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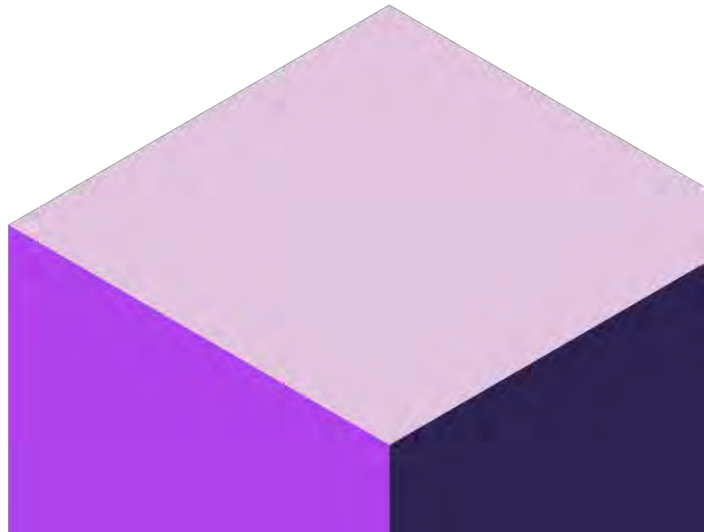

Development and validation of analytical methods

The latest Updates of ICH Q2(R2) and Q14

Lecturer
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July 12, 2023

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Purpose

Differences between previous and new (draft) ICH Q2 guideline Validation of analytical procedures, March 2022

High level review of ICH Q14 (draft) guideline: Analytical procedure development, March 2022

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Guidelines for Analytical Method

ICH_Q14_draft analytical procedure development

ICH-Q2(R2) “Validation on Analytical Procedures: Text and Methodology”, Draft, March 2022

USP <1225> Validation of Compendial Procedure

USP <1226> Verification of Compendial Procedure

USP <1227> Validation of microbial recovery from pharmacopeial articles

USP <1220> Analytical procedure life cycle

USP <1010> Analytical Data—Interpretation And Treatment

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ICH Q2- Validation of analytical procedures

"Old" vs. "New" – STARTING FROM THE END...

Old definition

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics

New definition

An evaluation of prior knowledge, data or deliberate experiments to determine the suitability of an analytical procedure for its intended purpose. (ICH Q2)

A validation study is designed to provide sufficient evidence that the analytical procedure meets its objectives. These objectives are described with a suitable set of *performance characteristics* and related *performance criteria*, which can vary depending on the intended use of the analytical procedure and the specific technology selected. The section "VALIDATION TESTS,

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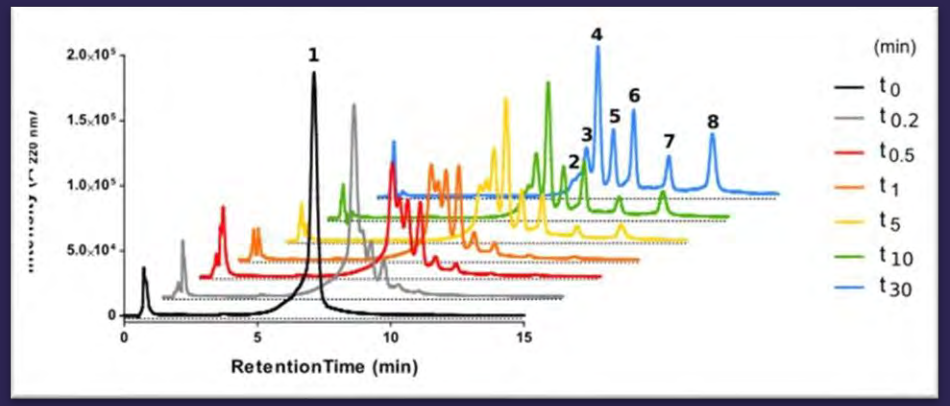
ICH Q2 - Scope



Added in the new guideline:

testing of commercial drug substances and products (chemical and biological/biotechnological). The guideline can also be applied to other analytical procedures used as part of the control strategy (*ICH Q8-Q10*) following a risk-based approach. The scientific principles described in this guideline can be applied in a phase-appropriate manner during clinical development. This guideline may also be applicable to other types of products, with appropriate regulatory authority consultation as needed.

