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Reliably Assessing Comparability in cell therapy

A compliance perspective

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Manufacturing changes

1. Why doing manufacturing changes?
   - Improving product quality
   - Expanding product supply
   - Externalize manufacturing to a CDMO
   - Improving manufacturing efficiency
2. The change may adversely impact product quality → quality risk management
   - a minor alteration in one CQA may have a substantial effect of the pharmacology of the product (Highly critical CQAs)
   - a major alteration can have no effect (Medium CQAs)
3. The most important to FDA is whether this is anticipated that any of these changes will translate into significant changes in clinical safety or efficacy
4. If a sponsor can demonstrate comparability, additional clinical safety/efficacy trials will generally not be needed

Manufacturing changes

5. Challenges to do manufacturing changes in ATMP / CGT
    - Low sample size
    - High donor-to-donor variability (for cell therapies, not for viral vectors)
6. Post-change process being within specification is not enough as a demonstration of comparability
7. FDA drafted a guidance: “Manufacturing changes and comparability for human cellular and gene therapy product (2023)”
    - Comparability between pre-change and post-change is demonstrated by evidence that the change does not adversely affect product quality.

FDA takes seriously the comparability problem

Extract from draft guidance

nonclinical laboratory studies that each manufacturing change does not adversely affect product quality before distributing a product manufactured using the change (21 CFR 601.12(a)(2)). For investigational products, sponsors must provide sufficient chemistry, manufacturing, and control (CMC) information to assure product safety, identity, quality, purity, and strength (including potency) of the product (21 CFR 312.23(a)(7)(i)), and some manufacturing changes without adequate comparability data may result in a clinical hold (21 CFR 312.42(b)).

quality should be prospectively assessed under the manufacturer's quality risk management processes (Refs. 1, 2). We note that while improvement of product quality is always desirable and encouraged, if the results of comparability studies indicate an improved product quality suggesting a significant benefit in effectiveness and/or safety, the pre- and post-change products may be different products and, therefore, not comparable.

If you have 2 different products, you need
2 different series of clinical trials

Two main statistical tools (based on the risk a change of the CQAs implies for the patient)

Equivalence test (TOST)

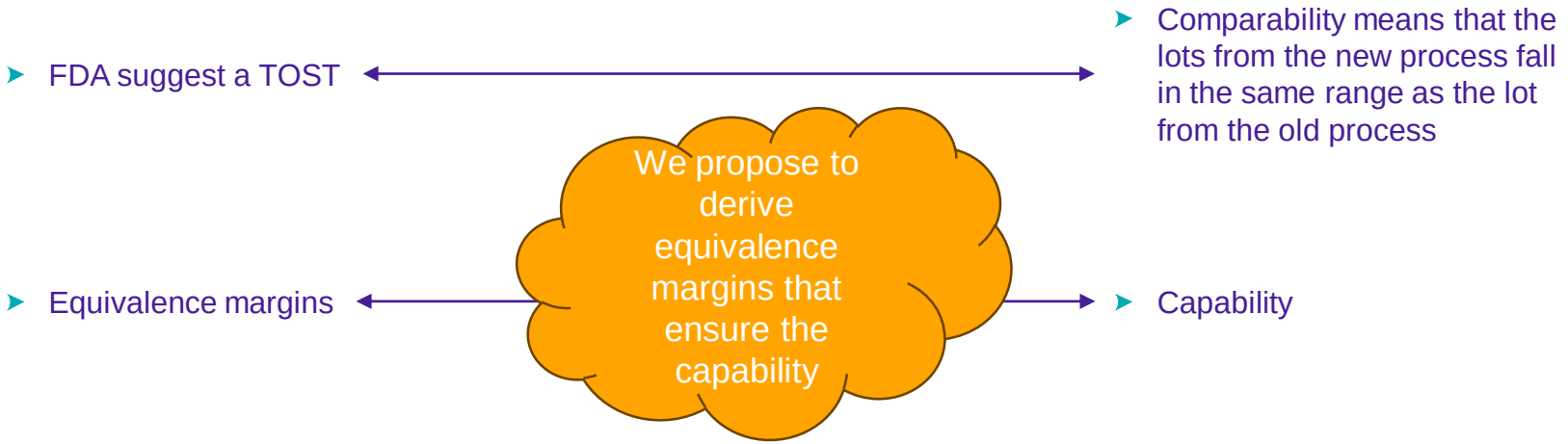
- For *high* CQAs
- Check if confidence interval of the difference is within the margins
- How to define the margins?

