



ICH Q2(R2): VALIDATION OF ANALYTICAL PROCEDURES

Training Module 2: Fundamental principles of ICH Q2(R2)

Part A - Analytical Procedure Validation Strategy

Part B - Details of Validation Terms

Part C - Combined Accuracy and Precision

Part D - Considerations when Setting Performance Criteria

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for Pharmaceuticals for Human Use

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The materials presented in this ICH Q2(R2) / Q14 module are example approaches relating to selected aspects of analytical procedure development, validation and lifecycle. The approaches presented have been constructed to illustrate potential applications of the principles contained within the ICH Q2(R2) / Q14 guidelines and are not considered to be exhaustive. The examples are not intended to be mandatory, and alternative approaches (fulfilling the intent of the guidelines) may also be acceptable.

In some cases, additional elucidation of specific approaches is provided to aid in general understanding of a concept. This is not intended to be a promotion of the elucidated approach, nor indicate a preference for a specific approach.

Provision of acceptance criteria has been deliberately limited within this training material.

In practice, scientific rigor must be applied on a case-by-case basis when determining an appropriate approach or criterion.

Module 2 – Fundamental Principles of ICH Q2(R2)

Part A: Analytical Procedure Validation Strategy

Objective and Scope of ICH Q2(R2)

Objective

- **Provide elements for consideration during the validation of *analytical procedures* included as part of registration applications**
 - Guidance on *validation studies*, including selection and evaluation of *validation tests*
 - Relevant terms and definitions
 - Linkage with analytical procedure lifecycle, as described in ICH Q14

What is in Scope?

- **Validation of analytical procedures**
 - Release and stability tests
 - Commercial drug substances and products
- **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**
 - *E.g.*, selected in-process controls, cleaning validation
- **Principles can be applied in a phase-appropriate manner to analytical procedures used during clinical development**
 - *E.g.*, selected relevant validation tests are applied
- **Generally, ICH Q2(R2) is not applicable retrospectively, *i.e.*, where a procedure has been validated prior to adoption of ICH Q2(R2), unless changes to an existing procedure are made that require re-validation and appropriate regulatory filing.**

Analytical Procedure Lifecycle

- ICH Q2(R2) analytical procedure validation is an element of the analytical procedure lifecycle described in ICH Q14

ICH Q14

Analytical procedure development & robustness

- Objectives/performance characteristics
- Analytical procedure
- Appropriate development data
- Prior knowledge

Analytical procedure lifecycle management

- Analytical procedure lifecycle management

ICH Q14
ICH Q2

ICH Q2(R2)

Validation protocol

Validation strategy:

- Evaluation of prior knowledge, including available development or validation data with justification
- Additional experiments and evaluation according to ICH Q2 methodology or alternative approach with justification

Validation report

Document validation results and data:

- Evaluation against acceptance criteria or parameter ranges
- Conclusions and acceptance of analytical procedure performance

Validation tests and/or evaluation of data

Analytical procedure validation study

Analytical Procedure Validation Strategy

Selection of Performance Characteristics (ICH Q2(R2) Table 1)

Generation of appropriate Performance Criteria

Assessment of Prior Knowledge:

What prior knowledge is available? E.g.

- Development data
- Platform validation data
- Robustness data
- Data from prior validation studies
- Product knowledge

Has the prior knowledge been obtained with suitable level of quality oversight?

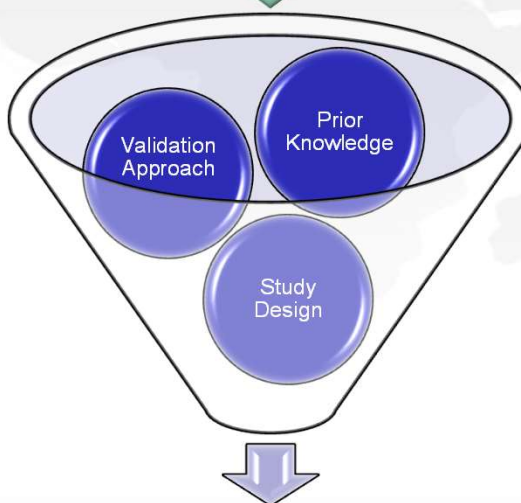
Will the prior knowledge satisfy the performance characteristics / anticipated acceptance criteria?

Overall Validation Approach:

Will this be a single lab validation or a co-validation?

How many laboratories will be involved?

Which performance characteristics will be assessed at each laboratory?



Analytical Procedure
Validation Strategy

Analytical Procedure
Validation Protocol

Validation Study Design:

Which performance characteristics are not covered by prior knowledge?

Which performance characteristics will need to be experimentally assessed within the validation study?

What validation tests will be selected for each performance characteristic (ICH Q2(R2) Annex1)

Validation Protocol should contain all elements of the Analytical Procedure Validation Strategy, including:

- Performance characteristics and criteria to be assessed
- Justification for use of prior knowledge (where applicable)
- Intended approach to validation
 - (incl. number of labs involved)
- Detailed experimental design



Analytical Procedure Validation Study

Documented study designed to provide sufficient evidence that the analytical procedure meets its objectives

- **Protocol:**

- Intended purpose of the analytical procedure
- Based on the intended purpose, provide the appropriate *Performance Characteristics* to be validated (as per ICH Q2(R2) Table 1) and the associated *Performance Criteria*
- Overview of analytical procedure validation strategy
 - Justification of appropriateness of any prior knowledge
 - "Suitable data derived from development studies can be used as part of validation data" (ICH Q2(R2))
 - "In cases where prior knowledge is used (e.g., from development or from previous studies), appropriate justification should be provided" (ICH Q2(R2))
 - See also Module 3, Part B (Use of Development Data)
 - Experimental design to assess performance characteristics for which suitable prior knowledge is not sufficient or is not available.
 - Experimental design should reflect the number of replicates used in routine analysis to generate a reportable result. If justified, it may be acceptable to perform some validation tests using a different number of replicates or to adjust the number of replicates in the analytical procedure based on data generated during validation.

- **Report**

- Results of the study, including comparison to Performance Criteria
- A tabular validation summary to demonstrate ICH Q2(R2) compliance may be useful
- A conclusion regarding the suitability of the procedure for its intended use should be included

ICH Q2(R2) / Q14 Training Module 2

Performance Characteristics Validation Table

The performance characteristics validation table (ICH Q2(R2) Table 1) has been updated compared to ICH Q2(R1), but still contains the high level concepts.

