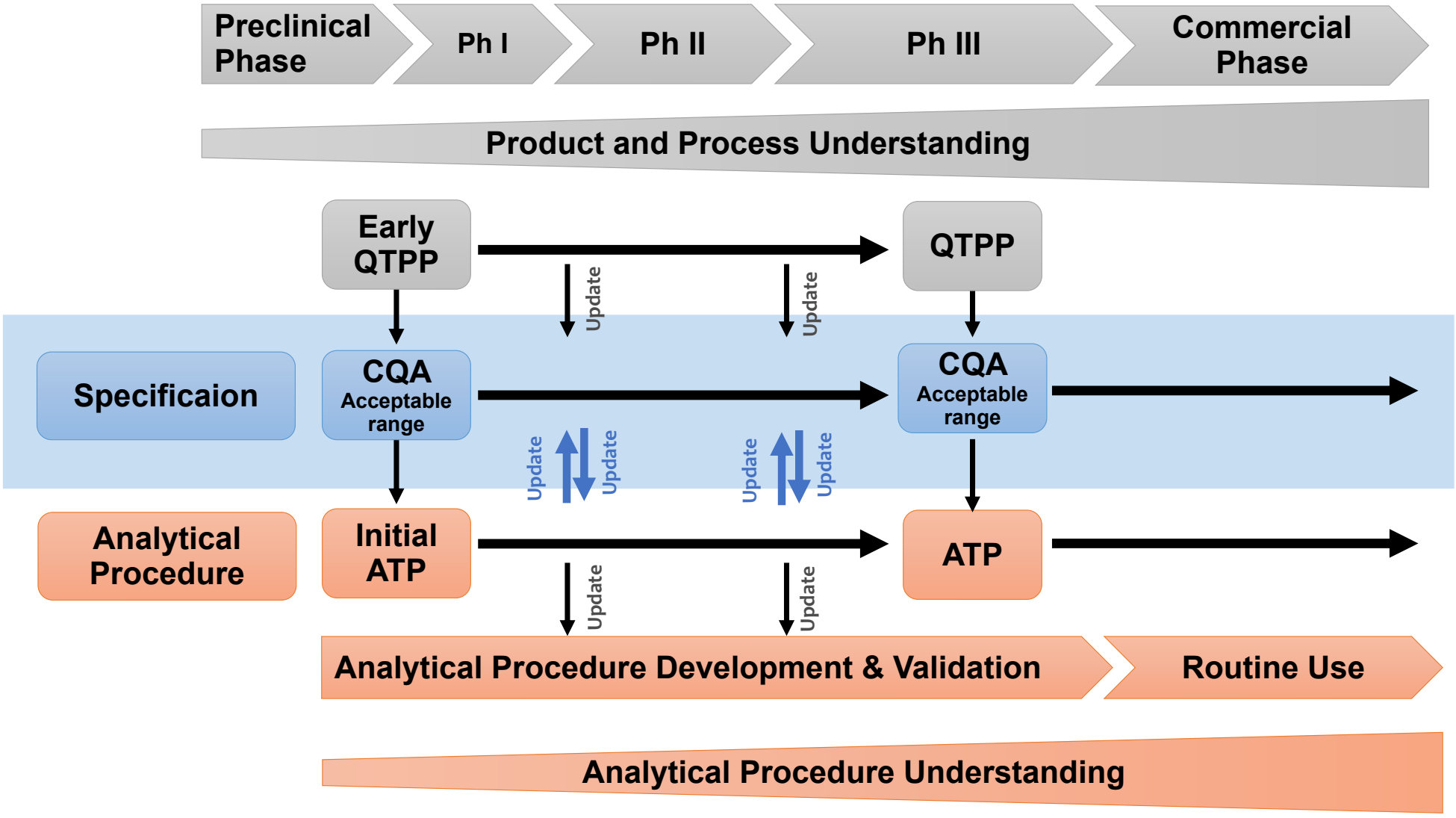
Setting ATP

- Intended purpose
- Analytical procedure performance criteria





Personal Perspective

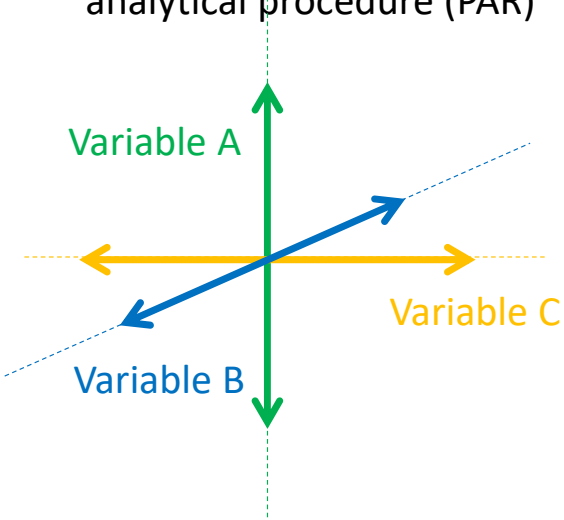


Q14 Chapter 5

Parameter Ranges of Analytical Procedures

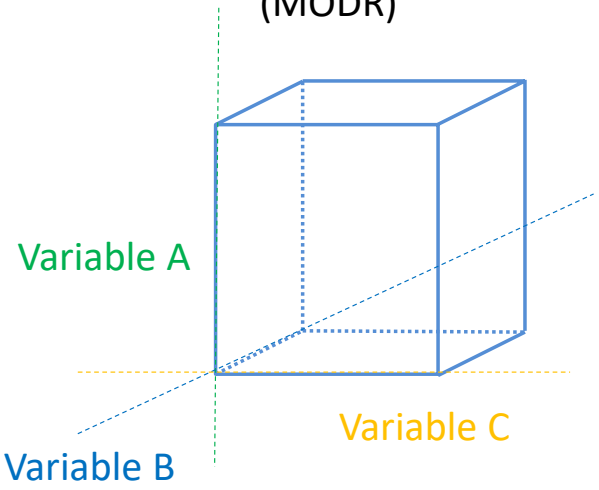
- One way to utilize knowledge gained through DoE etc. (understanding the relationship between input and output)