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ICH Q2 – requirements per assay type Old vs. New

Type of analytical procedure characteristics	IDENTIFICATION	TESTING FOR IMPURITIES quantitat.	 limit	ASSAY - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

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)

MAJOR CHANGES, however, mostly not lab-relating

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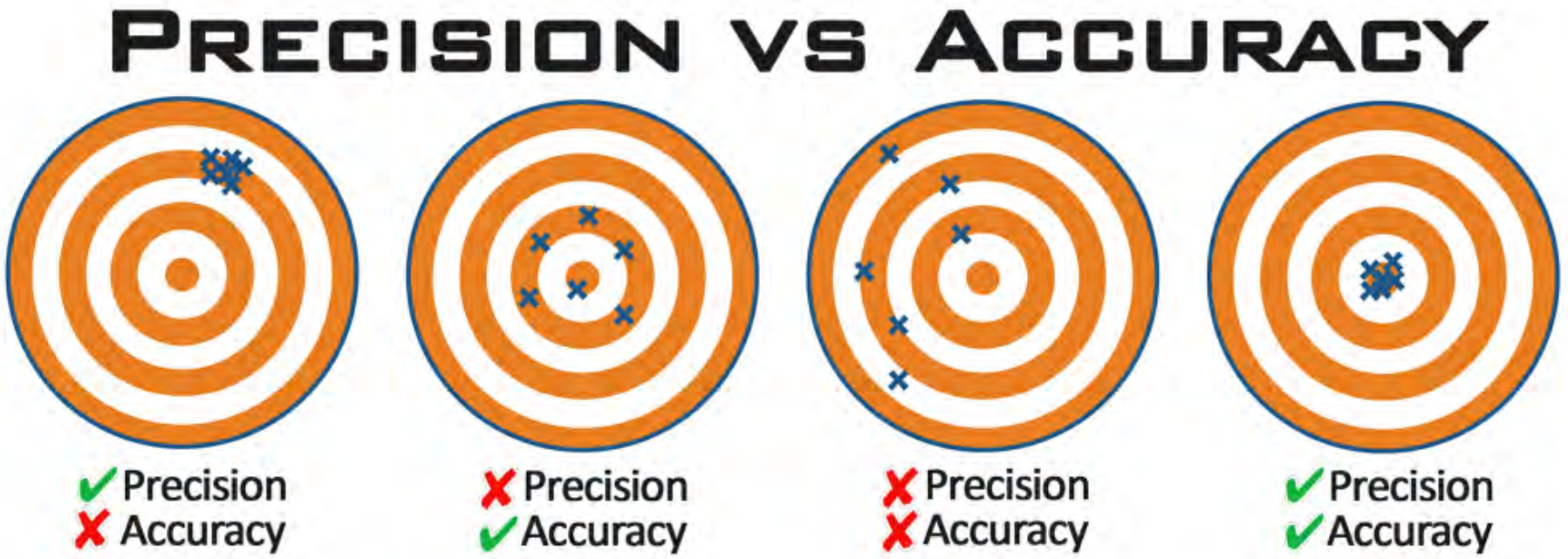

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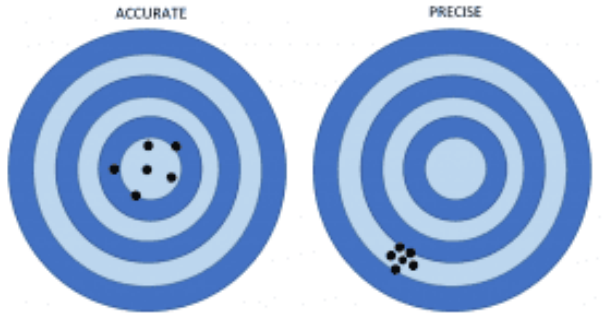
ICH Q2 – Accuracy

Mostly similar to previous version (Spiking added)



4.3.1.1 Reference material comparison

The analytical procedure is applied to an analyte of known purity (*e.g.*, a reference material, a well characterized impurity or a related substance) and the measured *versus* theoretically expected result is evaluated.

4.3.1.2 Spiking Study

The analytical procedure is applied to a matrix of all components except the analyte where a known amount of the analyte of interest has been added. In cases where all the expected components are impossible to reproduce, known quantities of the analyte can be added to the test sample. The results from measurements on unspiked and spiked samples are evaluated.

4.3.1.3 Orthogonal Procedure comparison

The results of the proposed analytical procedure are compared with those of a second well-characterized procedure that ideally applies a different measurement principle (independent

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ICH Q2 – Precision

No major change

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ICH Q2 – Accuracy and Precision

Combined approaches

An alternative to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion. The approach should be reflective of the individual criteria that would have been established for accuracy and precision.