Terminology and table structure have been updated in line with the modernisation of concepts within ICH Q2(R2).

Appropriate performance characteristics for a validation study are based on the objective of the analytical procedure.

Options for 'Other quantitative measurements' have been included.

The ICH Q2(R1) concept of linearity is incorporated within the ICH Q2(R2) concept of response.

The use of a combined approach to evaluation of accuracy and precision has been enabled.

Detection limit (DL) and quantitation limit (QL) have been combined into the concept of 'lower range limit'.

Table footnotes have been expanded to provide additional clarity.

Table 1: Typical performance characteristics and related validation tests for measured quality attributes

Measured Quality Attribute Analytical Procedure Performance Characteristics to be Demonstrated (2)	IDENTITY	IMPURITY (PURITY) Other quantitative measurements (1)		ASSAY Content or potency Other quantitative measurements (1)
		Quantitative Test	Limit Test	
Specificity (3) Specificity Test	+	+	+	+
Range Response (Calibration Model)	-	+	-	+
Lower Range Limit	-	QL [†]	DL	-
Accuracy (4) Accuracy Test	-	+	-	+
Precision (4) Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+(5)	-	+(5)

- signifies that this test is not normally conducted

+ signifies that this test is normally conducted

[†] in some complex cases DL may also be evaluated

QL, DL: quantitation limit, detection limit

(1) other quantitative measurements can follow the scheme for impurity, if the range limit is close to the DL/QL; other quantitative measurements can follow the scheme for assay (content or potency), if the range limit is not close to the DL/QL

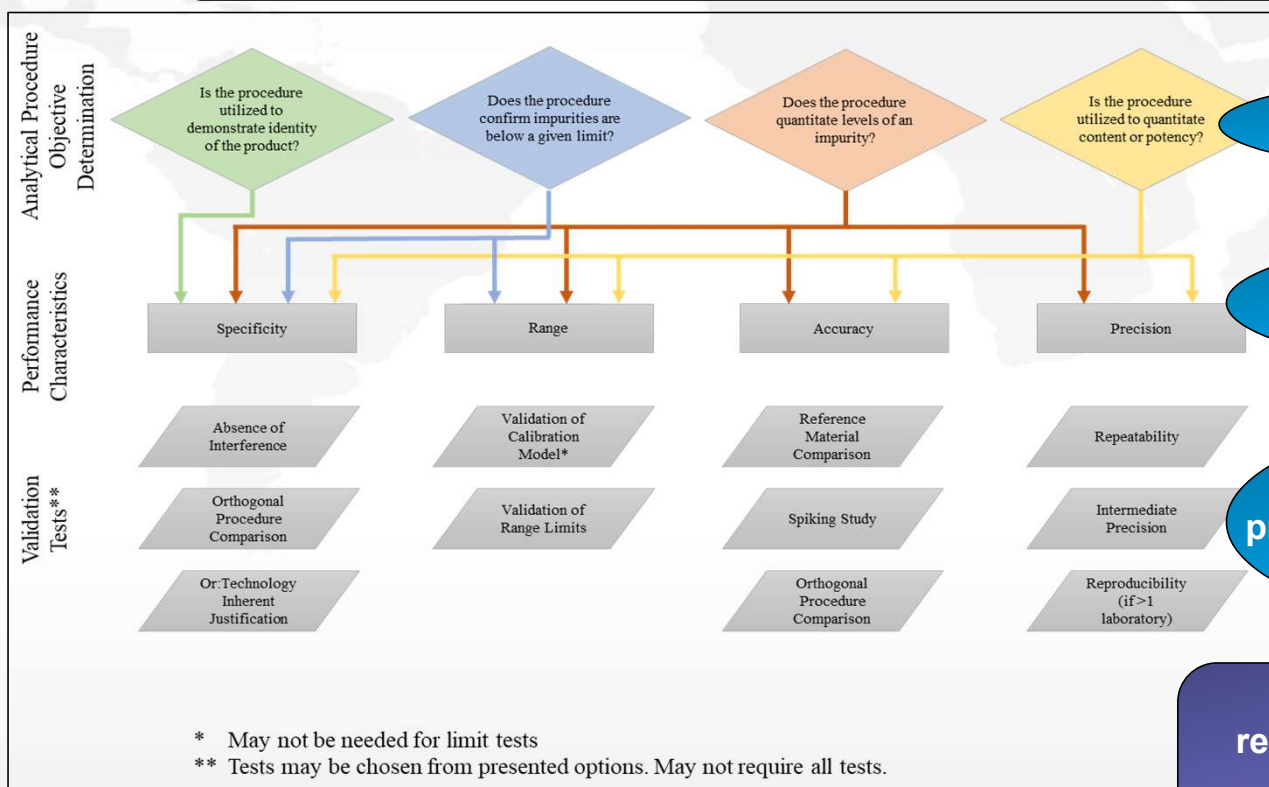
(2) some performance characteristics can be substituted with technology-inherent justification in the case of certain analytical procedures for physicochemical properties

(3) lack of specificity of one analytical procedure should be compensated by one or more other supporting analytical procedures, unless appropriately justified

(4) alternatively, a combined approach can be used to evaluate accuracy and precision

(5) where reproducibility has been performed and intermediate precision can be derived from the reproducibility data set, an independent study for intermediate precision is not required

ICH Q2(R2) provides a framework for the approach to analytical procedure validation, which can be applied irrespective of the measured quality attribute or the technology used.



Objectives of the analytical procedure are determined

Relevant performance characteristics are selected based upon the intended use of the analytical procedure

Suitable validation test(s) are chosen based on specific procedure and product considerations, e.g., available reference materials, inherent properties of the technology used.

Figure 2 (Annex 1) provides a flow chart representation of the performance characteristic selection from Table 1, as well as example validation tests that may be considered for each characteristic.

