General Principles for Reference Standards Life-Cycle Management

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CASSS CMC Strategy Forum Europe
Basel, 21 October 2025

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General Principles for Reference Standards Life Cycle Management

What ICH Q6B Says

ICH Q6B section 2.2.1

1. A Primary Reference Material should be implemented for submission

At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials.

2. Requirement for a ‘two-tiered’ system

In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it.

3. Specific Reference Materials can be implemented

While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established.

4. Submission requirements

When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application.

Documentation of the characterization, storage conditions and formulation supportive of reference material(s) stability should also be provided.

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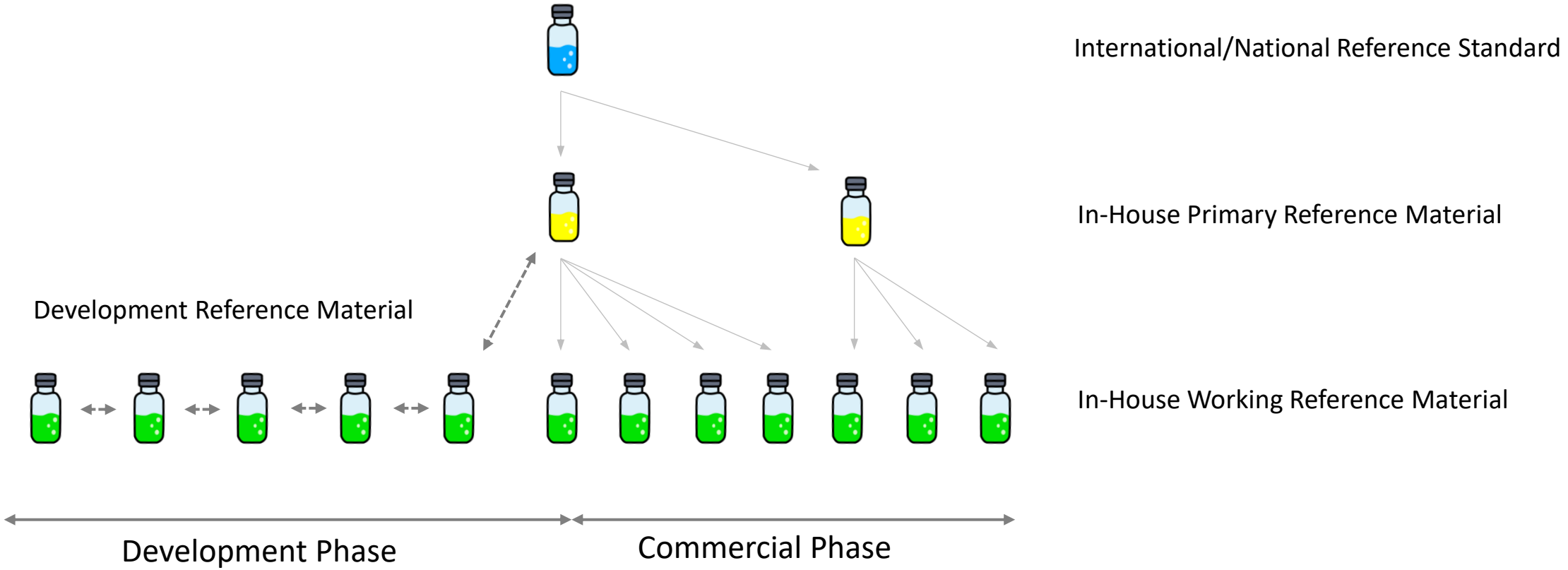
Two-Tiered System in Application



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Expanding on current Q6B guidance

ICH
harmonisation for better health

Final Concept Paper

Q6(R1) EWG: Maintenance of the ICH Q6A and Q6B Guidelines

Dated 25 June 2024

Endorsed by the Management Committee on 18 July 2024

Reference Standards/Materials:

"Update expectations and principles for development and lifecycle management of reference standards/materials where appropriate."

