Comparability with Statistical Rigor in Manufacturing Development

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Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

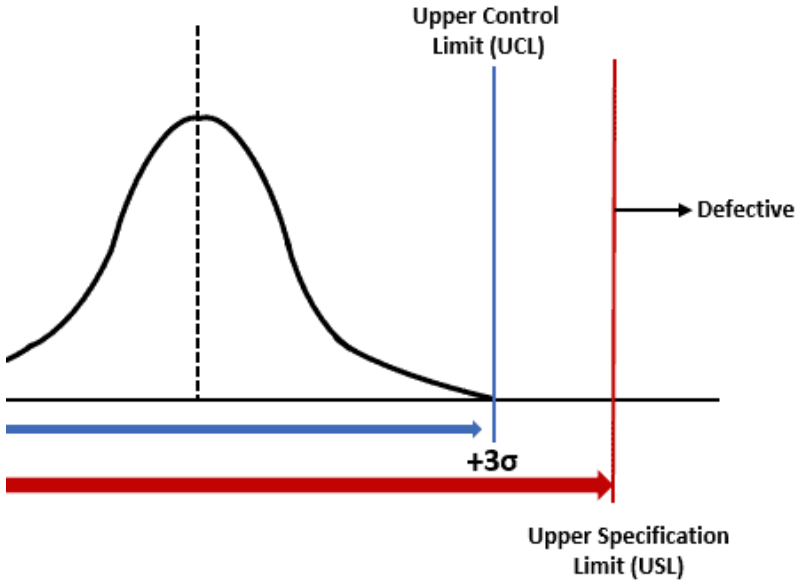
Johnson&Johnson

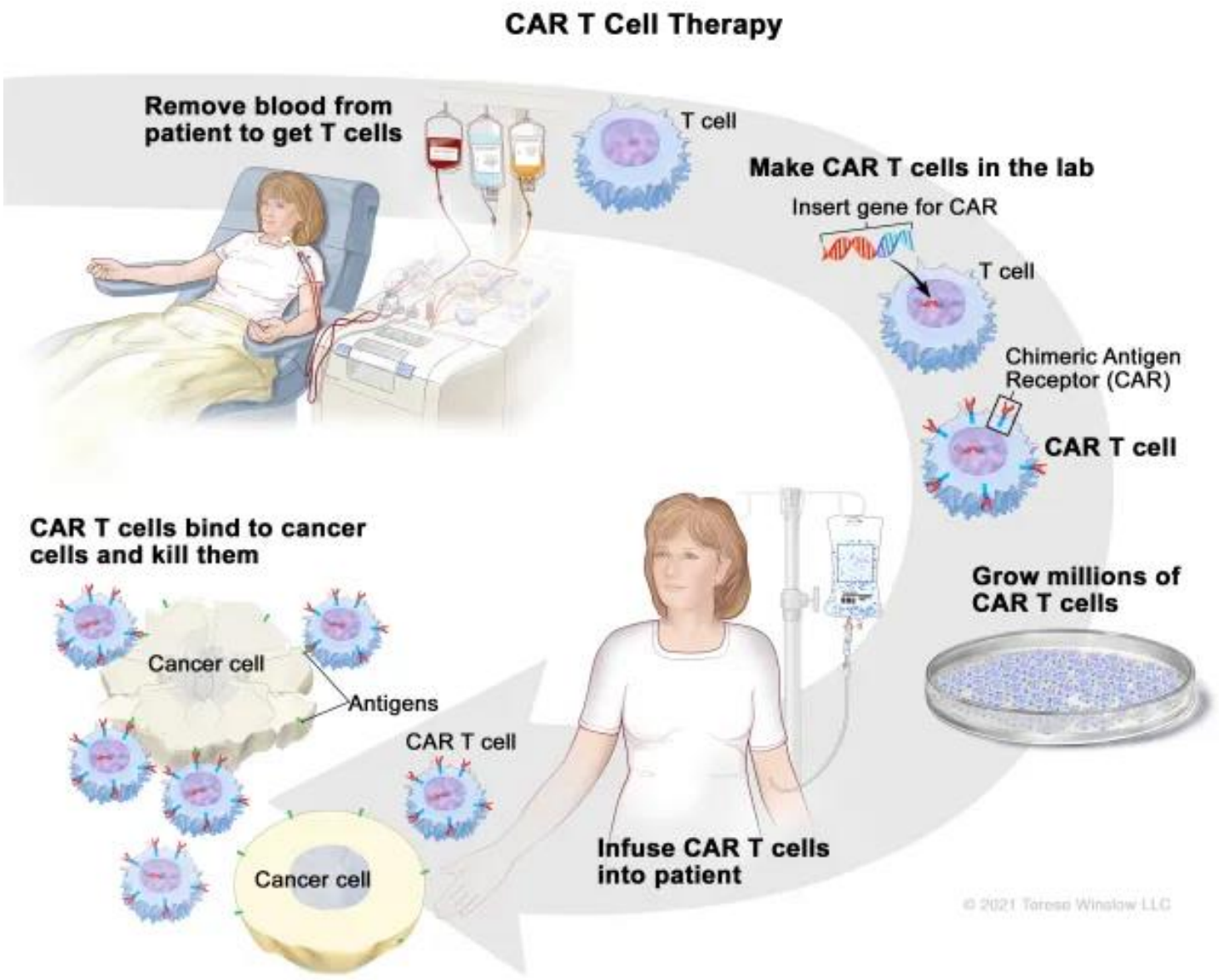
Acceptance Criteria and Statistics in Therapeutics Manufacturing

