Analytical Method Replacements

Regulatory-Approved Strategies and Case Studies

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Replacing Analytical Methods

Presentation Agenda:

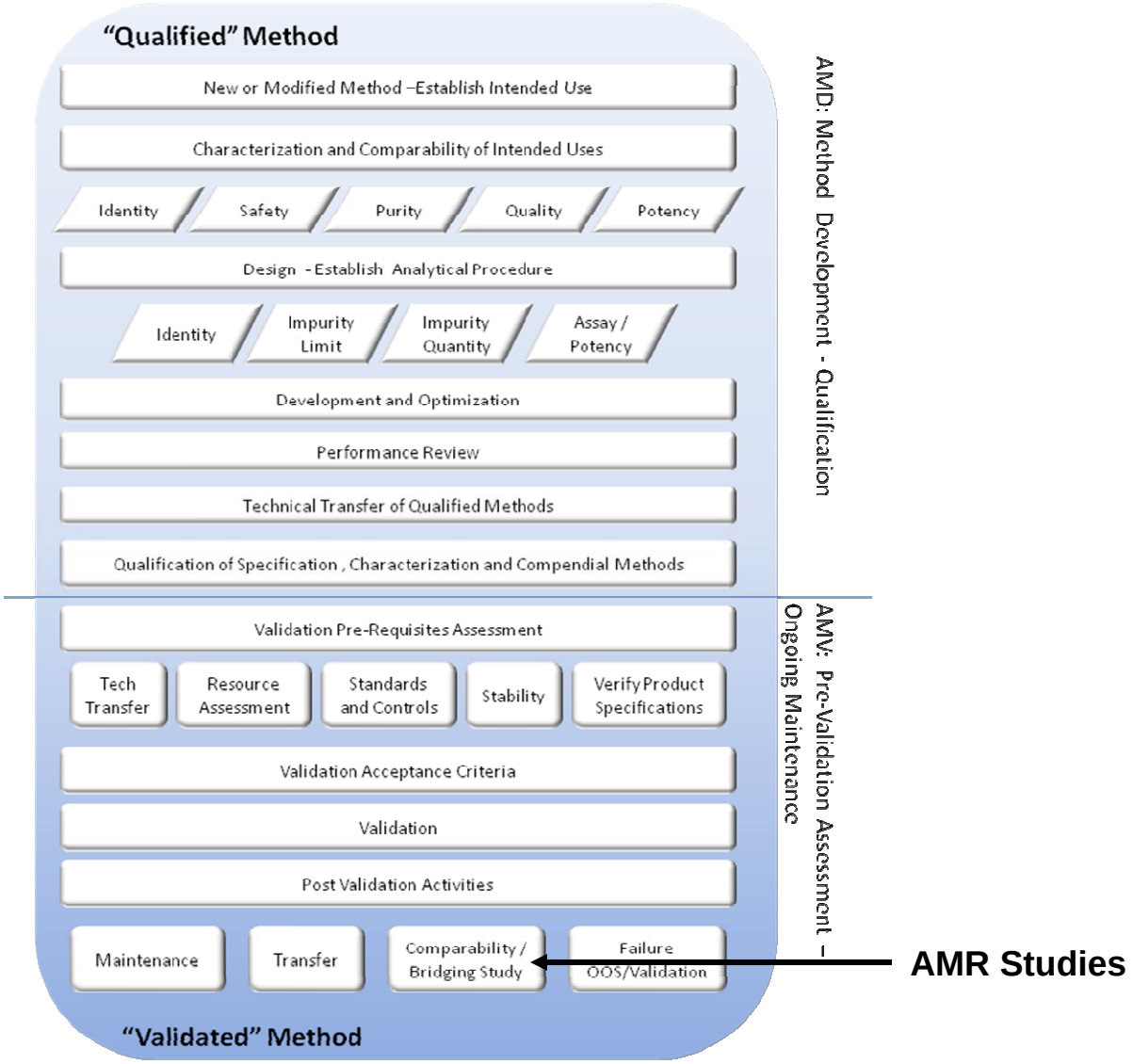
I. **Introduction and Strategies**

- The Analytical Method Life Cycle (Process Map)
- AMR background and rationale
- General Strategies for Qualitative and Quantitative Methods
- General test method performance characteristics compared

II. **Analytical Method Replacement (AMR)**

- Case Studies

Analytical Method Life Cycle
AMR Studies



Analytical Method Replacement Studies
Why do we need it ?

