Workshop: Analytical method bridging pre- and post-approval

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Content Overview

The need to adapt and update analytical methods is critical to ensure the accuracy and reliability of product testing. During the product lifecycle, analytical methods are changed to accommodate technological advances, simplify test schemes, and address equipment or reagent availability issues. The workshop will cover assumptions and considerations involved in switching to new analytical methods, including the ability of methods to distinguish acceptable from unacceptable materials and the implications for clinical and post-approval batches. The importance of assay bridging studies in informing specification updates and the various approaches required for different methods will be discussed.

Disclaimer

- The thoughts presented herein are the viewpoints of the moderators as individual scientists who are familiar with this subject matter.
- These viewpoints are not intended to reflect the views, policies, procedures, or evaluation criteria of the organizations where these individuals are employed.

Why Change an Analytical Method?

- Analytical Method changes are implemented in order to:
  - Accommodate advances in technology
  - Automation of manual steps
  - Simplify or optimize test schemes
  - Transfer assays from one site to another
  - Extend shelf-life of reagents or components
  - Address lack of availability of equipment, kits, or reagents for a method
  - Redress critical issues with a current method such as:
    - Increasing Reliability (e.g. replace old equipment or reagents)
    - Decreasing variability of test output (replacing a variable method with a more precise one)
    - 3R's (replacing a test method involving use of animals or animal components)
    - Reducing time on station for analytical method (e.g. changing to rapid micro test)
  - Based on country specific requirements or local preference for different method, including changes to pharmacopeial monographs.

While implementation of some types of changes are under the sponsor's control, others are not.

Qualification of New Method per ICH Q2/Q14

- Perform necessary development studies
  - Some development work may leverage prior knowledge from current method, if new method employs relatively similar technology.
- Perform necessary method qualification studies
  - Use materials either drawn directly from commercial manufacture or representative of such commercial materials.
  - Use materials that draw upon knowledge of commercial history – i.e. what is likely to go wrong and therefore needs to be investigated in new method.
  - If possible, use materials above/below proposed acceptance limits to demonstrate how new method distinguishes these materials. Forced degradation studies can support this.

ICH Q14 Identifies Bridging Studies' Role when Changing an Analytical Method

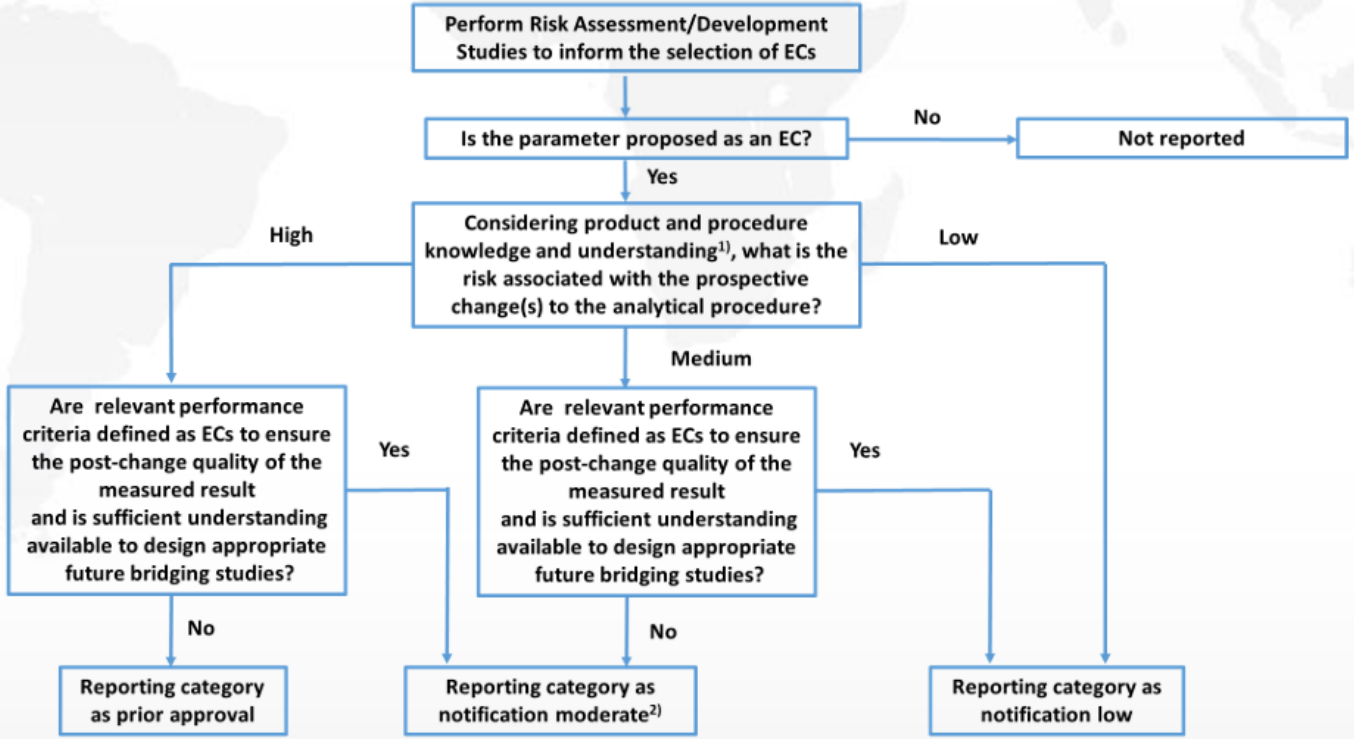
Knowledge of what factors are important to performance of the analytical method forms the key decision point for reporting changes.