- **Attributes** refer to outcomes/endpoints
  - Potency
  - Purity/Impurities
  - Identity

- **Specifications** define numerical ranges of quality assurance for safety and efficacy of medicines. Also known as **Acceptance Criteria or Quality Ranges**.

IF we have one individual observation fall out of the specification range, or even approach it…





Lentiviral Vector Stage (# Attributes)

Drug Product Stage (# Attributes)

Health Authority Expectations: July 2023 FDA Guidance

"Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products"

We recommend that you consult with a statistician before discussing the study design and statistical approach with FDA. In general, there could be multiple appropriate statistical methods that may be used to evaluate whether data from the post-change product are within predetermined acceptable limits. To avoid errors in the design and analysis of comparability studies, a careful consideration of fundamental statistical concepts is important. For example:

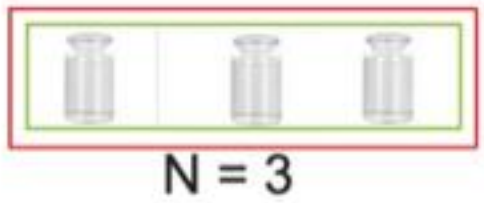
- Some statistical methods may be inappropriate for a given comparison due to invalid assumptions, a need for a very large number of samples, high variability in sample data, or limited information about the population distribution. For

Health Authority Expectations: Guidances

- EMA Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development: July 2021
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products: March 2022
- FDA (Withdrawn) Draft Guidance for Industry: Statistical Approaches to Evaluate Analytical Similarity: Sep 2017, withdrawn June 2018
- Statistical Approaches to Establishing Bioequivalence: February 2001 (Foundation is Schuirmann 1987)