ICH Q2(R2) Figure 2: Examples of relevant validation tests based on the objective of the analytical procedure

Use of Reference Materials

- ICH Q2(R2) states that analytical procedure validation studies should utilise reference materials (or other suitably characterised materials) where appropriate, and provides the following definition:

REFERENCE MATERIAL

A suitably characterised material, sufficiently homogeneous and stable with regard to one or more defined attributes, which has been established to be fit for the intended purpose. Reference materials may include national/international reference standards, pharmacopoeial reference standards, or in-house primary/secondary reference materials. (ICH Q2)

- This definition is compatible with the following pre-existing definitions:

ICH Q6B (glossary)

- **Reference Standards:** Refer to international or national standards
- **In-house Primary Reference Material:** An appropriately characterised material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.
- **In-house Working Reference Material:** A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

ICH Q5C (text)

- In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an **appropriate reference material**. For that purpose, a **reference material** calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay

International Vocabulary of Metrology

- **Reference Material (RM):** material, sufficiently homogeneous and stable with reference to one or more specified properties, which has been established to be fit for its intended use in measurement or in examination

System Suitability Tests (SSTs)

- As described in ICH Q14, SSTs are an integral part of analytical procedures and are generally established during development as a regular check of performance.
 - SSTs in the analytical procedure executed during the validation study may be confirmed or revised post-validation based on the outcome of the validation study
- SST is defined as:

SYSTEM SUITABILITY TEST (SST)

System suitability tests are developed and used to verify that the measurement system and the analytical operations associated with the analytical procedure are fit for the intended purpose and increase the detectability of unacceptable performance. (*ICH Q14*)

- For further information on SSTs and sample suitability assessment, please refer to ICH Q2(R2) / Q14 Training Module 4, Part F.

Validation of PAR and MODR

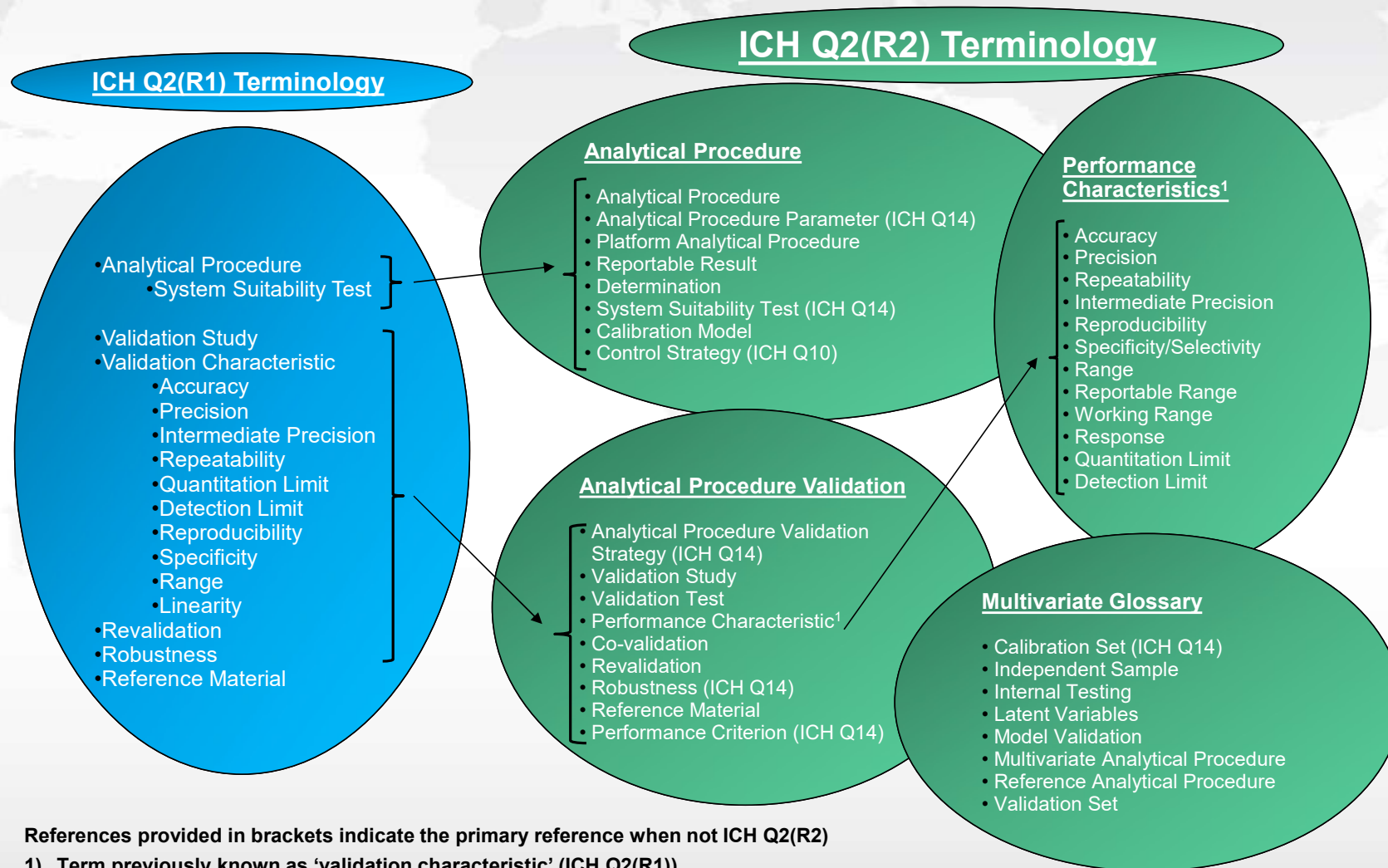
- As described in ICH Q14, analytical procedure validation for a proven acceptable range (PAR) and/or a method operable design region (MODR) is required only for those performance characteristics not covered by data from analytical procedure development.
- For practical reasons and following a risk-based approach, it may not be necessary or possible to validate the entirety of an MODR.
- The part of a PAR or an MODR intended for routine use (typically the intended operational conditions or the set point) in the analytical procedure must be covered by validation data.
- The extent of validation tests should be justified on a case-by-case basis.
- Information related to the robustness and validation of a PAR or MODR is located in Module 4, Part E and Module 7, MODR.