⚠ Bridging Studies confirm hypotheses derived from existing knowledge-base.

ICH harmonisation for better health

ICH Q14: Analytical Procedure Development

Chapter 7: Lifecycle Management and Post-Approval Changes of Analytical Procedures



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

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Diagram from ICH Q2/Q14 training materials at ICH.org

ICH Q14 Provides Guidance on Extent of Bridging Studies

- Extent of change influences bridging strategy.
- Successful outcome supports claim that new method is at least as capable to distinguish "good" from "bad" materials as prior method.

Table 2: Examples of analytical procedure change evaluation

Risk Factor: Extent of change	Bridging strategy	Evidence of the suitability of a new procedure
Change of analytical procedure principle (physicochemical/biochemical basis)	Full validation of new procedure And Comparative analysis of representative samples and reference materials. And/or Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable	Analytical procedure performance characteristics are evaluated and criteria are met after the change And Results are comparable after change or differences are acceptable and potential impact on specification evaluated
Change within same analytical procedure principle	Partial or full *revalidation* of the analytical procedure performance characteristics affected by the change And, as appropriate Comparative analysis of representative samples and reference materials And/or Demonstration that the analytical procedure's ability to discriminate between acceptable and non-acceptable results remains comparable	Analytical procedure attributes are evaluated and criteria are met after change And, as appropriate Results are comparable after change or differences are acceptable and potential impact on specification evaluated
Transfer of analytical procedure to a different site with no change in procedure itself	Partial or full revalidation of the analytical procedure performance characteristics And/or Comparative analysis of representative samples and reference materials Or Justification for not performing additional transfer experiments	Analytical procedure attributes are evaluated and criteria are met after change And/or Results are comparable

Bridging to a New Analytical Method Involves Key Assumptions about the Prior Method:

1. Current analytical method is capable of distinguishing acceptable material from unacceptable material.
2. Batches released using current analytical method are part of a population of acceptable material.
3. Batches released using current method are either:
   a) Suitable for use in clinical study (pre-approval).
   b) Possess similar attributes to previous clinical materials to assure safety and efficacy aligned to approved registrational studies (post-approval).
   c) Consistent with previously released commercial supplies (post-approval)

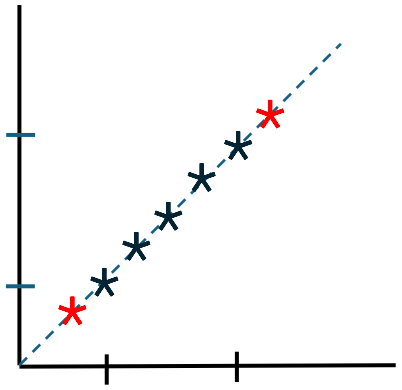
Design of Bridging Study is Important

- Consider intent of bridging study:
  - Trying to incorporate all sources of variability in new method?
  - Proving Non-inferiority vs comparable variability in new method?
  - Assessing bias between methods?
- Make sure the study design is appropriate
  - Lack of paired data across assay full range Impacts ability to assess with statistics
  - Bridging studies with large gap in time (6 months or more) may mask issues with attribute loss over time
  - “Bridging studies” that are not testing the same samples make drawing conclusions of comparable performance difficult.
- Limited materials/retains to perform bridging (esp. for CGT products)
  - Small sample size in bridging study may not capture true population variability for CGT.
  - Could use mock samples, control samples (diluted to multiple concentrations), etc.
- Academic assays (inefficient/cumbersome/high skill level required) vs need for a ‘validatable’ commercial-use assay