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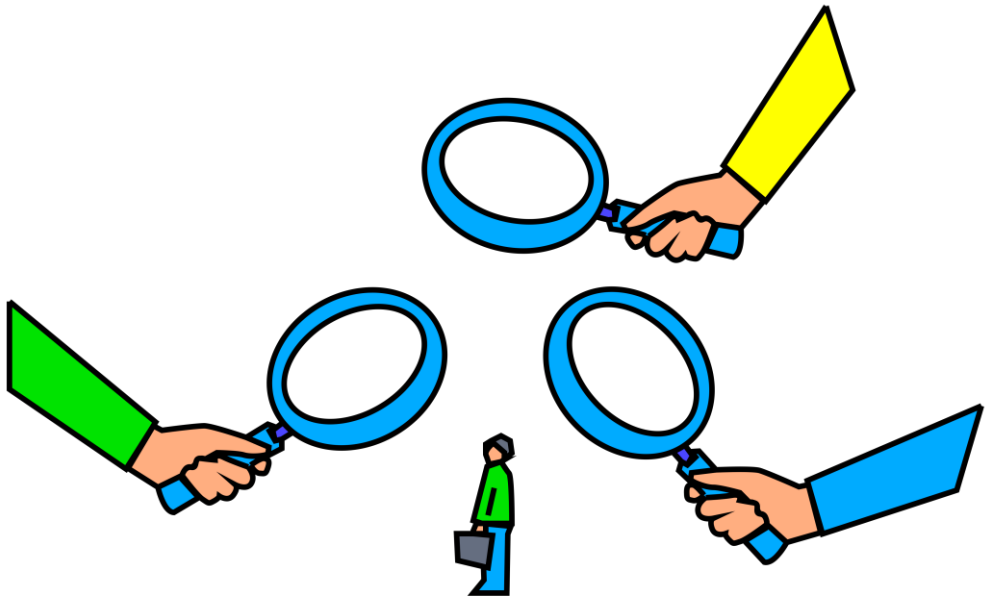
Extended Characterization



Regulatory Feedback:

"… Studies assessing CQAs (e.g., primary, secondary, and tertiary structures, charge variants, potency, etc.) of the new reference standard are needed to demonstrate comparability to the previous reference standards. Update the reference standard qualification protocol to include extended characterization. Provide details on all extended characterization assays to be performed including pre-defined acceptance criteria."

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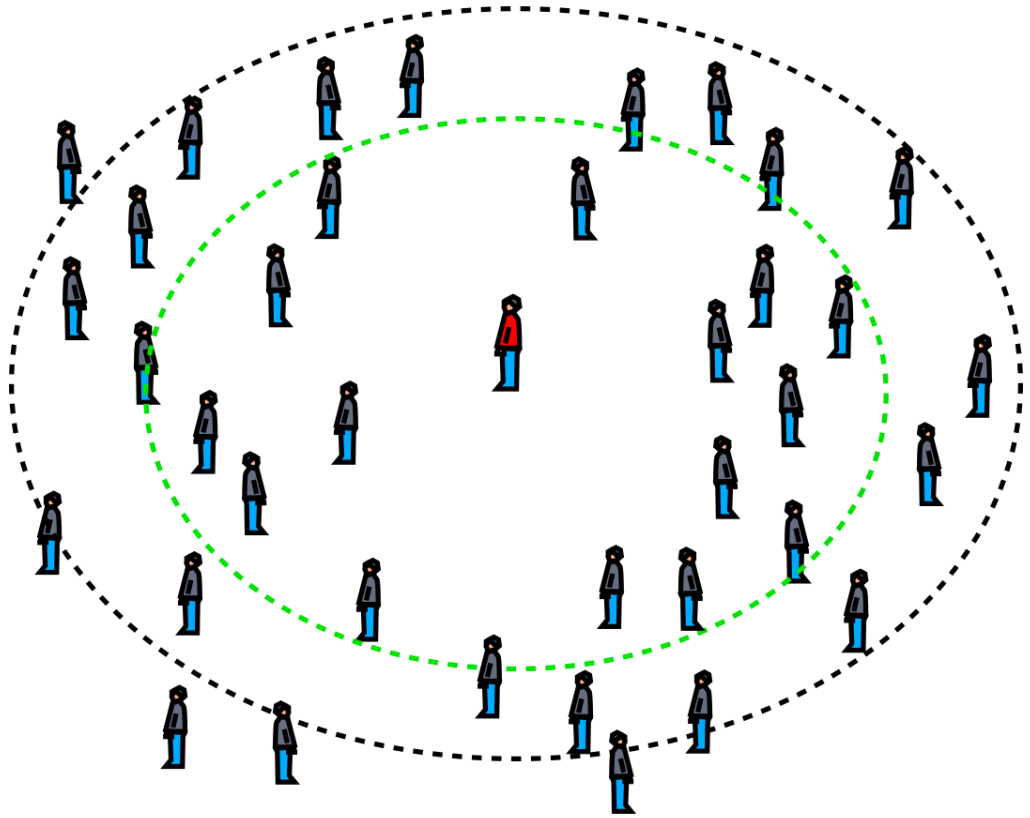
Narrow Acceptance Criteria for Selected Attributes