Statistical intervals

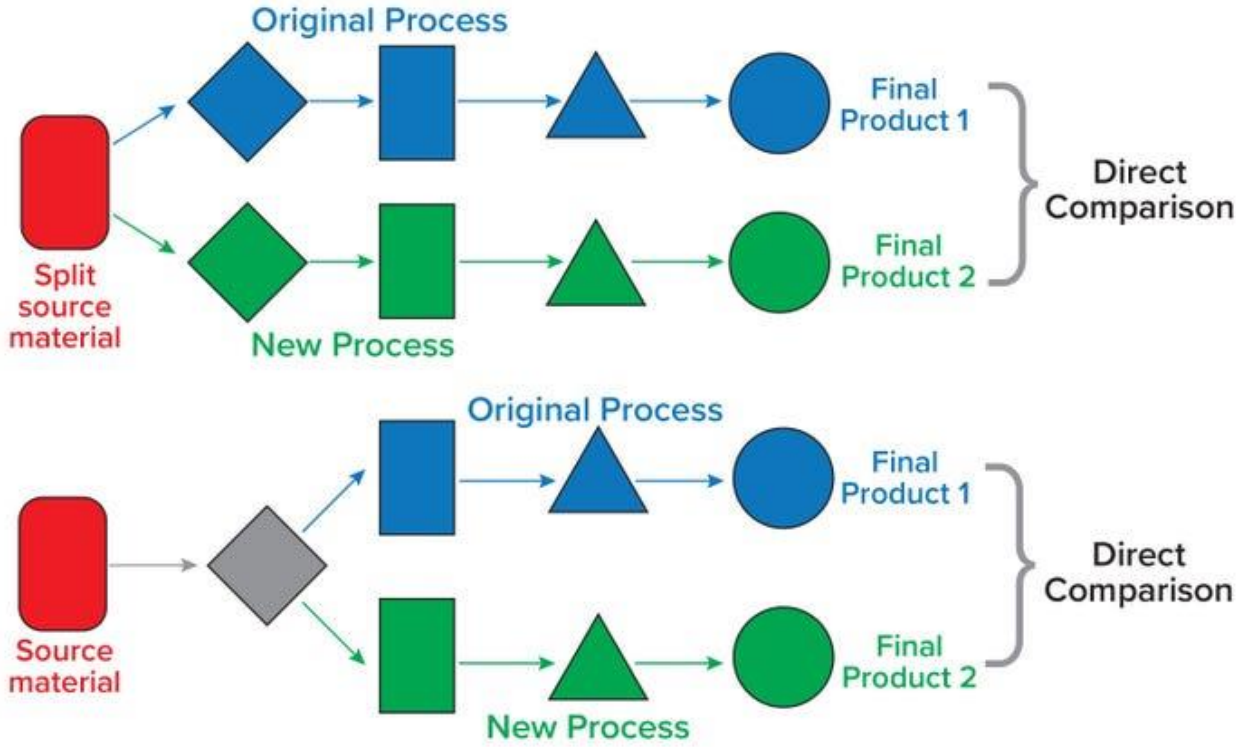
- For *medium* CQAs
- Calculate an interval (usually a prediction interval) on pre-change process
- Check if post-change batches are within the interval

Manufacturers are being ask to demonstrate comparability

1. FDA guidance insists on risk assessment, selecting relevant quality attributes, analytical methods, acceptance criteria and statistical methods
2. For autologous therapies where each lot is derived from a different donor,
   - Split-source design is recommended (cells of a single donor is divided into 2 pools of cells for each of the version of the process)
3. Guidance suggests performing a TOST with an equivalence margin defined before the study
4. In addition, the measurement also needs to meet the in-process and relevant acceptance criteria