What is AMR ?

- AMR is the demonstration of comparable ("equivalent or better") test method performance of a modified/new method done during or after AMV completion.
- AMR should be demonstrated for methods replacing approved methods (in-house licensed, compendial, or otherwise recognized).

Why is it important ?

- A continuous suitable test method performance must be assured for safety/efficacy/quality to patients (linking to licensed specs and clinical data).
- This also assures a quality continuum (=> release) for the firm.

How exactly can we demonstrate AMR ?

- Follow ICH E9 and CPMPs Points to Consider guidelines.
- Demonstrate "equal or better" by testing for non-inferiority, equivalence, or superiority depending on assay type and need (risk).
- Compare particular test method performance criteria per ICH Q2(R1).

Analytical Method Replacement

Suggested Performance Characteristics and Statistics

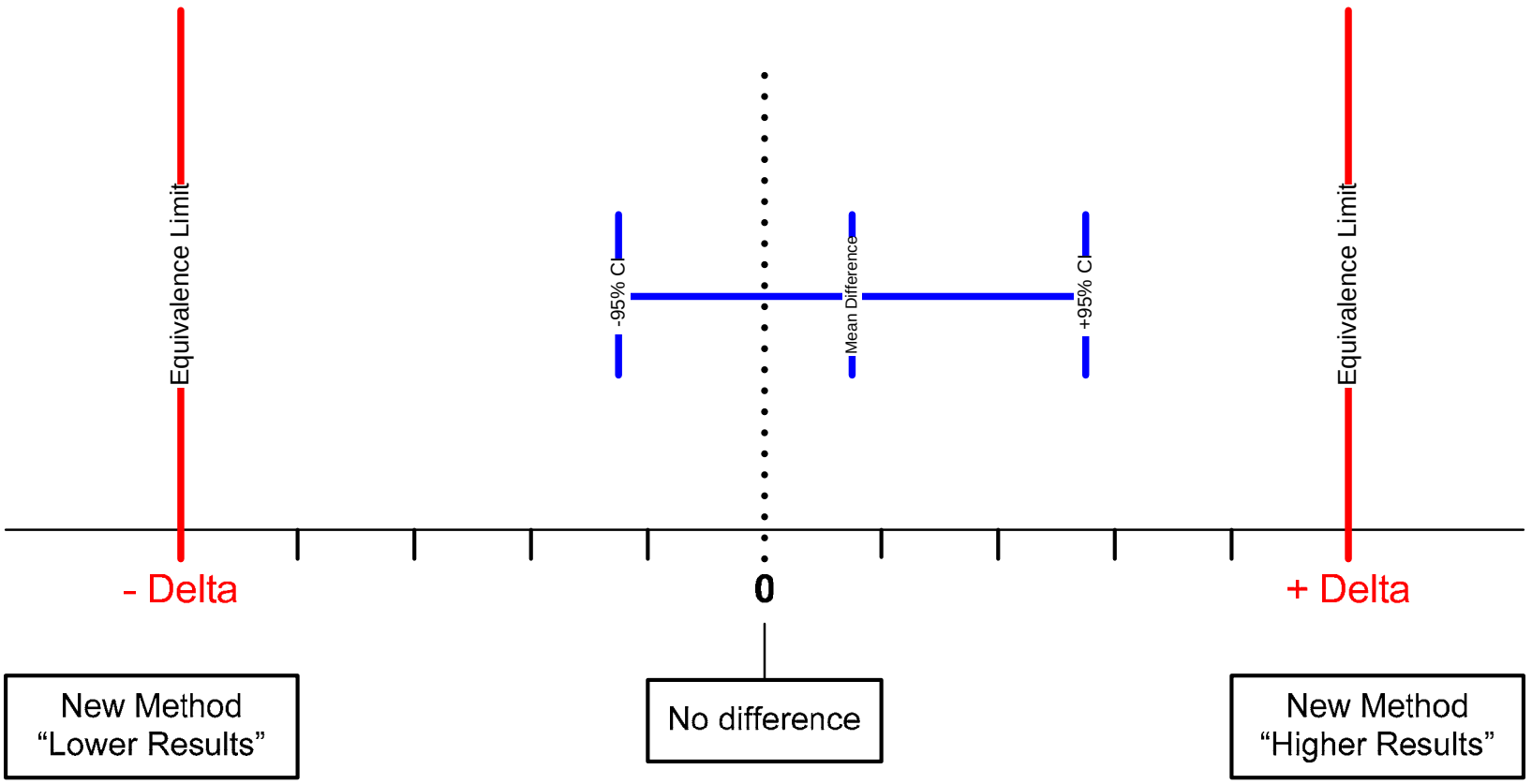
ICH Q2(R1) Category	Identification Test (Qualitative)	Limit Test (Qualitative)	Limit Test (Quantitative)	Potency or Content (Purity or Range) (Quantitative)
Accuracy	Not Required	Not Required	T-test, TOST; Some Data could be at QL level	T-test, TOST
Intermediate Precision	Not Required	Not Required	ANOVA, mixed linear model, or other F-test statistics	ANOVA, mixed linear model, or other F-test statistics
Specificity	Probability and/or Chi-Squared for Number of Correct Observations	Probability and/or Chi-Squared for Number of Correct Observations	Not Required	Not Required
Detection Limit	Not Required	Depends on how DL was established. Probability calculations may be used	Not Required	Not Required