Regulatory Feedback:

"Provide a tabular summary of the product quality attributes (e.g., release and extended characterization attributes), associated analytical procedures including the number of independent samples/replicates to be tested, and pre-defined acceptance criteria to be used in the future RS qualification protocol. Note that the pre-defined acceptance criteria should generally be narrower than those used for release testing, particularly for attributes for which the reference standard is used as a comparison."

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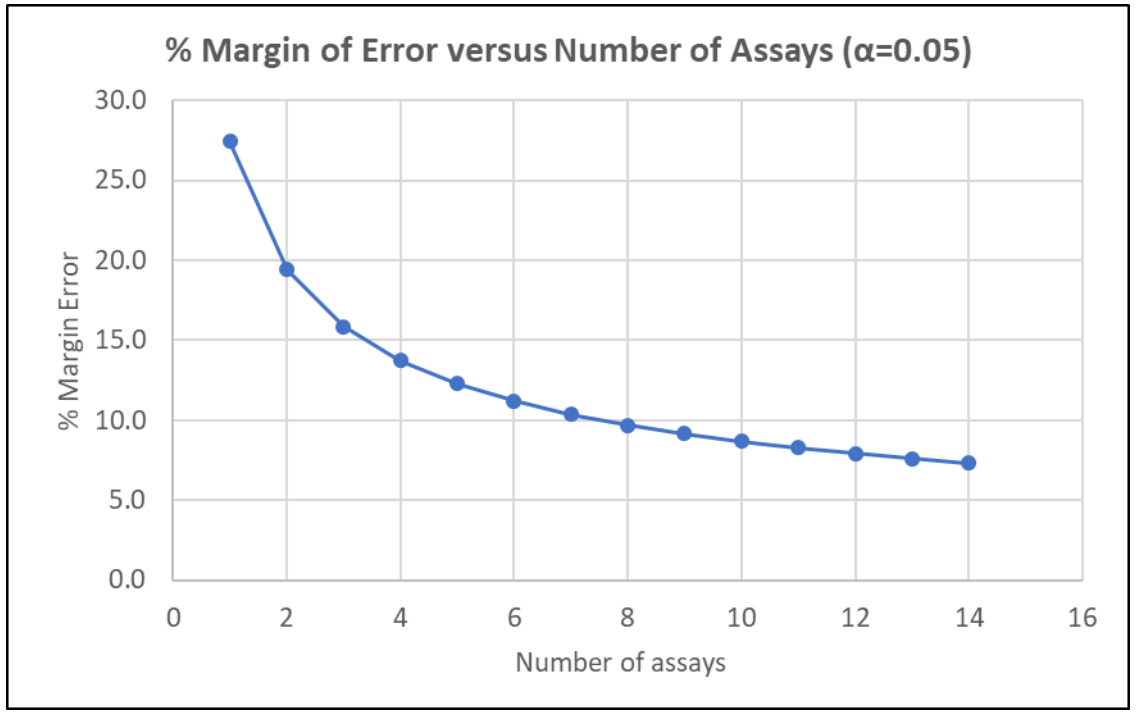
Calibration Results



Regulatory Feedback:

"A sufficient number of individual samples/replicates should be performed to achieve a statistically significant mean value accounting for assay variation for potency and protein concentration assays. Specify and justify the number of individual samples/replicates used for the potency and protein concentration assays."

Example (left): use of Margin of Error statistical tool to determine relevant number of determinations for potency calibration.