- Relevant analytical procedure attributes and their criteria used for defining the ranges are derived from ATP.
- Proposed by applicant based on development data and requires regulatory approval
- Changes to the parameters within established ranges or regions are not subject to regulatory approval.

Proven acceptable range for analytical procedure (PAR)



Ranges/regions proven to meet relevant performance criteria

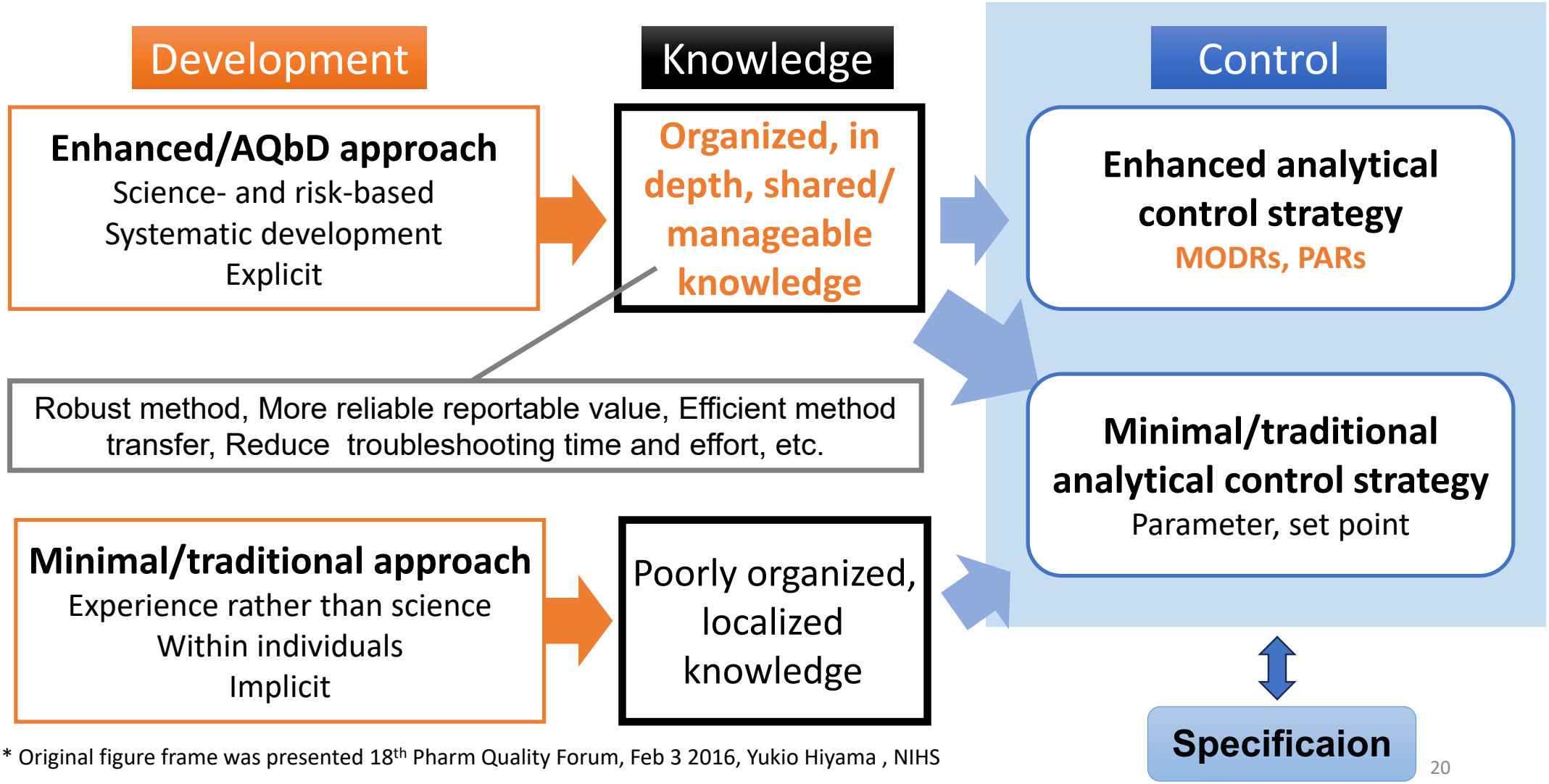
Method operable design region (MODR)