Quality Ranges Precedence

Post Change limited sample size relative to Current (Pre– Change) Experience



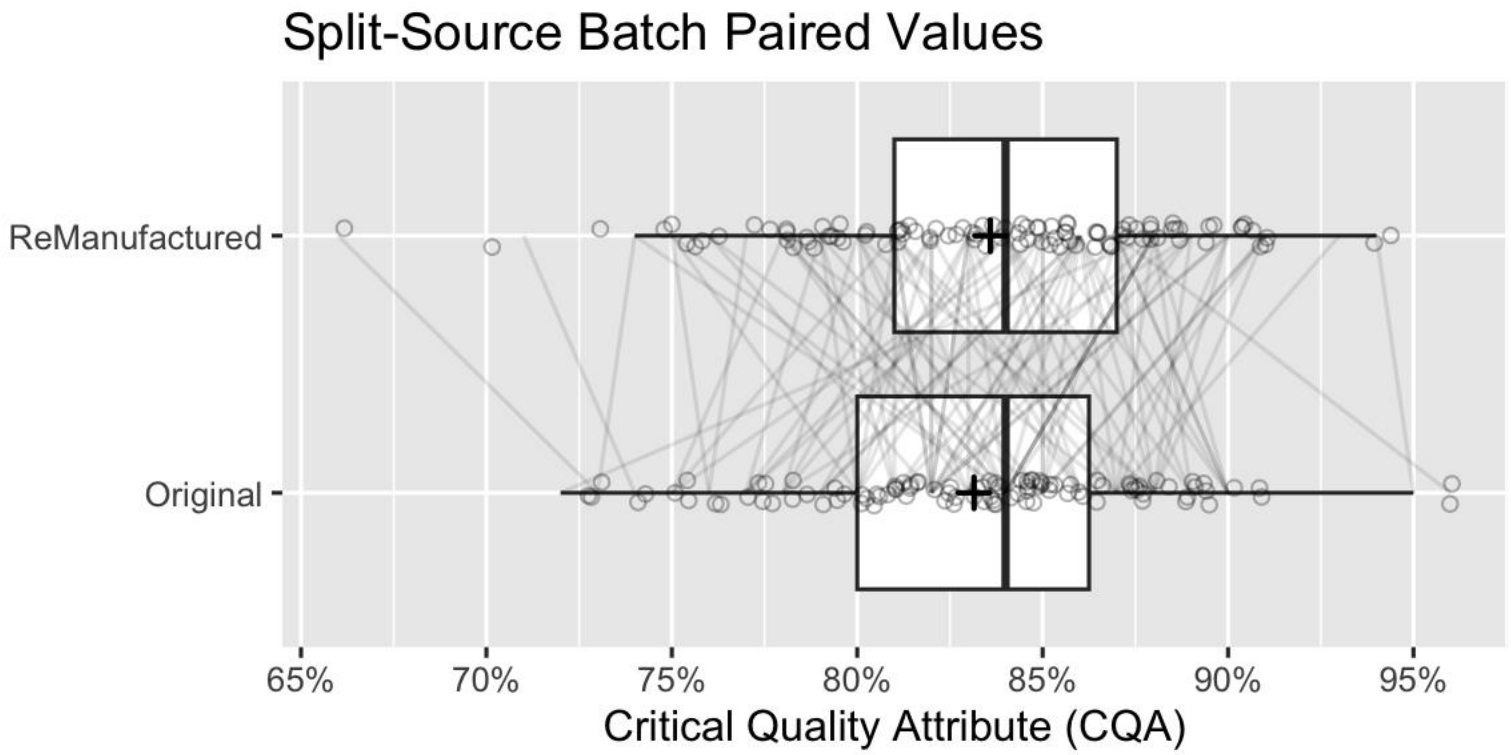
vs.

- Establish Pre-Change Acceptance Criteria (Quality Range) on Individual Reportable Values, with the help of Statistical Prediction Intervals, for example 99% coverage.
- Test and Determine 3 or similar Post-Change Individual Reportable Values and see if they lie with the established Pre-Change Quality Range.

Health Authority Information Requests to Assess Post-Change to Pre-Change

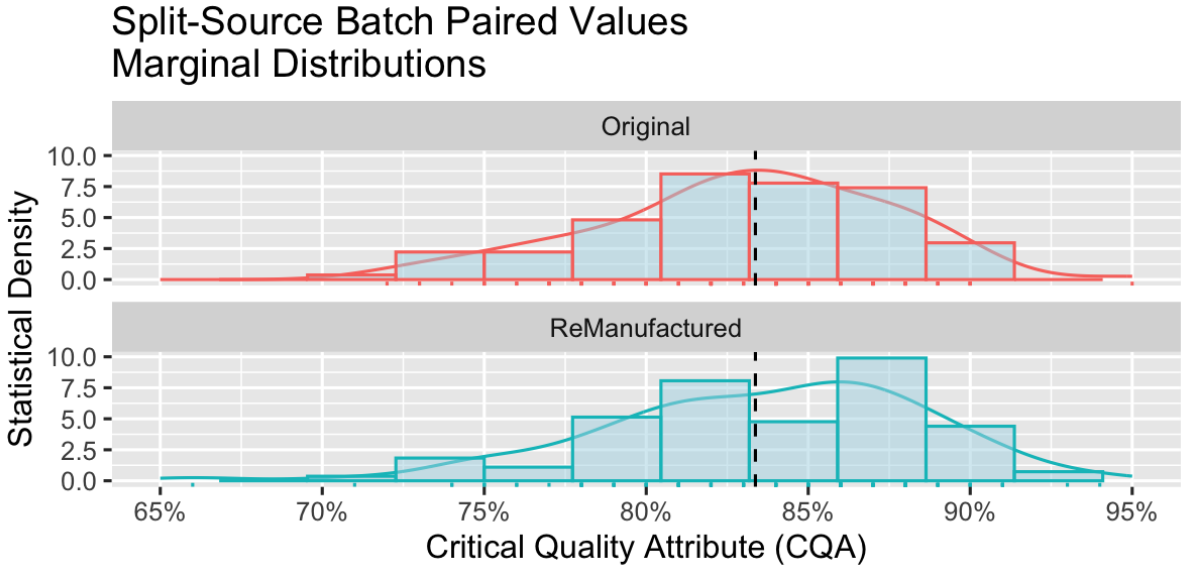
- Split-Source Structure (Paired Batches within a Donor)
- Small Sample Sizes
- Establish “Comparability Equivalence Margins” / “Comparability Range”
  (synonymous to Equivalence Acceptance Criteria)