Combined accuracy and precision can be evaluated by use of a prediction interval (to assess the probability that the next reportable value falls within the acceptable range) or a tolerance interval (to assess the proportion of all future reportable values that will fall within the acceptable range). Other approaches may be acceptable if justified.

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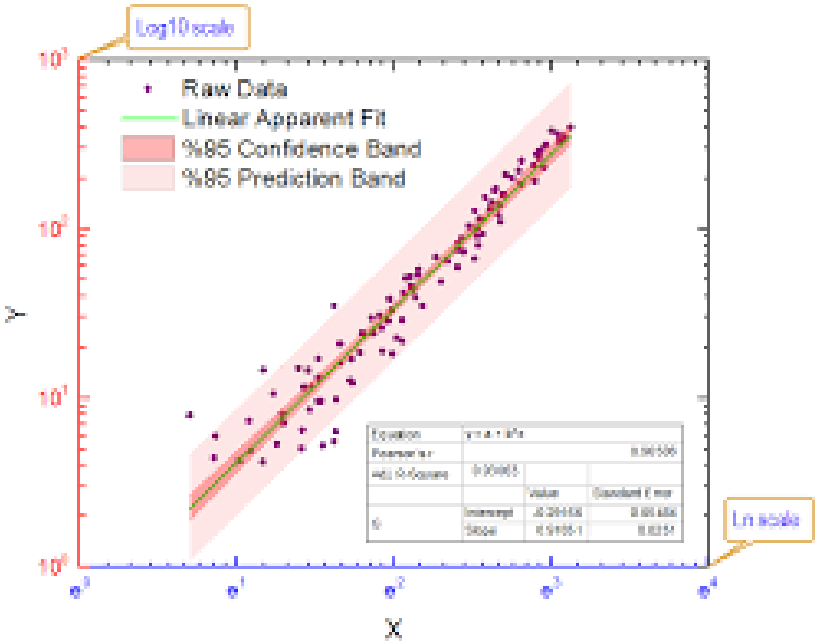
ICH Q2 – Linearity: additional evaluation recommended

Data derived from the regression line may help to provide mathematical estimates of the linearity. A plot of the data, the correlation coefficient or coefficient of determination, y-intercept and slope of the regression line should be provided. An analysis of the deviation of the actual data points from the regression line is helpful for evaluating linearity (*e.g.*, for a linear response, the impact of any non-random pattern in the residuals plot from the regression analysis should be assessed).

For the establishment of linearity, a minimum of five concentrations appropriately distributed



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ICH Q2 – Specificity – ID, no major change

Comparison to known RS
Negative result from placebo
Negative result from closely related substances

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ICH Q2 – Specificity for Assay, purity and impurity tests

Old version

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately labelled. Similar considerations should be given to other separation techniques.

Critical separations in chromatography should be investigated at an appropriate level. For critical separations, specificity can be demonstrated by the resolution of the two components which elute closest to each other.

Addition in new version

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.

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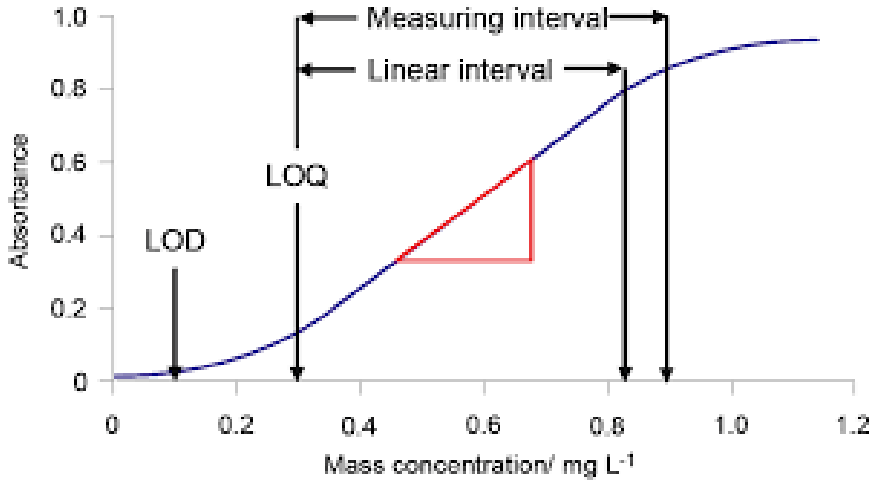
ICH Q2 – Quantitation limit

Old and new version (10 S/N)

7.4 Recommended Data

The quantitation limit and the method used for determining the quantitation limit should be presented.