◆ Range for each variable
◆ Univariate experiment
＊It is not intended to move multiple variables at the same time.

◆ Combining ranges of two or more variables
◆ Multivariate experiment (DoE)
◆ Parameter interactions

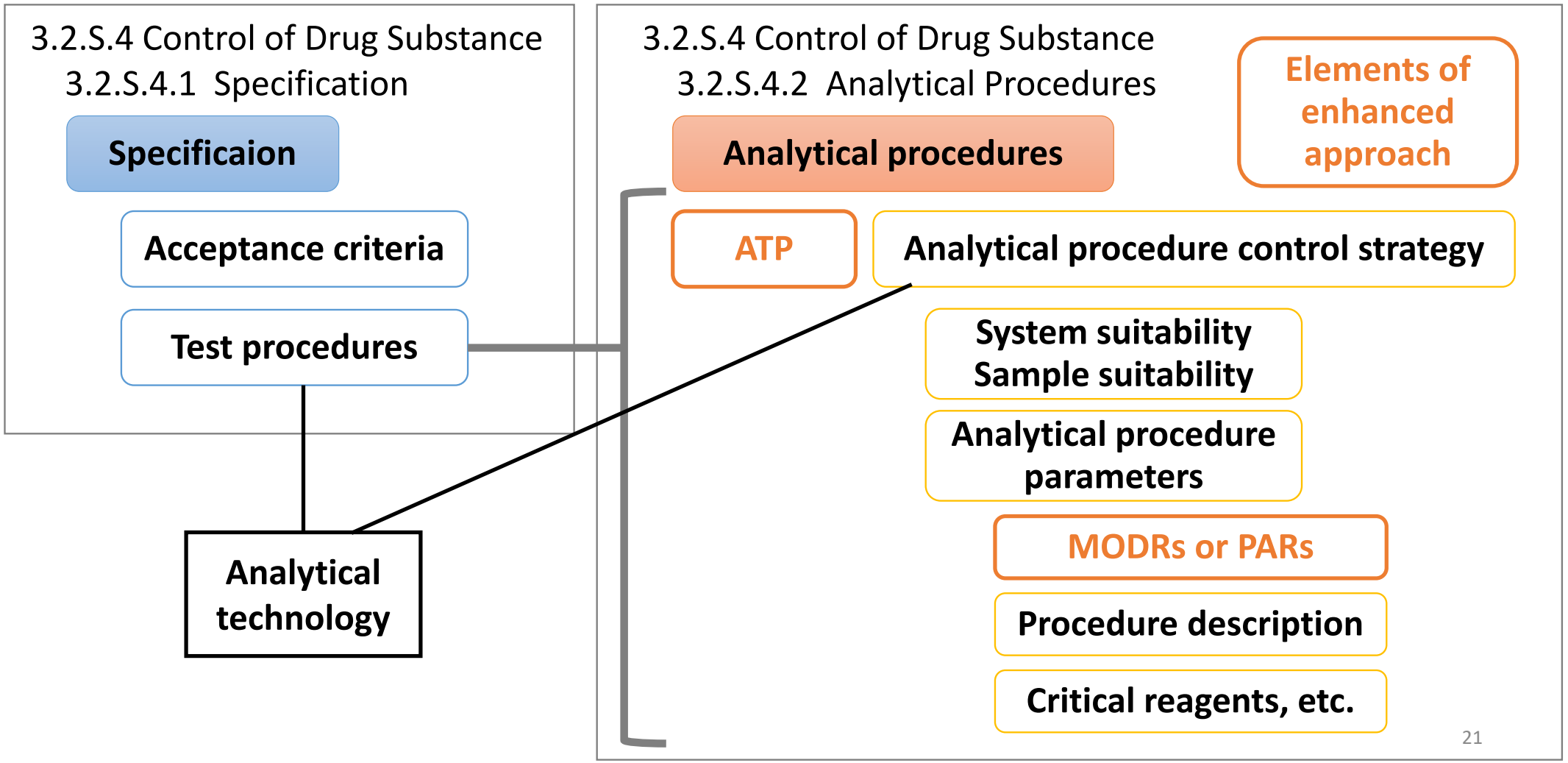
Relationship with Development Approach and Knowledge/Control