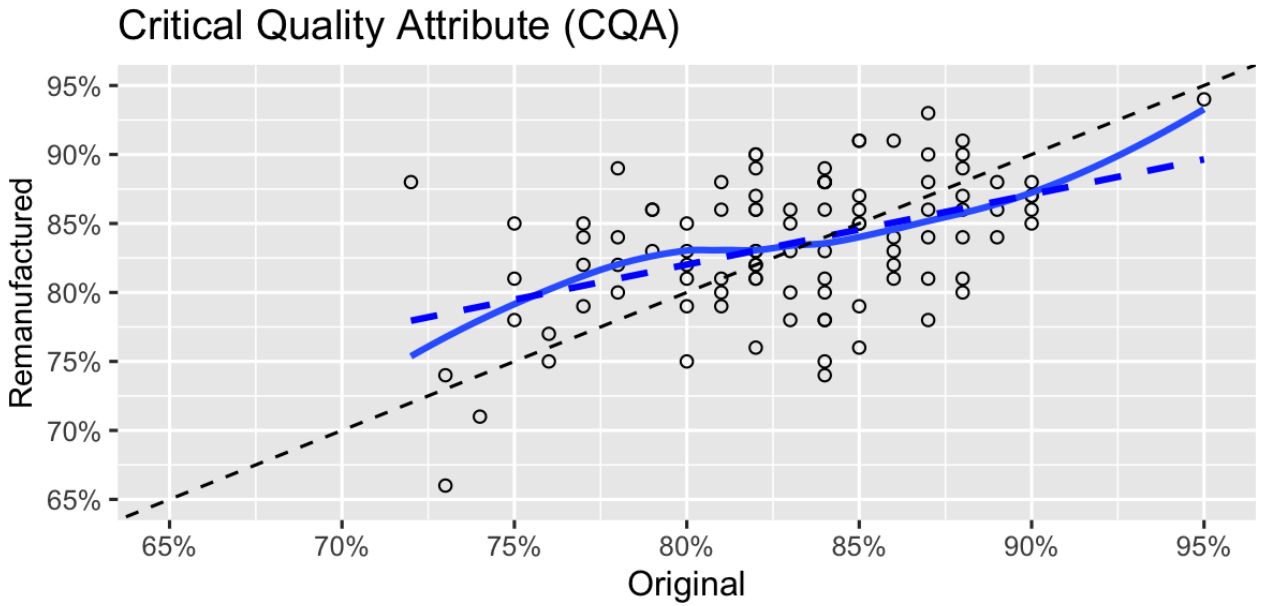
Mock Data Set



- Current Manufacturing Experience where re-manufacturing was needed
- Hypothetical number of n=100 patient donors