Module 2 – Fundamental principles of ICH Q2(R2)

Part B: Details of Validation Terms

ICH Q2(R2) / Q14 Training Module 2

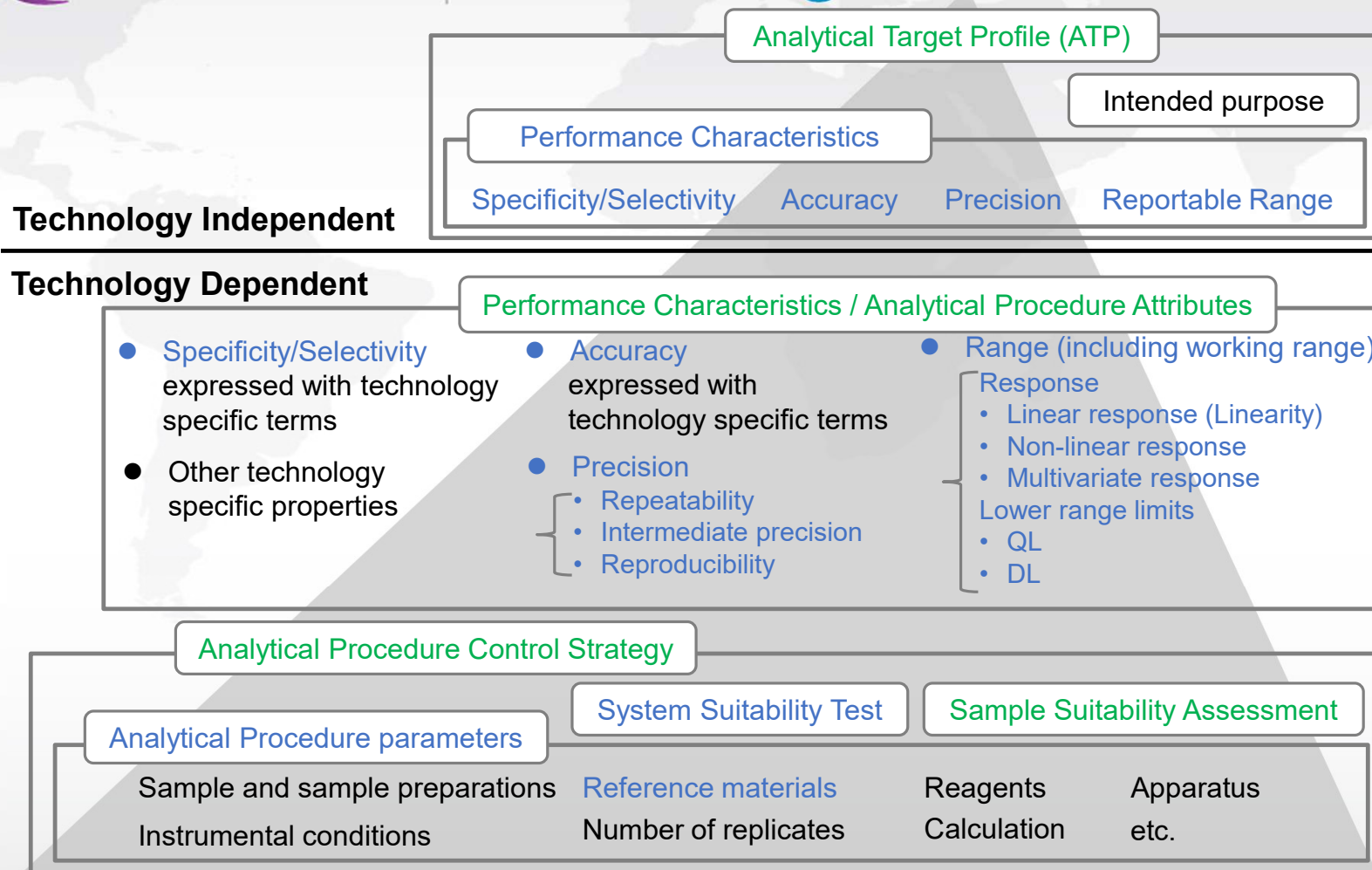
Overview of ICH Q2 Terminology



Terminology Hierarchy

Note

This figure illustrates terminology hierarchy by merging both ICH Q2(R2) and ICHQ14 terminologies from the view of using an ATP, an element of the enhanced approach as described in ICH Q14.



Terms defined in ICH Q2(R2) are colored in blue, and those defined only in ICH Q14 are colored in green.

Analytical Procedure Development Flow in Line with ICH Q14

Analytical Target Profile (ATP)

Consisting of below elements

- Intended purpose of analytical procedure
- Details on quality attribute to be tested
- **Performance characteristics** and associated **performance criteria**

Technology selection

Analytical procedure development

Risk assessment: Identifying **analytical procedure parameters** with potential impact on performance, assessing the potential impact, and identifying **analytical procedure parameters** to be investigated experimentally.

Robustness evaluation: Testing by deliberate variations of **analytical procedure parameters** considering duration of analysis.

Analytical procedure parameter ranges: Investigating the impact of **analytical procedure parameter** (input) ranges to **analytical procedure attributes** (output) and associated criteria that can be derived from an ATP.

Analytical procedure control strategy: Includes **analytical procedure parameters** needing control and **SST**. SST is designed to verify selected **analytical procedure attributes**.

Validation study

Validation protocol: A written plan describing the analytical procedure to be validated, **performance characteristics** / **analytical procedure attributes** and associated criteria derived from an ATP, **validation tests** to be conducted, participating sites etc. Validation protocol is designed based on or includes **analytical procedure validation strategy** considering prior knowledge and existing data.

Validation tests and/or evaluation of data

Validation report: Document of validation results and data; and conclude suitability

Note

When using an ATP a “Performance characteristic” is a technology-independent description of characteristic with an associated and defined acceptance criteria. Once a technology is selected, technology-dependent performance characteristics can be determined, which are defined as “Analytical Procedure Attributes” in ICH Q14.

Terms defined in ICH Q2(R2) are colored in **blue**, and those defined only in ICH Q14 are colored in **green**.