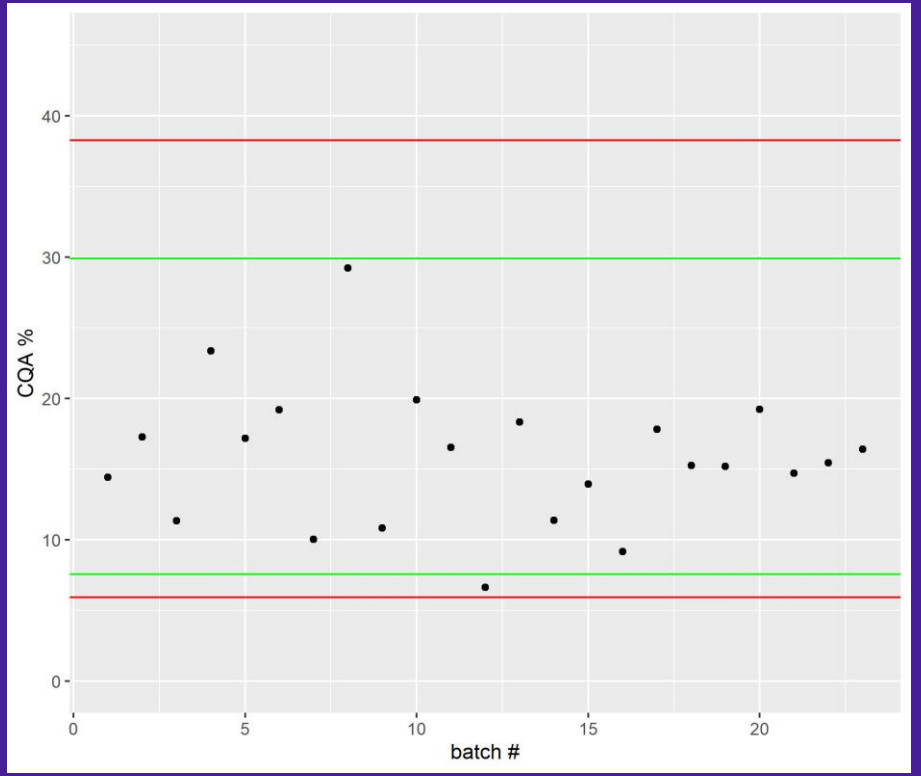
Split source design



Historical data of old process

Capability is the probability that the new process fall within limits of the old process (= PI)

Example of data that were accumulated before the change of manufacturing process.
The 2 intervals represents the prediction interval at 95% and 99% (assuming a log normal distribution)



Framework of simulation

Consider the transformation in the calculation wherever it is needed.

1. Generate data for the old and new process
   - Assume μ equals the mean of historical data
   - Generate $true\ donors \sim Normal(\mu\ , \sigma_{donor})$. We usually don't know between-donor variability, but it is the main component and should likely represent 1/3 or ½ of the variability of the historical data.
   - True donor values are replicated for each of the process
   - For the new process, add a hypothesized shift/ratio between the two processes
2. Calculate 90% confidence interval (CI) on the difference between the 2 process (or ratios if this is log data)
3. Calculate capability of the new process to be in the PI of the old process
4. Repeat steps 1 to 3 a lot of time varying the hypothesized shift/ratio
5. We obtain a plot of capability against the bound of the confidence intervals