Mock Data Set
Existing (Pre-Change) Manufacturing Experience



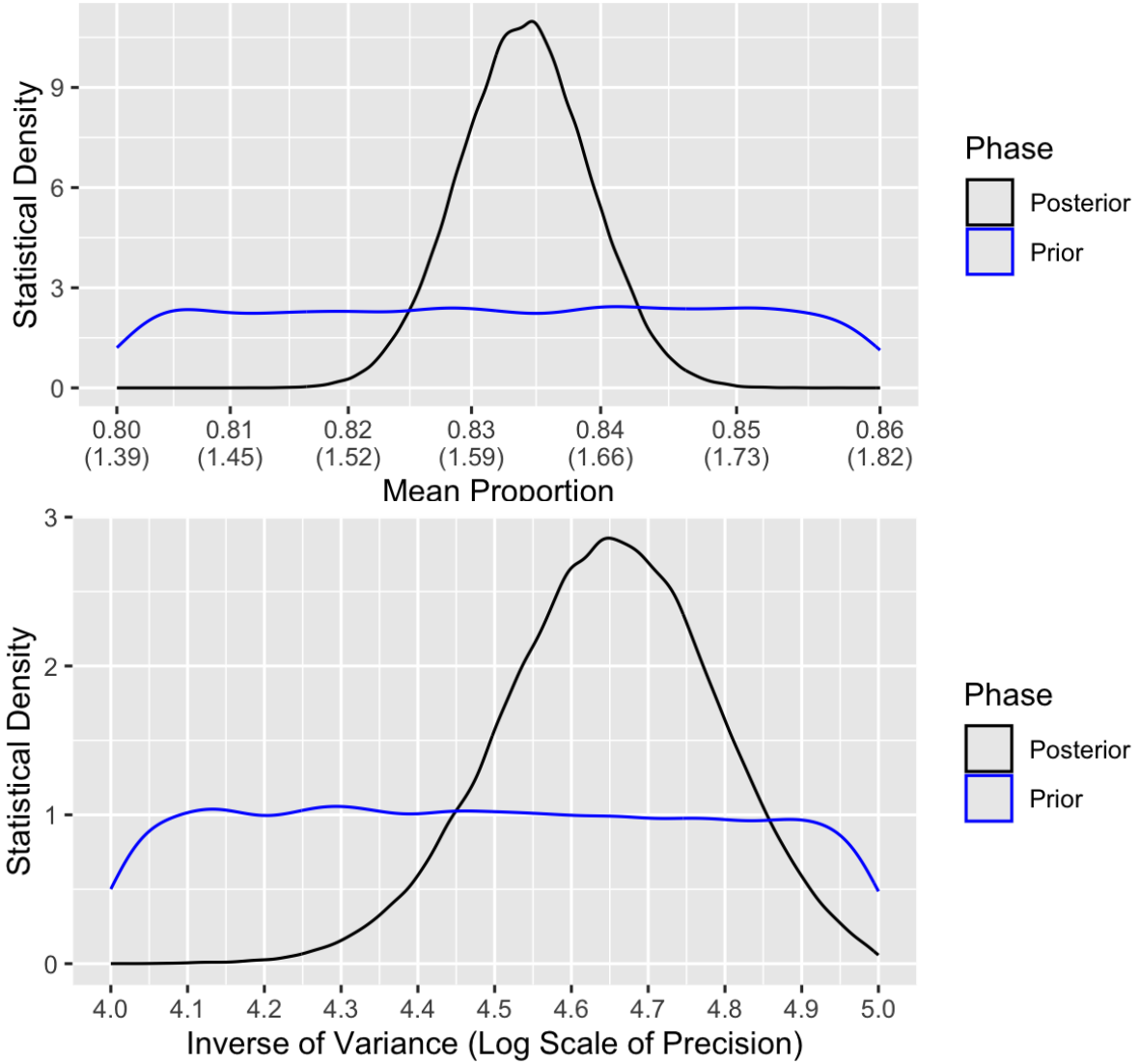


Step 1: Fit a Bayesian Multilevel **Model**

- Choices of Distribution, Priors, MCMC Draws, Chains, etc.
- For our Mock Example

  Beta Distribution for Outcome, Weakly Informative Priors, Population and Group Levels Effects*