Range

- In ICH Q2(R2), the terms of “reportable range” and “working range” were newly introduced, in addition to “range”.
- The terms are defined as:

RANGE

The range of an analytical procedure is the interval between the lowest and the highest results in which the analytical procedure has a suitable level of precision, accuracy and response. (*ICH Q2*)

REPORTABLE RANGE

The reportable range of an analytical procedure includes all values from the lowest to the highest reportable result for which there is a suitable level of precision and accuracy. Typically, the reportable range is given in the same unit as the specification acceptance criterion. (*ICH Q2*)

WORKING RANGE

A working range corresponds to the lowest and the highest level of the quality attribute to be measured (*e.g.*, content or purity) as presented to the analytical instrument and for which the analytical procedure provides reliable results. (*ICH Q2*)

Range

Example of reportable range and working range

	Dissolution with HPLC	Assay with HPLC	Impurity with HPLC	High molecular weight species (HMWS) with size exclusion chromatography
Background	Immediate release tablets, two strength 50 mg and 100 mg, 900 mL of media volume, Q=80%	Powder for oral solution, 20 mg/sachet, powder equivalent to 20 mg DS dissolved in 100 mL	Small molecule drug substance, process related impurity A $\leq 0.1\%$	Biological product, HMWS $\leq 5.0\%$
Reportable range	35% (Q-45%) of 50 mg strength to 130% of 100 mg strength of tablets	80-120%	0.05–0.12 % impurity A	0.2% (QL) - 6.0% HMWS
Working range	Sample concentration: 0.019-0.144 mg/mL	Sample concentration: 0.16-0.24 mg/mL	0.05–0.12% spiking level of impurity A (0.1–0.24 $\mu\text{g/mL}$ impurity A against drug substance 2 mg/mL)	Sample concentration : 50 - 150% of the nominal sample concentration (8 mg/mL protein)

- **Case of dissolution, assay and impurity with HPLC : a typical example of reportable range and working range**
The reportable range derived from specification acceptance criteria or declared content is a target working range to be evaluated. % of strength level is transformed to the sample concentration by calculation.
- **Case of HMWS with size exclusion chromatography: an example in which the reportable and working ranges are not identical.** In addition to the evaluation of reportable range, the proportionality of the total peak area with sample load may be demonstrated.

Range

Corresponds to “Linearity” in ICH Q2(R1)

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Newly added to address non-linear response and multivariate calibration

Corresponds to “Detection Limit” and “Quantitation Limit” in ICH Q2(R1)

Module 2 – Fundamental principles of ICH Q2(R2)

Part C: Combined Accuracy and Precision

Use of Combined Assessment

- Use of a combined assessment of accuracy and precision is an alternative approach enabled in ICH Q2(R2).
- At a high level, two options relating to accuracy and precision are described in the ICH Q2(R2) guideline
 - **Independent evaluation of accuracy and precision**, each with a predefined acceptance criterion. Point estimates should be reported with *appropriate 100 (1- α) % confidence interval*, and *the observed interval should be compatible with the corresponding [...] criteria*.
 - **Combined assessment of accuracy and precision**, by considering their total impact against a combined performance criterion

Combined Approaches for Accuracy and Precision

An **alternative** to separate evaluation of accuracy and precision is to consider their total impact by assessing against a combined performance criterion.

Data generated during development may help determine the best approach and refine appropriate performance criteria to which combined accuracy and precision are compared.

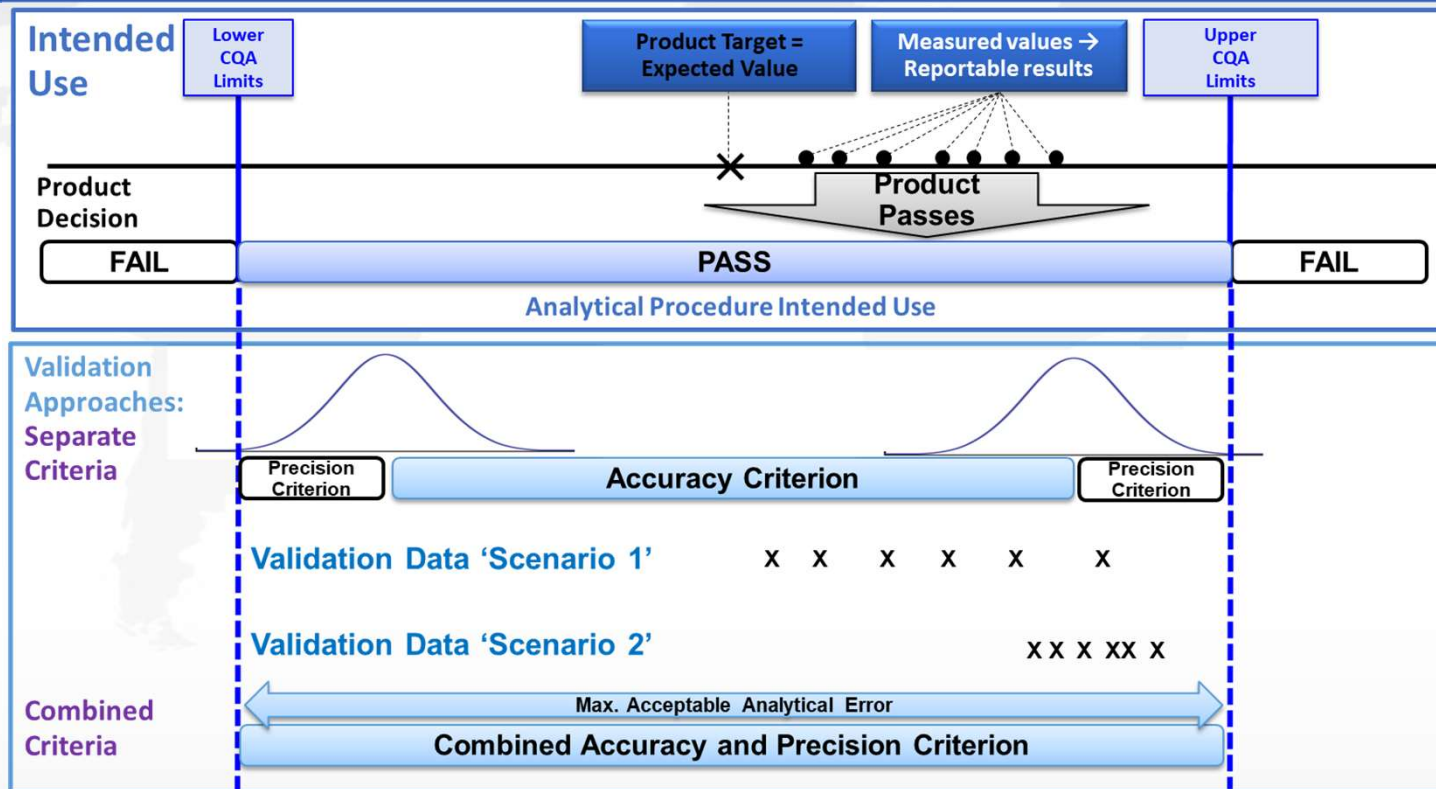
Combined accuracy and precision can be evaluated by use of a **prediction interval**, a **tolerance interval** or a **confidence interval**. Other approaches may be acceptable if justified.