The limit should be subsequently validated by the analysis of a suitable number of samples known to be near or prepared at the quantitation limit.



Nice addition in new version :)

If the QL was estimated, the limit should be subsequently validated by the analysis of a suitable number of samples known to be near or at the QL. In cases where the QL is well below (*e.g.*, approximately 10 times lower than) the reporting limit, this confirmatory validation can be omitted with justification.

For impurity tests, the quantitation limit for the analytical procedure should be equal to or below the reporting threshold.

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ICH Q2 – Stability indicating method

New section

quality attributes of a drug substance or drug product during storage, the procedure is considered a stability-indicating test. To demonstrate specificity/selectivity of a stability-indicating test, a combination of challenges should be performed with appropriate justification from development studies. These can include: the use of samples spiked with target analytes

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ICH Q2 – Robustness

Refers to ICH Q14

The robustness of an analytical procedure is a measure of its capacity to meet the expected performance requirements during normal use. Robustness is tested by deliberate variations of analytical procedure parameters. (ICH Q14)

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.

For further details, see ICH Q14.

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ICH Q2 –THE HIGHLIGHT

8 ANNEX 2 ILLUSTRATIVE EXAMPLES FOR ANALYTICAL TECHNIQUES

Table 3: Examples for Quantitative separation techniques

Technique	**Separation techniques (HPLC, GC, CE) for impurities or assay**	**Separation techniques with Relative Area Quantitation, e.g., product-related substances such as charge variants**
Performance characteristic	**Validation study methodology**	
Specificity / Selectivity	Absence of relevant interference: With DS, DP, buffer, or appropriate matrix, and between individual peaks of interest Spiking with known impurities / excipients or By comparison of impurity profiles by a secondary method Demonstration of stability-indicating properties through appropriate forced degradation samples, if necessary.	Absence of relevant interference: With DS, DP, buffer, or appropriate matrix, and between individual peaks of interest Demonstration of stability-indicating properties through appropriate forced degradation samples if necessary.

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And now, for something completely different.

Or NOT?

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ICH Q2- Validation of analytical procedures

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ICH Q14- Scope

This guideline applies to new or revised analytical procedures used for release and stability testing of commercial drug substances and products (chemical and biological/biotechnological). 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 during clinical development. This

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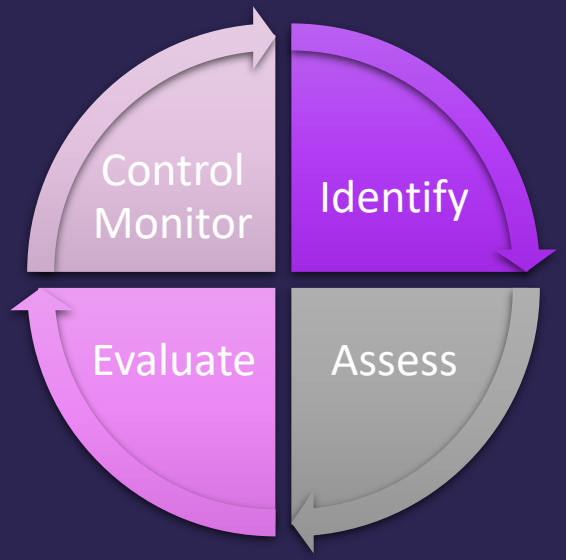
ICH Q14- How?

How should I do the analytical development?



Using the tools described in *ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*, the guideline describes 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*. Knowledge gained

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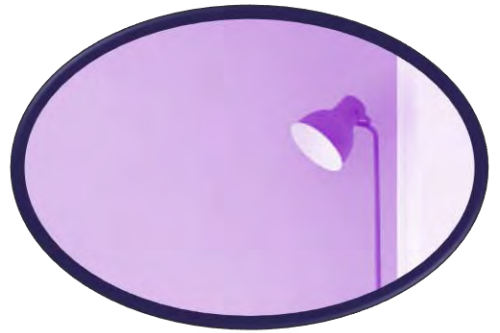
ICH Q14 – minimal vs. enhanced approach

What we are mostly used to, is now considered "**minimal**"..:



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).

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ICH Q14 –enhanced approach (not all, and definitions from Q8-Q12)

- 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.