AMR Categories (from ICH E9)

- **Equivalence**
- **Non-inferiority**
- **Superiority**

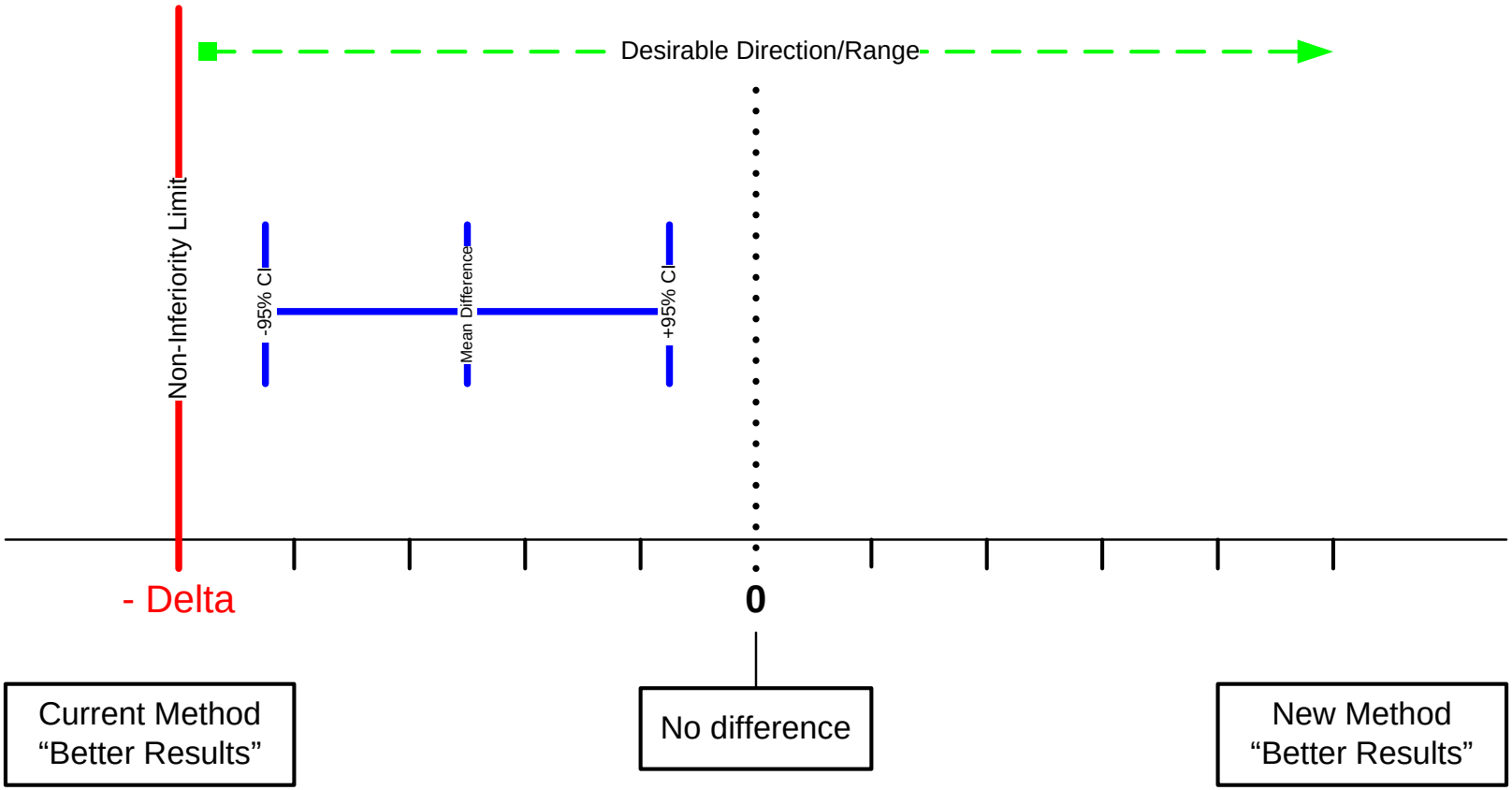
Demonstrating Equivalence

Equivalence Testing (ICH E9)
Current Method = Reference