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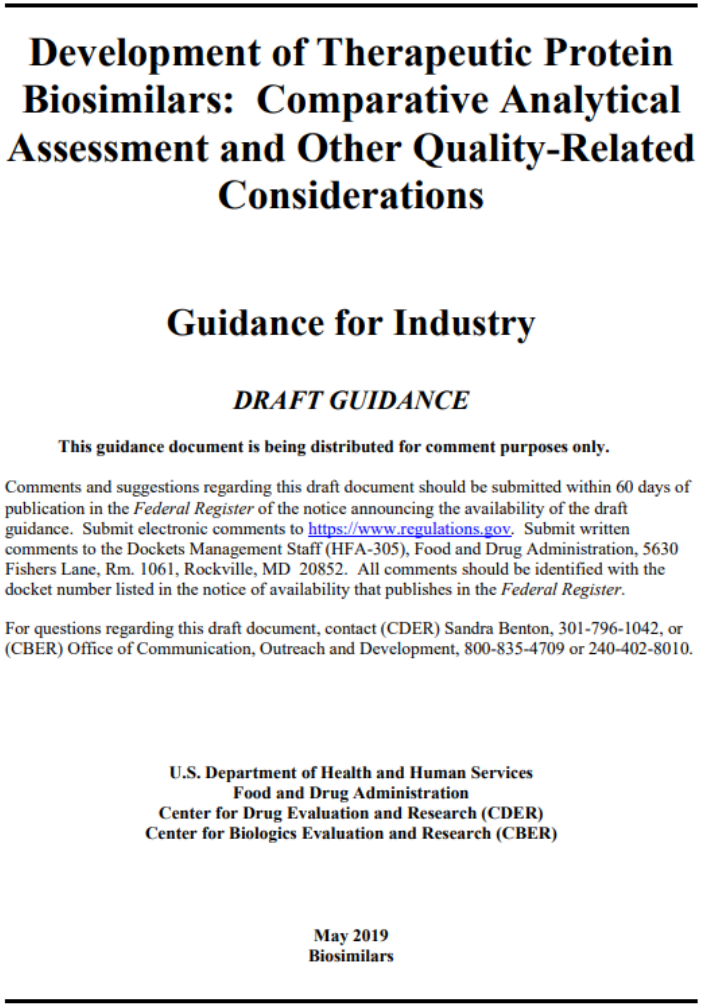
Potency Equivalence Assignment

Draft FDA Guidance on Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019)

"For all methods where the result is reported relative to the reference standard, the assignment of a potency of 100% should include a narrow acceptable potency range and ensure control over product drift. For example, a sponsor should consider the use of a pre-determined two-sided confidence interval (CI) of the mean of the replicates, where the mean relative potency and the 95% CI are included within a sufficiently narrow range (e.g., 90-110%). There should be an evaluation across the history of multiple reference standard qualifications to address potential drift. "



Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sandra Benton, 301-796-1042, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

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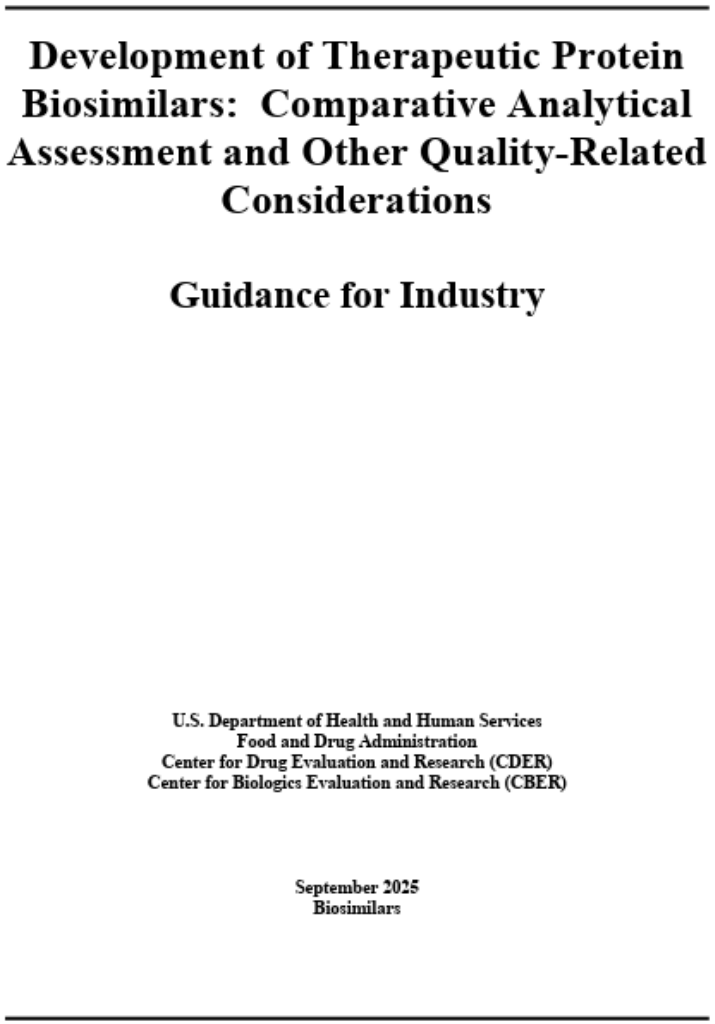
Potency Equivalence Assignment