Considerations for Combined Performance Studies

- Combining accuracy and precision into a single metric leverages the interconnectivity of accuracy and precision, where the impact of systematic bias (accuracy) depends in part on random measurement error (precision): a procedure with low variability (high precision) can accommodate a greater bias (less accuracy) compared to a procedure that has higher variability, in order to ensure a similar overall performance.
- Experimental designs similar to the classical Design of Experiments (DoE) used for separate assessment of accuracy and precision may be appropriate for a combined approach, encompassing elements of both accuracy and precision studies. Specific designs for a combined approach might also be considered.
- An experimental design used for implementing the combined approach may also allow the calculation of individual assessments of accuracy and precision, if desired.

Unique Aspects of Combined Approaches

For the purpose of this example, anticipated process and product variability has not been taken into consideration



The combined approach considers the combination of both systematic error (bias) of the procedure and random measurement error (variance), by assessing the performance of reportable results (measured values) versus a single criterion.

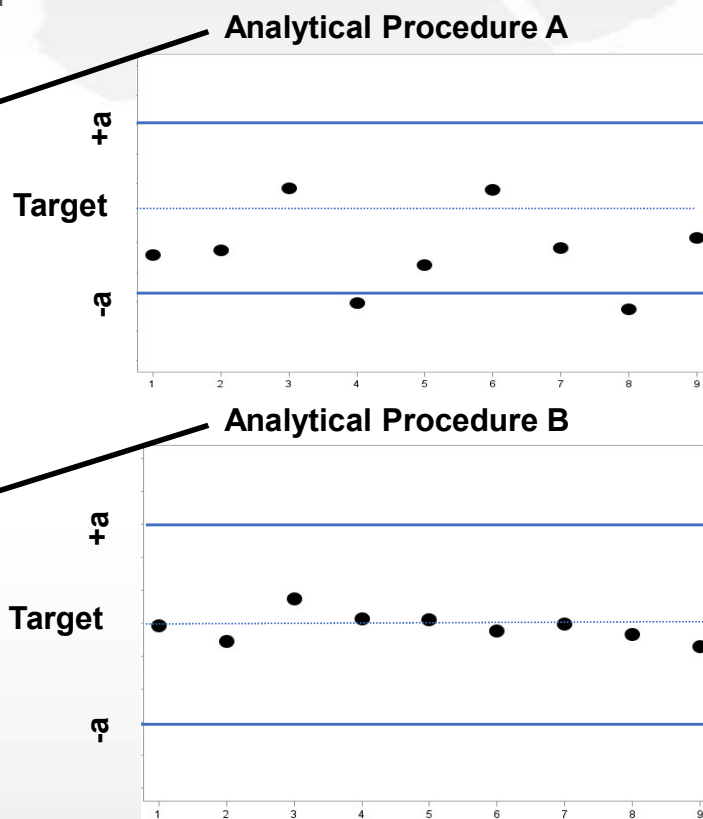
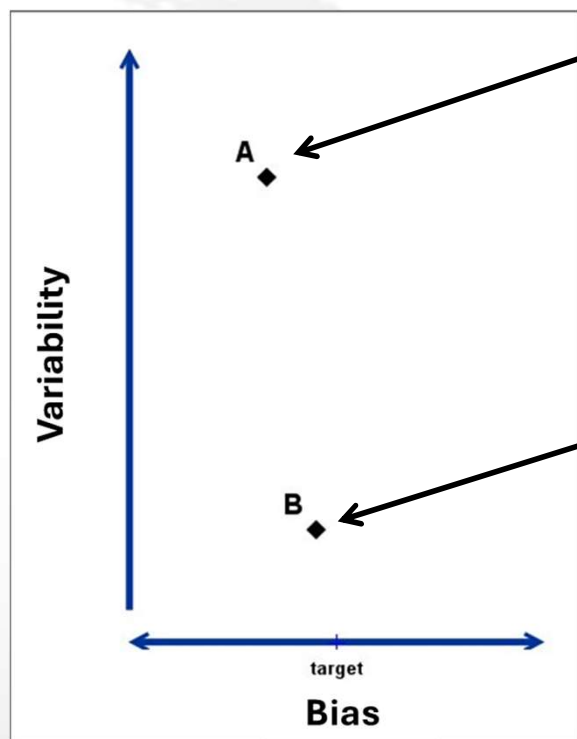
- Scenario 1: Analytical procedure validation data indicate that the analytical procedure has greater accuracy but reduced precision. Using **combined criteria**, the analytical procedure is fit for intended purpose even though it would not pass the **separate** precision criterion
- Scenario 2: Analytical procedure validation data indicate that the analytical procedure has greater precision but reduced accuracy. Using **combined criteria**, the analytical procedure is fit for intended purpose even though it would not pass the **separate** accuracy criterion

Analytical procedure is suitable for its intended purpose

Why a Combined Approach?

Example of assessment for accuracy and precision (illustrative purposes only with $n=9$ measurements)

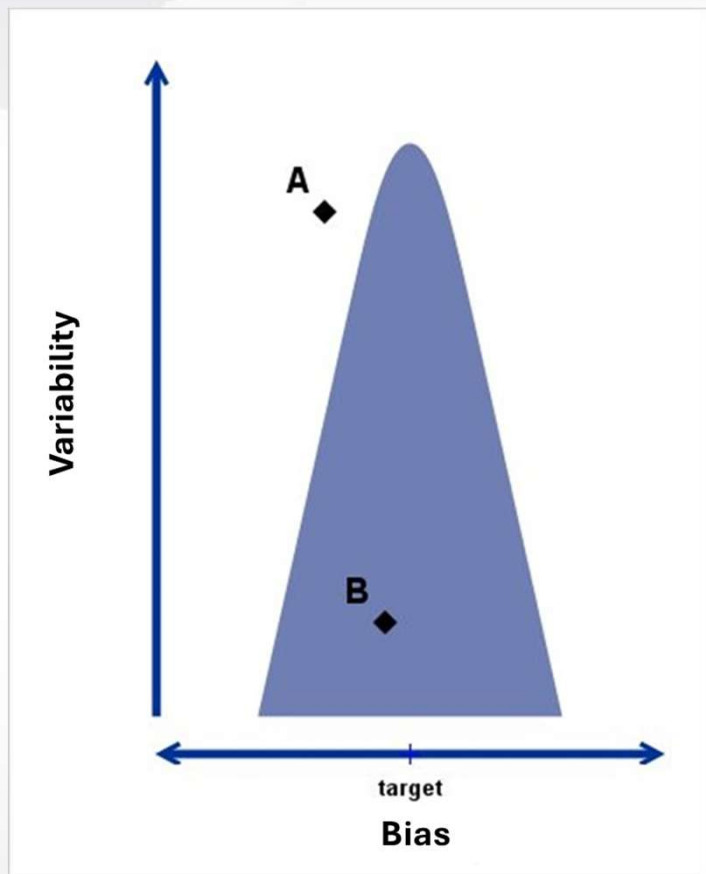
Accuracy (mean of $n=9$) vs Precision
(standard deviation of $n=9$)