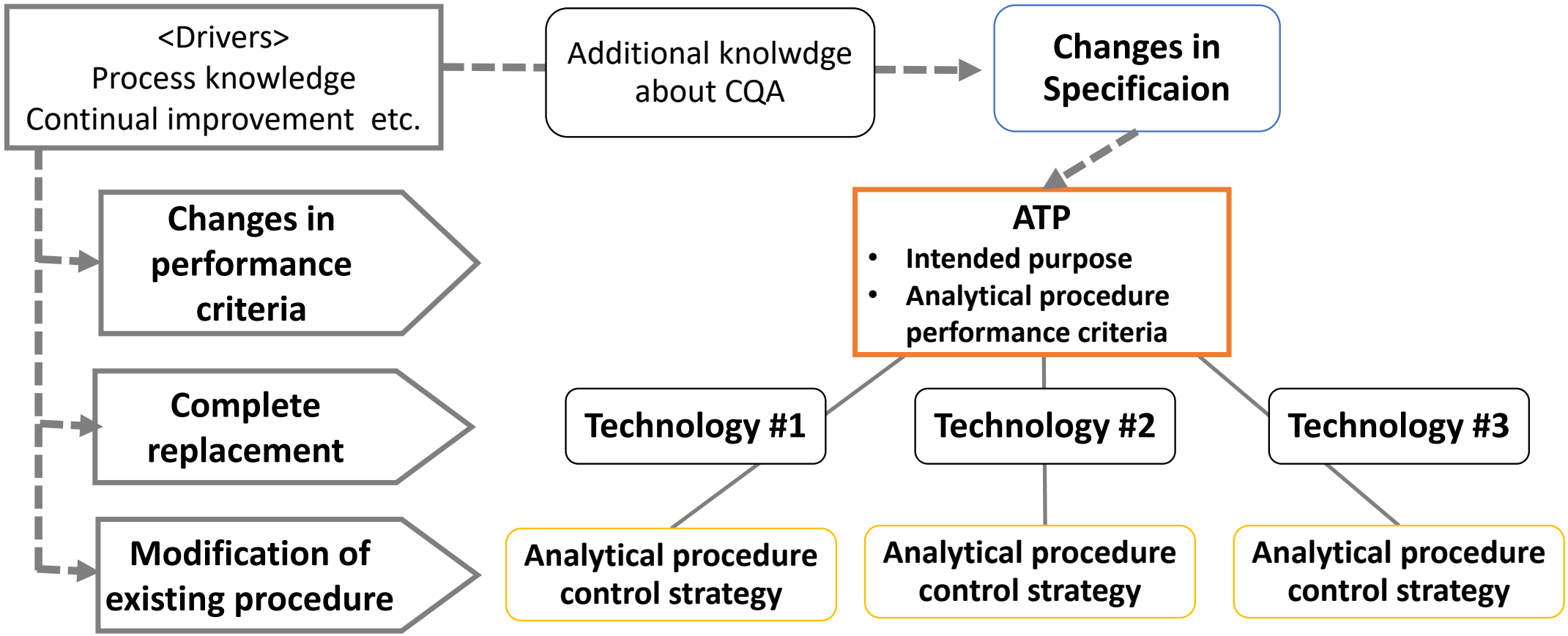
* Original figure frame was presented 18th Pharm Quality Forum, Feb 3 2016, Yukio Hiyama , NIHS