Equivalence Demonstrated



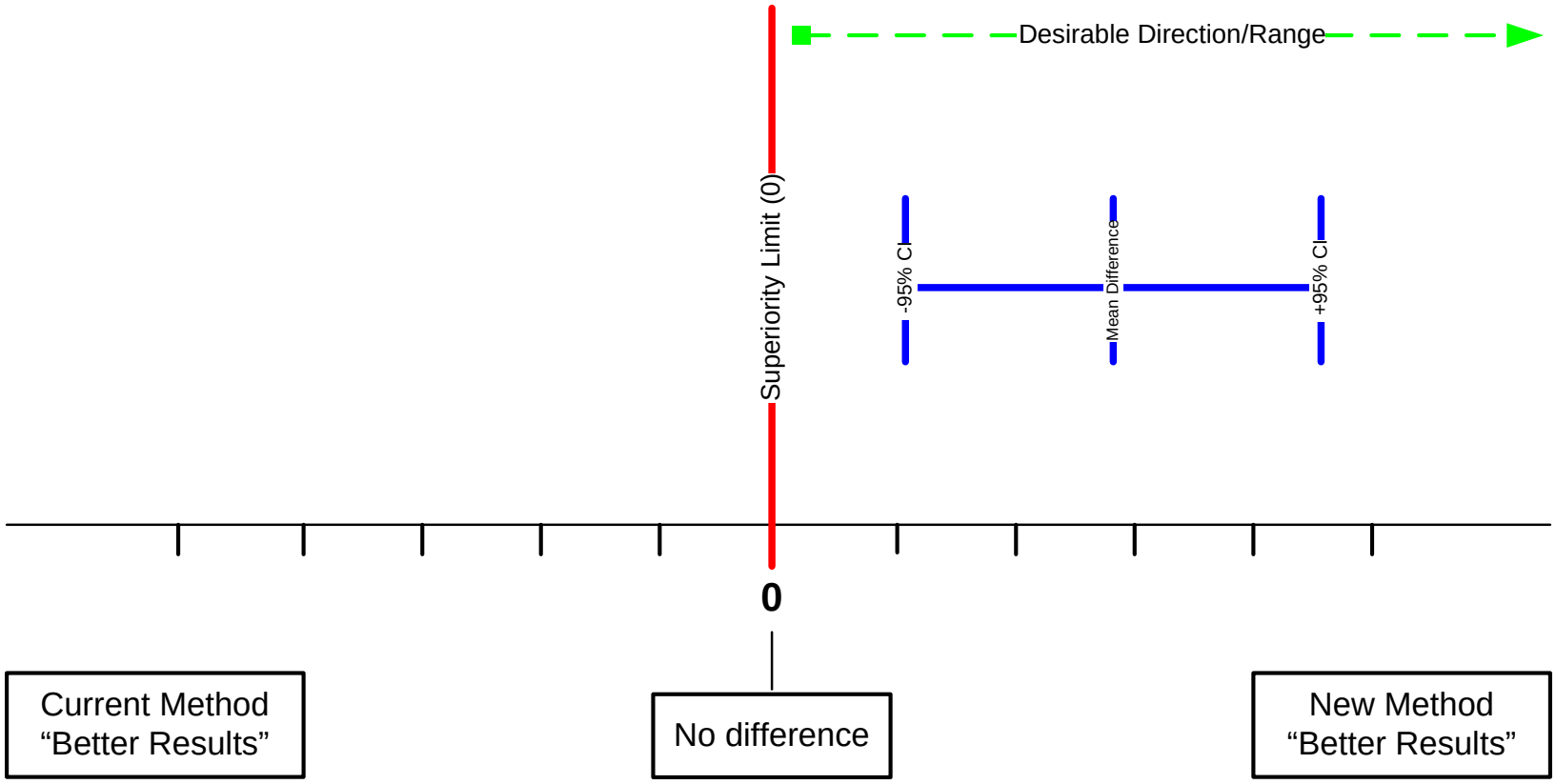
Demonstrating Non-Inferiority

Non-inferiority Testing (ICH E9)
Current Method = Reference
Non-Inferiority Demonstrated