Final Guidance on Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (September 2025)

A correction factor may be proposed:

“Under certain situations, the use of a small correction factor or factors may be considered if proposed and scientifically justified by the sponsor. If a sponsor intends to propose the use of a correction factor, discussion with the Agency during product development is recommended. “



Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2025
Biosimilars

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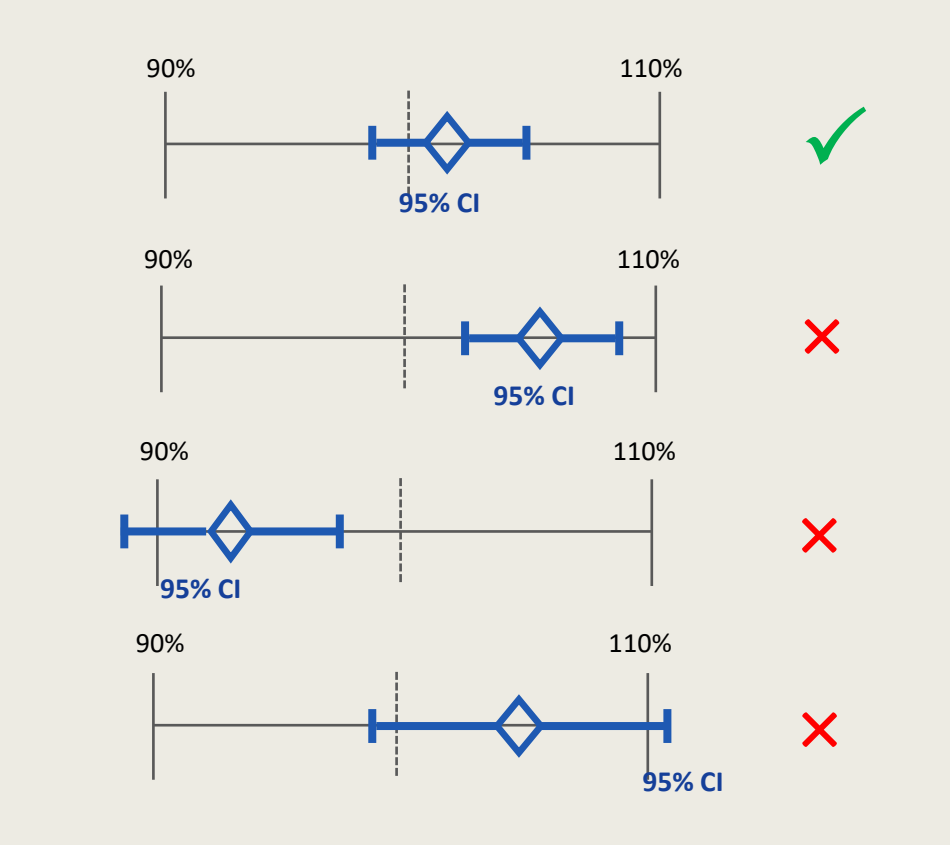
Potency Equivalence Assignment



When assigning 100% potency to a new working reference standard:

"… The 100% potency assignment requires that the mean relative potency and the 95% confidence interval (CI) are included within a sufficiently narrow range (90-110%).
In addition, it is recommended that the CI include 100% potency, in this case the CI is not repeatedly on one end of the 90-110% range to minimize drift."

Added by applicant:

- If either of these criteria are not met, then the potency will be assigned as the mean of the potency determinations of the new Reference Standard.

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Look at the data

Identify drifts looking from different angles:

- Trending of stability data
- Trending of reference materials qualification data
- Evaluate the distribution of individual determinations over reference materials

In a Nutshell

- Primary reference material at submission
- Two-tiered system
- Specific reference materials for specific tests
- Submission requirements
- Extended characterisation
- Narrow acceptance criteria for some attributes
- Calibration results
- Potency equivalence testing
- Data trending

Thank You

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