  Current (Pre-Change) Experience and Post-Change Study Data



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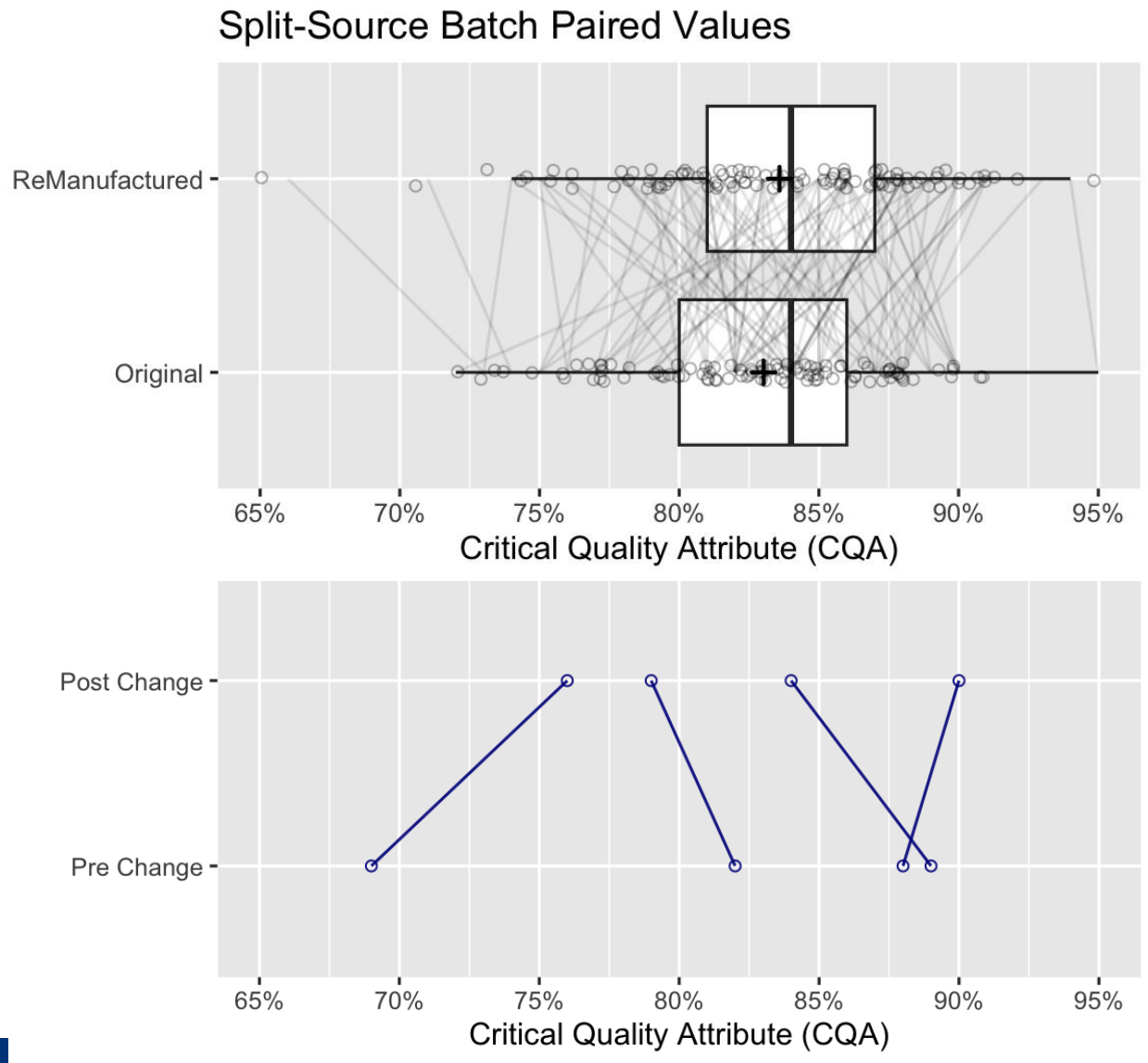
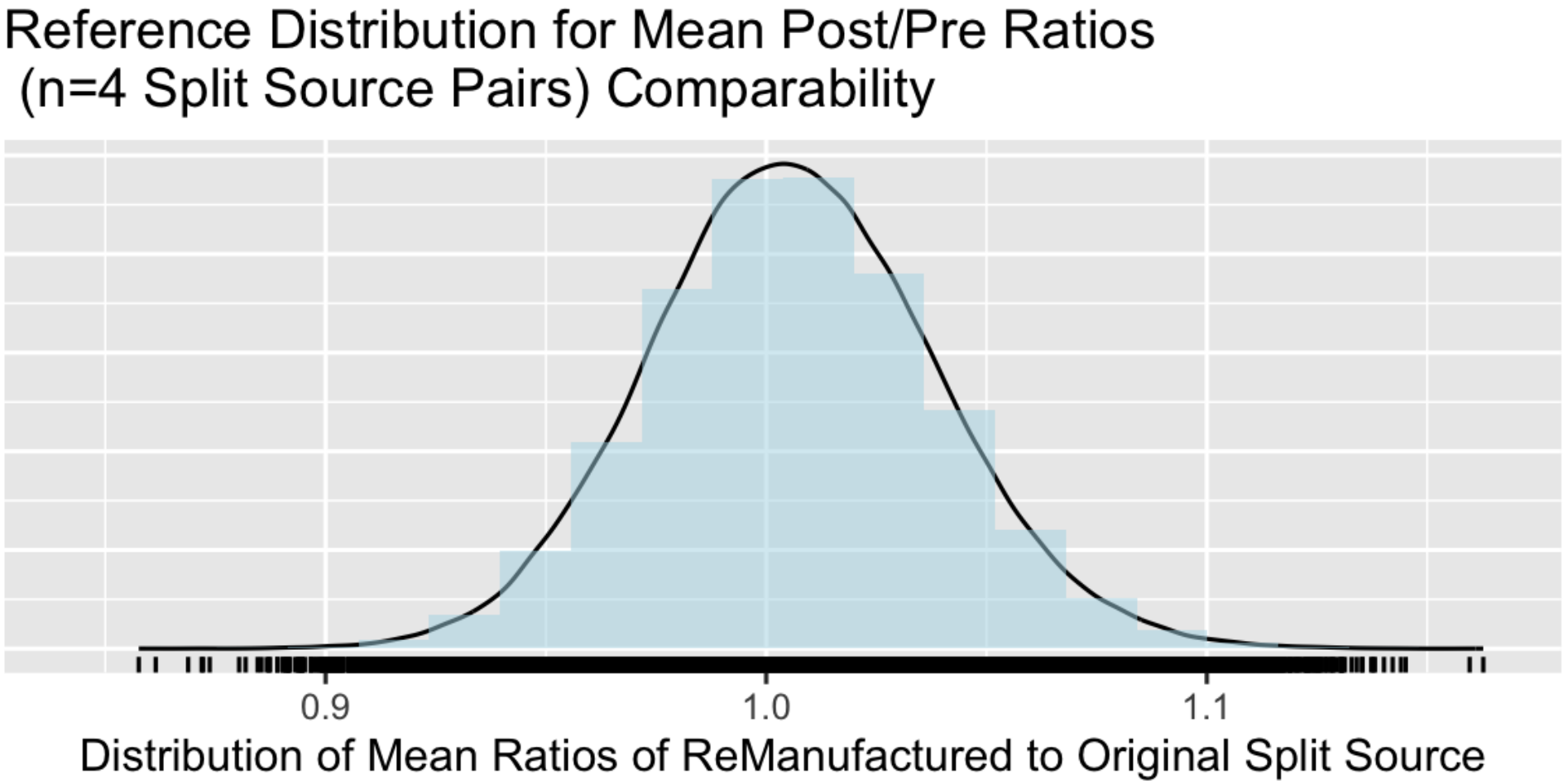
* In place of "fixed" and "random" mixed effects