Demonstrating Superiority

Superiority Testing (ICH E9)
Current Method = Reference
Superiority Demonstrated



AMR – Qualitative Method Models

- When comparing qualitative data, non-inferiority or superiority models should be used and three possible outcomes are illustrated below.
- **Inferiority**. A particular performance characteristic compared provides significantly inferior results for the current method, therefore failing to demonstrate AMR.
- **Non-inferiority**. The new method performs at a comparable level. The new method could be superior, equivalent, or insignificantly inferior. All three outcomes are acceptable outcomes to demonstrate non-inferiority.
- **Superiority**. The new test method is superior. When testing for superiority, only this outcome is acceptable.

AMR – Quantitative Method Models

- When comparing quantitative data (for accuracy/matching), two possible outcomes are illustrated below:
- **No equivalence for accuracy**: There is a significant difference between results from both test methods. Both differences, lower and higher, are statistically unacceptable outcomes. The new method may be acceptable if specifications changes or other adjustments can be made.
- **Equivalence**: The difference between both methods is insignificant and the new method performs at a comparable level.

General Points to Consider for AMR Studies

When using one of the suggested three AMR categories, the following major points should be considered:

- **The comparison category should be explained and justified. For example, a non-inferiority test may be suitable, if all outcomes (non-inferiority, equivalence, and superiority) are acceptable, and if the new method is superior in other aspects such as faster test results and/or increased sampling/testing.**
- **The AMR protocol should include a detailed study design and the statistical test(s) to be used.**
- **The pre-specified maximum allowable difference(s) should be justified. The difference limit(s) should strike a balance among possible opposing incentives: Impact on patient and/or manufacturing versus AMR results are "comparable" (when they may not really be).**

Demonstrating Non-Inferiority

Introduction

- **A faster and technologically advanced method for sterility testing was validated and compared to the compendial EP/USP Sterility Test.**
- **The non-inferiority comparison at the 95% confidence level (p=0.05) was chosen with a pre-specified delta of –10% versus the compendial (current) method.**
- **Justification: Non-inferiority, equivalence, and superiority are all acceptable outcomes, and the increased testing frequency of daily (n=7 per week) for the new sterility versus twice weekly (n=2 per week) for the EP/USP Sterility test significantly increases the likelihood of detecting organisms with the new method.**
- **Results/Conclusion: The 95% confidence level includes 0 (no difference) and lies entirely to the right of the pre-specified delta of –10%. The comparison results obtained indicate that the candidate method is not inferior to the EP/USP sterility test method.**

