Roundtable Session 2 – Table 11 – Interpreting Confidence Intervals in Analytical Validation under ICH Q2(R2): From Statistical Reporting to Decision-Making

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Abstract:

The 2024 revision of ICH Q2(R2) for *Validation of Analytical Procedure* introduces enhanced statistical expectations: confidence intervals (CIs) for precision and accuracy should be reported at an appropriate 100 (1- a) percent confidence level, and the observed intervals should be compatible with the corresponding precision and accuracy acceptance criteria. This shifts the expectation from point-based assessment to *interval-based assurance* when demonstrating analytical method performance. Understanding how CIs should be interpreted, applied, and justified in validation decision-making is essential for successful validation

Discussion Questions:

1. Interpretation & Intent: Should a CI be used only as supportive information, or should it form the basis for pass/fail decisions in method validation?

2. Setting CI Acceptance Criteria for precision and accuracy

- Does your company use the same acceptance criteria for the point estimate and for the CI?

- Are the acceptance criteria for the point estimate and for the CI aligned with the Analytical Target Profile (ATP)?

- Do you use historical data to assess the risk of CI failing the acceptance criteria, or do you determine appropriate acceptance criteria using Bayesian simulation?

-Have you developed or applied novel techniques for CI determination?

3. Confidence Interval Design: What confidence level (e.g., 90% or 95%) is appropriate for different analytical purposes (such as purity versus impurity), and how do you justify that choice?

4. Practical Implementation: If a CI falls outside the acceptance criteria, how do you report the result? What mitigations and justifications will you provide? Do you have a proactive process in place to follow in that scenario?

5. Regulatory and Industry Alignment: Are there recent submission examples where CI-based decision criteria were accepted or challenged?

Notes:

1. The purpose is to discuss challenges with ICH Q2(R2) confidence intervals (CI) implementation
2. CIs are the new expectation in ICH Q2(R2) for method validation data analysis and acceptance criteria (AC)
3. Some companies incorporate Cls as pass/fail criteria for method validation. Some companies use the Cls results for information only.
4. There are cases when method is new and amount of historical data is limited. In these cases, establishment of CI and acceptance criteria is more challenging.
5. Data on method precision and CI data are helpful for establishing specifications.
6. The underlying reason for new CI requirement in ICH Q2(R2) is regulator's preferences within the EWG (Expert Working Group) for. After lots of debates the EWG decided on the language: "CI must be compatible with ACs, unless appropriately justified". This language allows for some flexibility with respect to ACs.
7. CIs are reflective of long-term method performance
8. The potential problem is no explicit requirement to check data distribution normality. However, ICH training materials show examples of normal and non-normal distributions
9. Scientific data understanding is always very important for justifying final validation outcomes
10. Is there value of applying CI to accuracy vs applying them to precision?
11. Should accuracy be assessed for each level or pulled data are OK? - If statistical assessment confirms it, data can be pulled
12. Some assays have wide variability, like bioassay, residual DNA, HCP
13. Increasing number of replicates can with some variable assays, but not chromatography type assays

14. How to set the ACs appropriately? - ATP (analytical target profile) concept is helpful for rationalizing to ensure that method is suitable for intended purpose.
15. There is no expectation to retrospectively update earlier approved method validation
    a. For historical products method performance data are the best demonstration or method fit for purpose, revalidation needed only if there is a method change
16. What are the differences for CI and Acs for platform methods?
    a. There is a benefit of sufficient data to calculate appropriate AC and get a preview of CIs
    b. Usually only a sub-set of validation is done for new molecules and other validation data are used
    c. The specific actions should be determined case-by-case
17. CIs for method transfers: requirements were not specifically added to ICH Q2(R2) for direct transfers; however, the requirements will apply for co-validation
    a. Transfer is expected to be more of the method verification
    b. The level of confidence should be built into the transfer ACs for equivalence
    c. Scientific rationale is still expected to justify the chosen approach for ACs
18. What are the approaches for CI confidence level (95, 90, etc.)
    a. Default approach is 95, but for a more variable assay 90% can be chosen
    b. Balance between process need and analytical performance should be factored in
19. Are development data suitable for setting ACs? - Yes, and here are the examples:
    a. Stability data
    b. Development batch release data
20. When CIs slightly exceed ACs, QA often does not accept successful validation without investigation