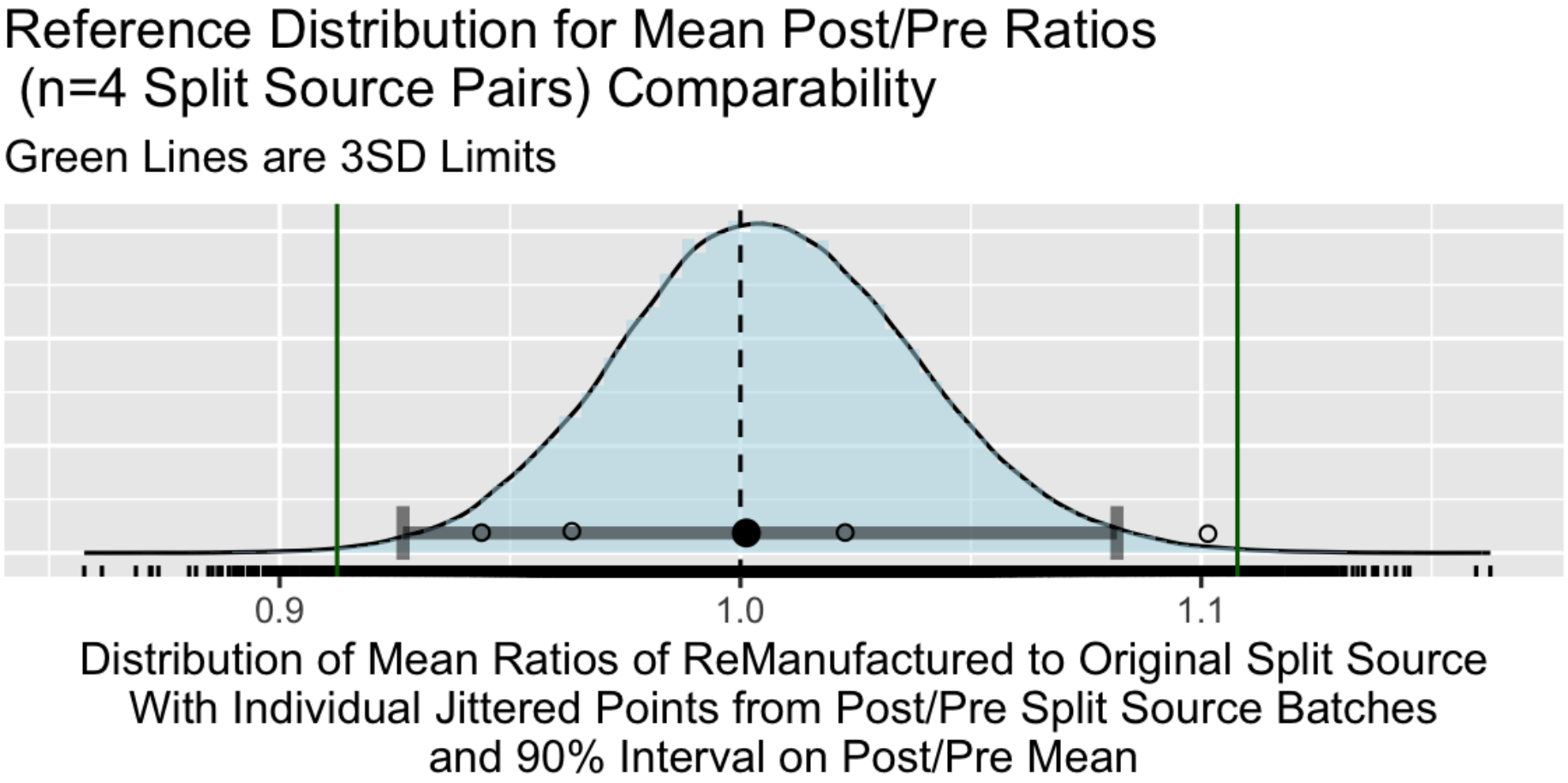
Step 2: **Simulate** a Reference Distribution for "Pre-Change"