Demonstrating Non-Inferiority

Results for the Non-Inferiority Test: Candidate Method vs. USP Sterility

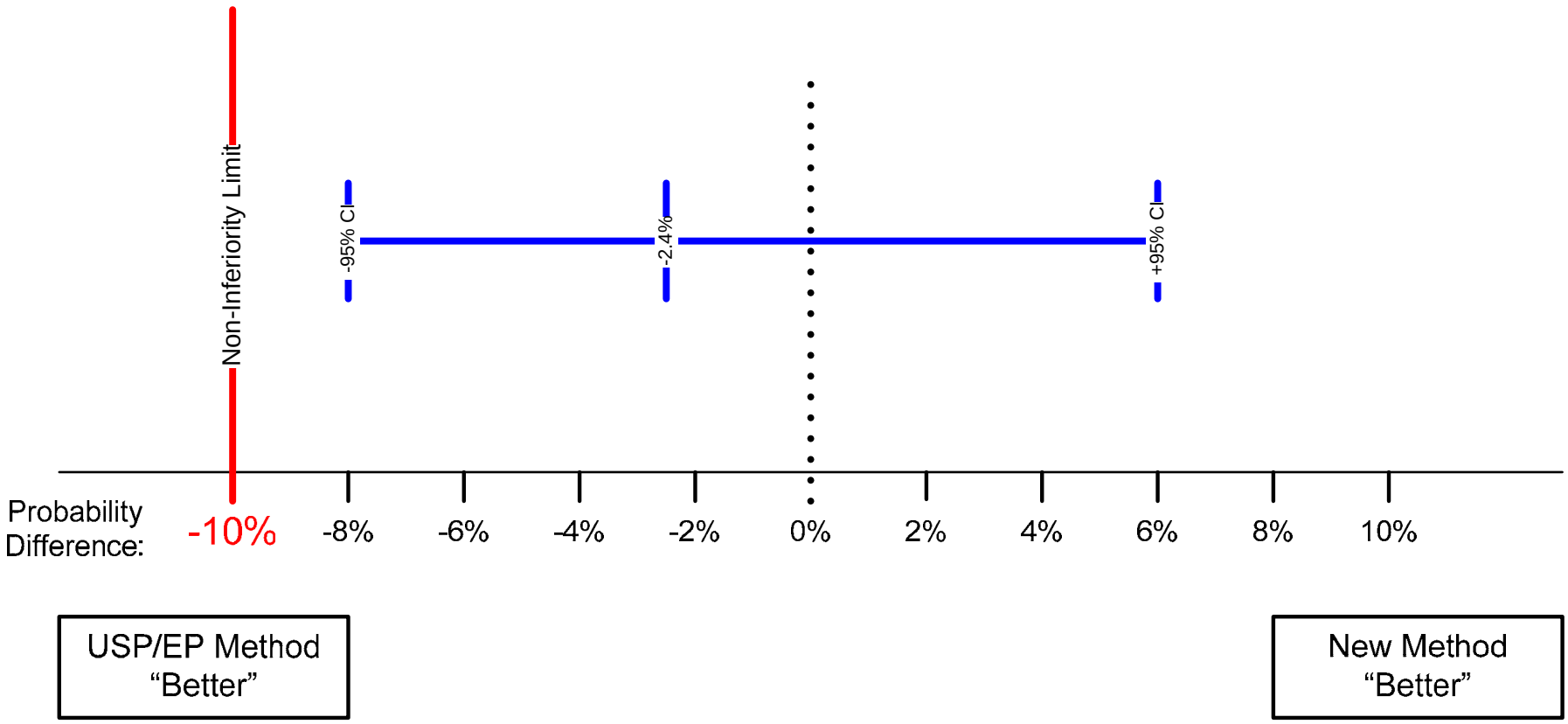
Method	Positives	Total Samples	Positives-to-Fail Ratios
Candidate	225	300	0.75
EP/USP	232	300	0.77
Statistical Results			
Difference = p (new method) - p (EP/USP) Estimate for difference: -0.024 95% lower confidence interval limit for difference: -0.08			

Results/Conclusion:

The 95% confidence level includes 0 (no difference) and lies entirely to the right of the pre-specified delta of –10%.

The comparison results obtained indicate that the candidate method is not inferior to the EP/USP sterility test method.

Non-Inferiority of New Method (vs. Current/Compendial) Demonstrated



Demonstrating Superiority
Introduction

From the previous example for non-inferiority: When the relative testing frequency of our example of n=7 (new method) versus n=2 for the compendial method is integrated in our comparison studies, the superiority of the new method could be demonstrated.