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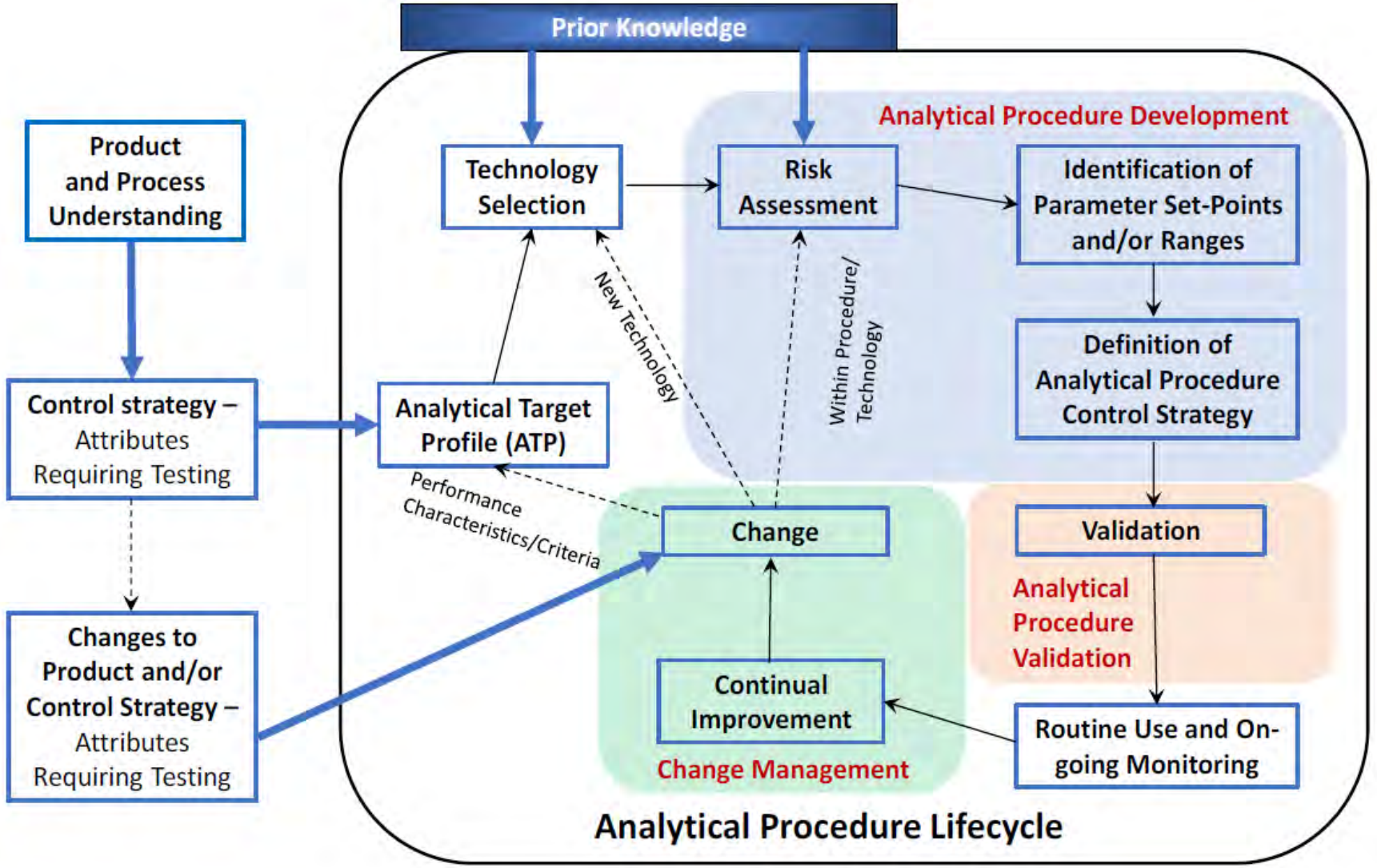
ICH Q14 – Analytical procedure lifecycle



ICH Q14 – WHY?

Why should I invest in it?

Applying elements of the enhanced approach to development can lead to more robust analytical procedures, better understanding of the impact of analytical procedure parameters and more flexibility for lifecycle management such as wider operating ranges, a more appropriate set of ECs and associated reporting categories for changes.

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.

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ICH Q14 – WHY else?

In general, data gained during the development studies (e.g., robustness data from a design of experiments (DoE study)) can be used as validation data for the related analytical procedure performance characteristics and does not necessarily need to be repeated.

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