While both analytical procedure A and B may be appropriate for use (e.g., meet defined individual acceptance criterion), considering the combined impact of accuracy and precision is useful.

As shown by the location and dispersion of the analytical procedure A and B samples about the target, procedure A samples show greater variability and bias.

Combined Assessment - Using a Probability Statement



One approach to the combined assessment of accuracy and precision is to use a probability statement. The blue parabola illustrates a combined accuracy and precision probability statement such that there is e.g. $\geq 95\%$ probability that results are within 'a \pm allowable distance' of the target (these bounds are the edges of the parabola).

Assessment for Analytical Procedures A and B:

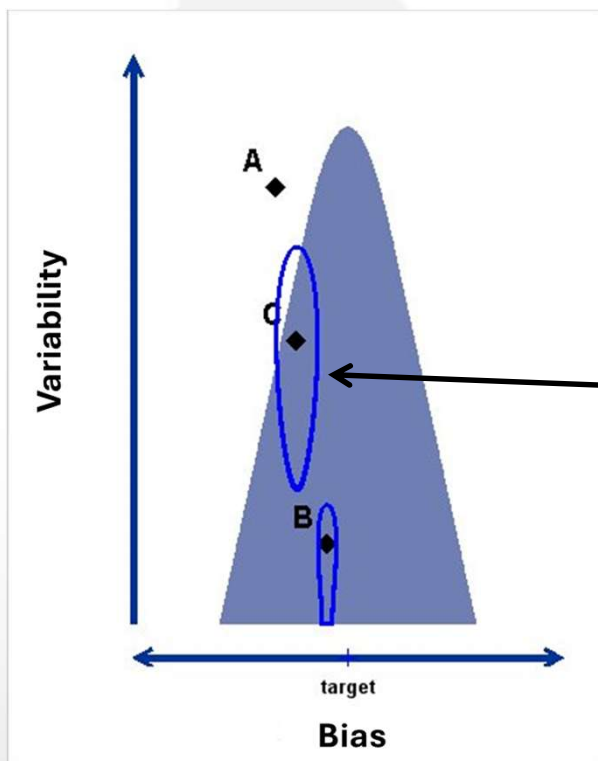
The accuracy and precision of analytical procedure B are well within the performance criterion (illustrated by the blue parabola) since the average and standard deviation of the validation data reside within the acceptance region (diamond in the parabola). Analytical procedure B is allowed a statement such as "the analytical procedure is capable of providing reportable values within \pm the threshold of target with at least 95% probability".

Analytical procedure A does not pass this criterion, thus a statement that 'at least 95% of results reside within \pm the threshold of target' is not warranted for this analytical procedure.

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Use of Intervals – joint confidence interval illustration

- Analytical procedure A performance (accuracy average & precision SD) clearly are outside the joint accuracy and precision performance criterion
- The joint accuracy and precision **confidence interval** illustrated provides 90% confidence that the mean and standard deviation of the validation data reside within the pictured ellipse for analytical procedure B.
- Fully residing within the bounds (compatibility with criterion) demonstrates 90% confidence the procedure is capable to perform as intended, i.e., the probability of results produced by the procedure within a \pm stated threshold of target is $\geq 95\%$, there is 90% confidence in this statement as provided by the validation data.



What about Analytical Procedure C?

Does not meet the joint accuracy and precision criterion since the 90% confidence interval fails to fully reside within the criterion (the parabola).

Implication is that the validation data set does not demonstrate at least 90% confidence that the procedure can produce 95% of results within \pm the allowable distance from target.

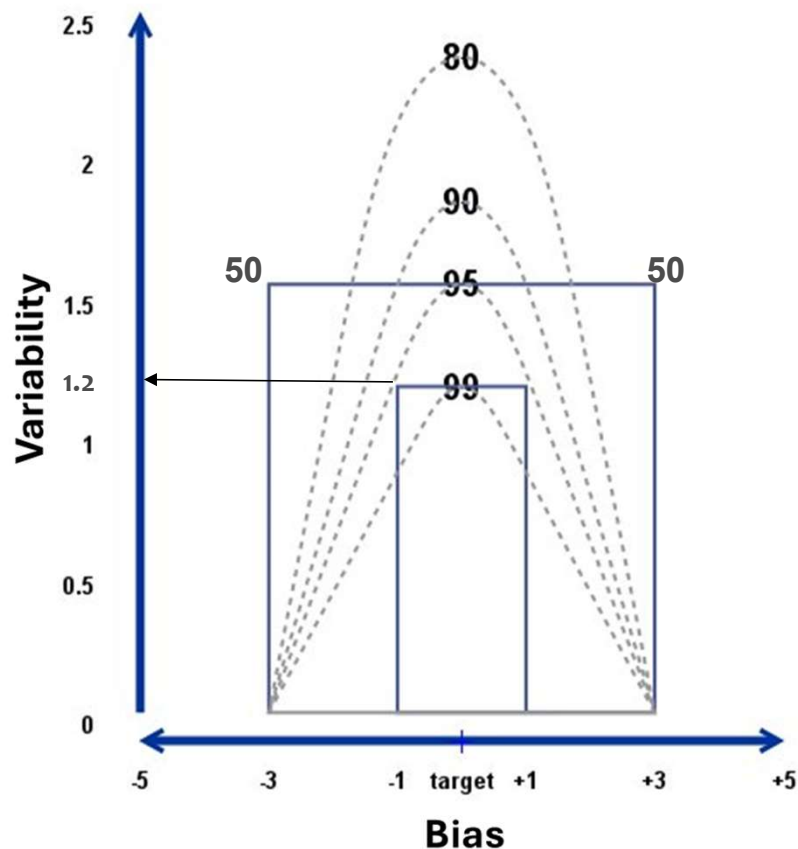
Confidence, prediction, or tolerance intervals are identified in ICH Q2(R2) as applicable intervals for use.