Demonstrating Superiority

Results

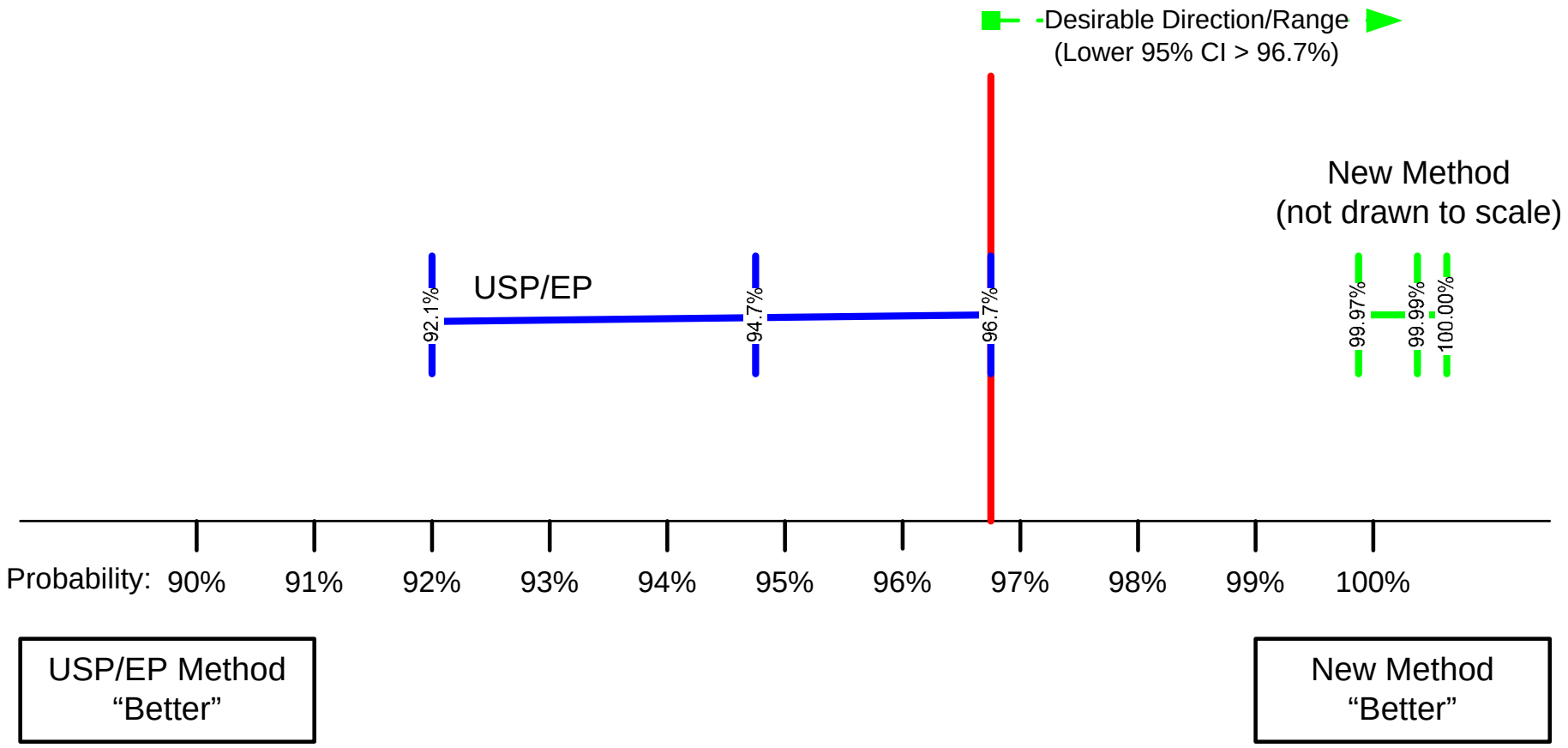
Candidate Method (7x) vs. EP/USP Sterility (2x):

Sample	Positives	Total	Probability	95% CI for Probability
Candidate	225	300	0.9999	0.9997 – 1.0000
EP/USP	232	300	0.947	0.921 – 0.967

Results/Conclusions:
Superiority at the 95% confidence level could be demonstrated because the new method's 95% confidence interval (0.9997-1.0000) for the positive-to-fail probability (0.9999) lies entirely to the right of the 95% confidence interval (0.921-0.967) of the compendial method's positive-to-fail probability (0.947).

The superiority test was passed with a much greater relative margin than the non-inferiority test. This is a good example why we should always consider upfront which comparison study to select and how to defend our strategy in regulatory submission.

Non-Inferiority of New Method (vs. Current/Compendial) Demonstrated



Demonstrating Equivalence

Introduction

Because of anticipated supply problems for critical SDS-PAGE materials, it was decided to develop and validate a capillary zone electrophoresis (CZE) method that will replace the current (licensed) electrophoretic method.

The method performance characteristics for a quantitative limit test, accuracy and intermediate precision, are compared.

For accuracy: A delta of plus/minus 1.0% was chosen for the equivalence category between both impurity levels from the analysis of historical release data with respect to the current release specifications (for SDS-PAGE).

Both methods were run simultaneously (side-by-side) for each of a total of n=30 reported results were compared by two-sided matched-paired t-test statistics with pre-specified equivalence limits of plus/minus 1.0% (% = reported percent and not relative percent).