Impact of using Enhanced Approach for Analytical Procedure Development on Specification

ICH Q14



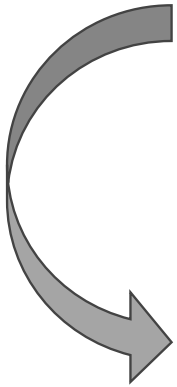
Impact of using Elements of Enhanced Approach on Change Management of Analytical Procedures

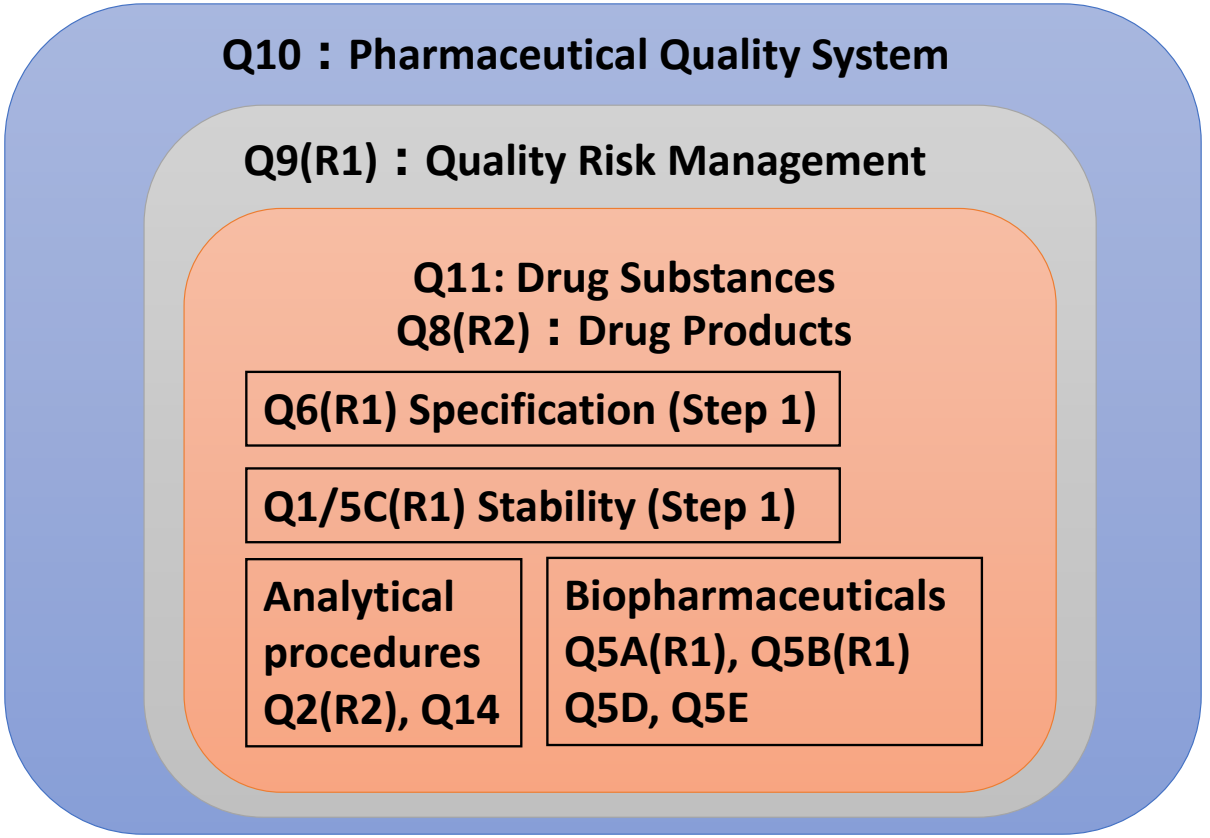


ATP may facilitate to improve or revolve analytical technology and analytical procedure through the lifecycle.

Future Prospects

Risk and Science-based Approach





Q12：Lifecycle Management

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