Applying 90% prediction and 90%/95% tolerance intervals to the illustrated analytical procedure C provide the same decision as the illustrated confidence interval

With additional knowledge (*i.e.*, data) Bayesian credible intervals may also be applicable if justified.

Suitability of analytical procedure C could be justified as compatible with the combined accuracy / precision acceptance criteria, as described in discussion on confidence intervals (Module 3, Part B).

Comparing Individual Criteria to a Combined Criterion



Combined criteria define acceptance regions within the precision/accuracy space. Two sets of individual criteria for variability and bias as illustrated by the rectangles. Combined criteria are illustrated by the contour lines demonstrating 80% to 99% probability that results will reside within ± 3 of target. These contours define a different acceptability space as compared to the blue rectangles.

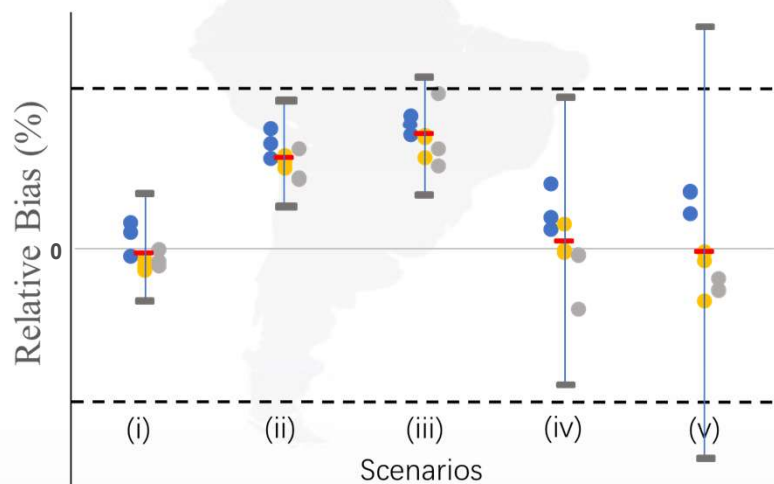
The larger rectangle intersects the 95% contour at the target (0 bias) level, where the maximum variability is 1.5%, thus 95% of results are expected to reside within ± 3 of target for a procedure with 0 bias and 1.5% variability. However, the probability is 50% at the upper corners of the larger rectangle where variability is 1.5% and bias is ± 3 from target.

For the smaller rectangle, the two upper corners intersect the 95% contour. As illustrated, this provides $\geq 95\%$ probability that results will reside within ± 3 of target when the procedure bias is ± 1 from target and variability is equal to or less than 1.2%. At target (0 bias) and 1.2% variability, the probability is 99% that results will reside within ± 3 of target.

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Decisions using a Combined Approach - Examples of prediction intervals

Five scenarios are exemplified to demonstrate the inter-connectivity between accuracy and precision using a criterion that the prediction interval must reside within a \pm threshold of the relative bias (dotted lines).



- Triplicates Day 1
- Triplicates Day 2
- Triplicates Day 3
- Mean of the relative bias
- Acceptance criterion
- Prediction interval higher and lower bounds

For scenarios (i), (ii) and (iii), the prediction interval bounds are relatively narrow and close to each other as compared to scenarios (iv) and (v).

- Scenario (i) passes the criterion of the combined approach with the relative bias very close to the target (zero relative bias) and a narrow prediction interval (low variability).
- It's still acceptable for scenario (ii) to pass the criterion with relatively narrow prediction interval bounds, though the interval excludes a relative bias of zero bias.
- In scenario (iii), the prediction interval upper bound exceeds the acceptance criterion, which signifies the relative bias and precision do not meet the criterion that the prediction interval must reside within a \pm threshold from zero relative bias.

For scenarios (i), (iv) and (v), the relative bias are all very close to zero.

- It's still acceptable for scenario (iv) to pass the criterion. Although the prediction interval bounds are relatively wide, it can be accommodated by the low relative bias.
- In scenario (v), the prediction interval upper and lower bounds both extend beyond the acceptance criterion, though the relative bias is low. The variability of the analytical procedure is too big to be accommodated by the low relative bias.

Example of Prediction Interval: Data Interpretation of the Combined Approach - Summary

Scenarios	Relative Bias	Variability	Conclusion and Recommendation for Next Step
i	Low	Low	Will pass the acceptance criterion
ii	Medium	Low	Pass the acceptance criterion
iii	High	Low	Inconclusive as the prediction interval upper bound exceeds the acceptance criterion. Evaluate the risk and decide if acceptable per company pharmaceutical quality system (PQS) requirements, and / or improve relative bias of the analytical procedure .
iv	Low	Medium	Pass the acceptance criterion
v	Low	High	Inconclusive as the prediction interval upper and lower bounds both exceed the acceptance criterion. Evaluate the risk and decide if acceptable per company PQS requirements, and / or improve variability of the analytical procedure

Module 2 – Fundamental principles of ICH Q2(R2)

Part D: Considerations when Setting Performance Criteria

Considerations when Setting Performance Criteria

- It is not possible or desirable to define generally applicable performance criteria for analytical procedure validation. However, some considerations on how to set criteria for performance characteristics are:
 - The exact nature of the performance criteria will depend on the specific analyte, matrix, concentration and technology under consideration and should be in accordance with the quality target product profile (QTPP) expectations.
 - Validation acceptance criteria for performance characteristics can be set based on both prior knowledge and performance expectations.
 - It is also possible to consider permitted error when setting performance criteria for the validation protocol (and especially for criteria to be included in an ATP).
- Consider the requirements of the specification acceptance criteria.
- Regarding stability studies, it is important that analytical procedures are sufficiently accurate and precise to reveal relevant changes in the limited data included at the time of submission.

Contact

- For any questions please contact the ICH Secretariat:

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