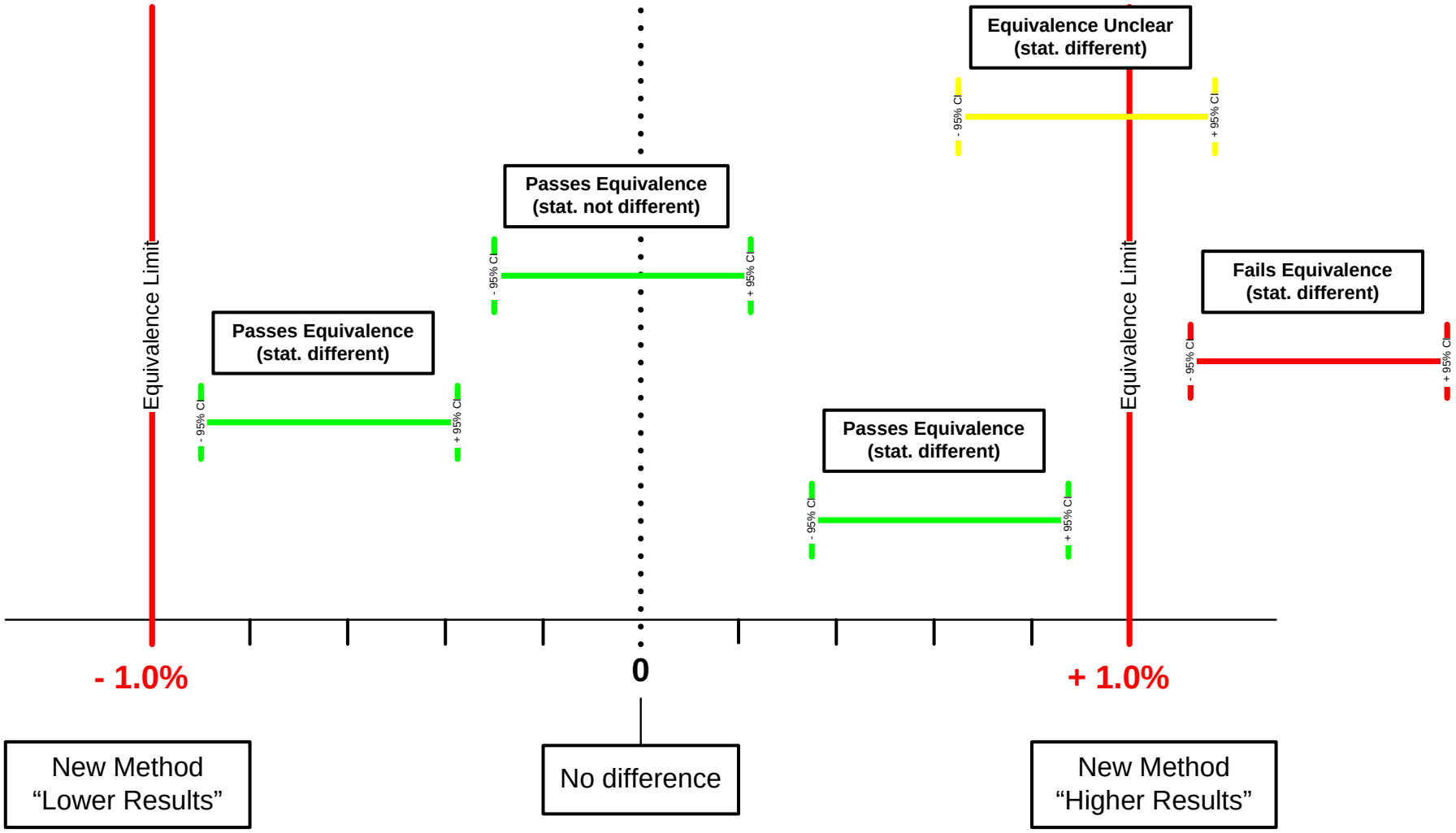
Demonstrating Equivalence

Results

Equivalence Test Results Comparing Current Method to CZE:

Sample Size (n): 30
Hypothesized Difference in Mean: 0%
Minus Delta: -1.0%
Plus Delta: +1.0%
SDS-PAGE Mean (n=30): 3.8%
CZE Mean (n=30): 5.1%
95% confidence interval of CZE results (vs. SDS-PAGE): 4.88-5.32%

Equivalence of New Method Not Demonstrated (New method's result are different)



Demonstrating Equivalence
Results

The 95% confidence interval of the CZE method (4.88-5.32) lies entirely over the current assay mean (3.8%) plus the positive delta (3.8% + 1.0% = 4.8%). This means that the CZE results for our impurity are significantly higher than our licensed method.

The expected drift in results is significantly higher than our pre-specified limit that was based on the gap of our historical release results relative to the release specifications.

Unless available from AMV studies, some additional data pairs for impurity levels around the specification limit may need to be run. Specifications may need to be changed for the use of CZE method.