Step 2: **Simulate** a Reference Distribution from "Pre-Change" (n=4 donors, 2 paired measurements from split source)



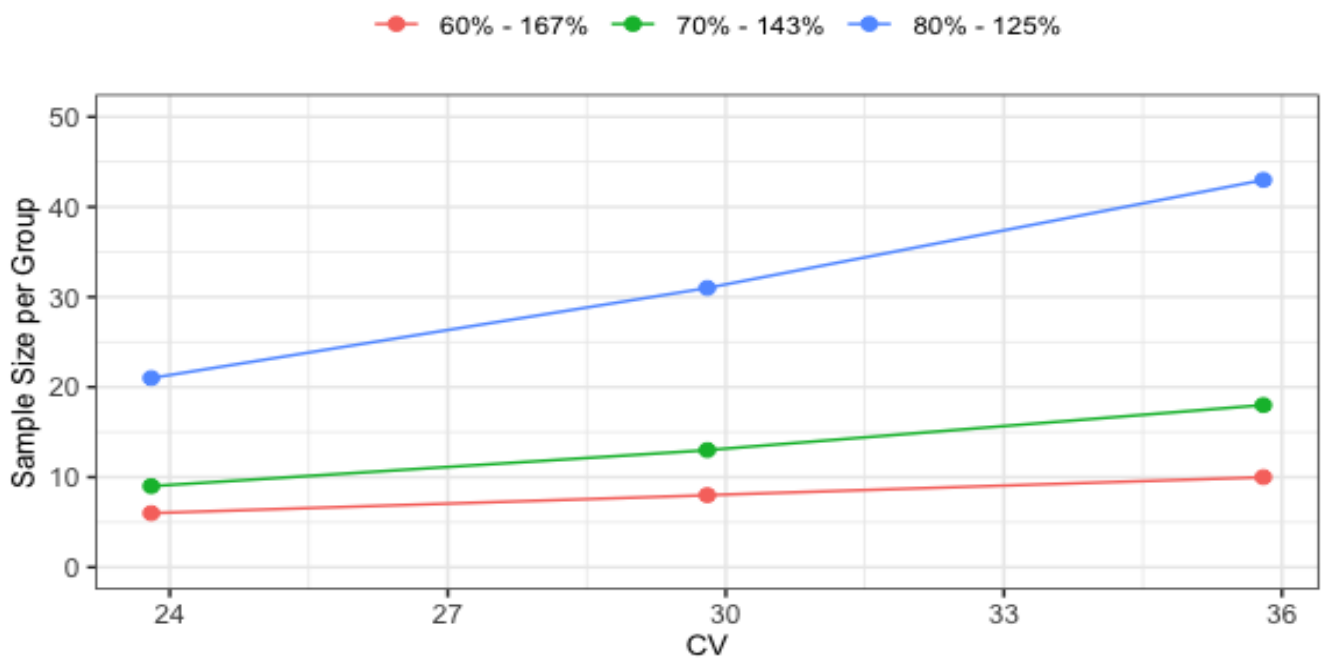
Step 3: Determine CEM from Reference Distribution and Compare Mean Post/Pre Ratio 90% Interval from Comparability Study



Going Forward

- **Prospectively** Define CEM / EAC
- Power / Assurance Characteristics

Generic Attribute with More Variability →



CV	60% - 167%	70% - 143%	80% - 125%
24%	6	9	21
30%	8	13	31
36%	10	18	43

Going Forward

- Prospectively Define CEM / EAC
- Power / Assurance Characteristics

Another Mock Example for a different Attribute