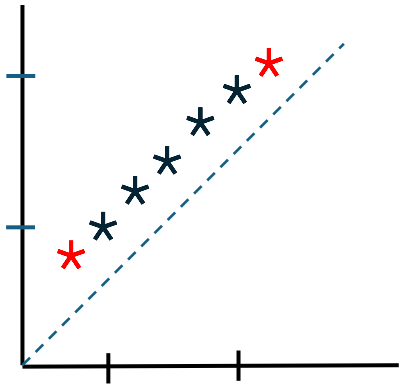
Key Point to Rember: the bridging study is a scientific exercise, not solely a GMP exercise

Bridging Study Results Inform Need for Specification Updates

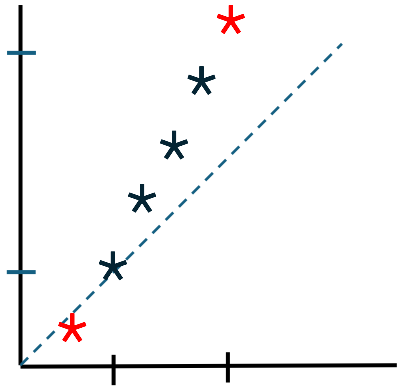
X-axis = current test method. Y-axis = new test method. Hatch marks indicate specifications.
Stars = data generated from test article in each test method, covers beyond specification range



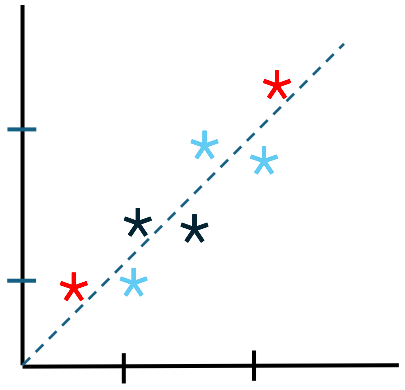
Tests are well aligned, current specification maintained.



Tests are offset but parallel, specification can be adjusted accordingly.

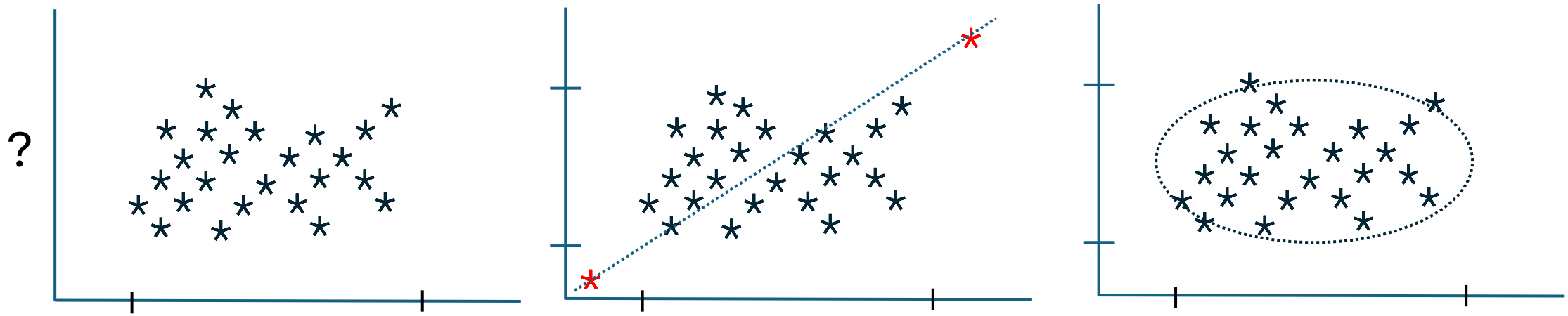


Tests have skewed linear relation, specification can be adjusted accordingly.



Tests exhibit correlation, but with variability. Specification setting may require more data.

Some Methods Require a Different Approach



- No discernable correlation between methods (in the range investigated).
- Could attempt generating data beyond specification range.
  - Not always possible to generate (or not ethical to generate) data beyond current specification range.
- May need to approach specification setting for new test method by characterizing the population of successful batches.
  - Likely requires large value of n batches for this purpose.

Questions for Audience, to Start Discussion

- How are sponsors approaching bridging for new technologies?
  - e.g. multi-attribute methodology (MAM)
- How are sponsors handling highly variable assay replacement?
- When do you employ standard bridging vs a reduced bridging approach?
  - What feedback can you share on the reduced bridging approach?
- What additional information/studies does one need prior to bridging to ensure success?
- In what cases do you seek regulator input in design of a bridging study?
- Thoughts on use of 'correction factor' vs adjusting specification as a result of bridging study?
- How have sponsors handled identification of new product variants/impurities when transitioning to a new method?