Were varied

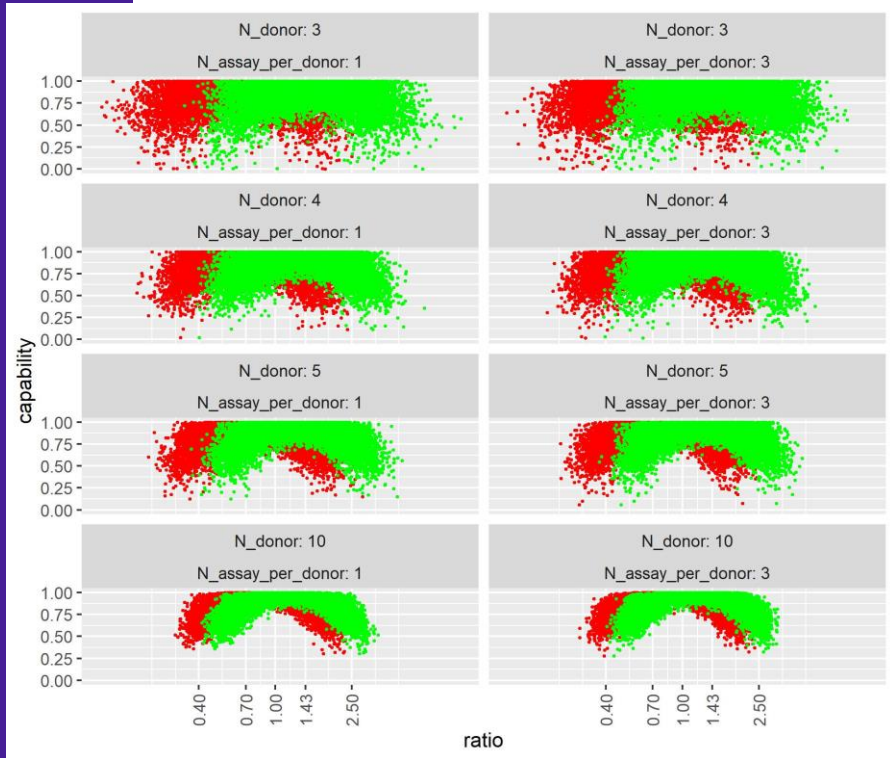
- Number of donor
- Number of measurements per donors

The red and green colors represent respectively the lower and upper bounds of the confidence interval.

We can read from the plot what is the lower and upper bounds of the confidence interval ensuring a minimum capability.

Due to the spread of the data, we use a logistic regression (see details on next slides).

Results



Logistic regression on simulation results

1. Assuming we want a minimum capability of 80%
2. The column containing the capability results is converted into 0 or 1 (if > 80% then 1 else 0)
3. Fit two logistic regressions where the predictor is
   - Intercept + Lower bound of CI + (Lower bound of CI)^2
   - Intercept + Upper bound of CI + (Upper bound of CI)^2
4. Solve the 2nd order equation to ~~solve~~find what are the Lower/Upper bounds of CI that ensure a minimum probability (80%) to reach 80% capability
5. Get the lower and upper bounds of CI ensuring 80% probability to get 80% minimum capability
6. Criteria doesn't depend on the number of donors or the assay variability
7. The test will consist of calculating the CI based on the ratio between the 2 process. If this is included in [0.50, 2.00], the comparability is demonstrated, because we have 80% probability that the capability of the new process is at least 80% to be in the PI of the old process.

N_donor	N_assay_per_donor	criteria_lower	criteria_upper
3	1	0.54	1.82
3	3	0.52	1.91
4	1	0.49	1.95
4	3	0.49	2.00
5	1	0.49	2.04
5	3	0.49	2.04
10	1	0.49	2.00
10	3	0.49	2.00

To evaluate the sample size

1. Let's draw operating curves
2. Generate data for the old and new processes
   - Assume μ equals the mean of historical data
   - Generate $true\ donors \sim Normal(\mu\ , \sigma_{donor})$. We usually don't know between-donor variability, but it is the main component and should likely represent 1/3 or ½ of the variability of the historical data.
   - True donor values are replicated for each of the process
   - For the new process, add a hypothesized shift/ratio between the two processes
3. Calculate 90% confidence interval (CI) on the difference between the 2 process (or ratios if this is log data)
4. If this is [0.50 , 2.00], it is a PASS otherwise it is a FAIL
5. Repeat steps 1 to 3 a high number of times to calculate the probability of acceptance for a given value of the hypothesized shift/ratio
6. Repeat steps 1 to 4 with varying hypothesized shift/ratio to get operating curves

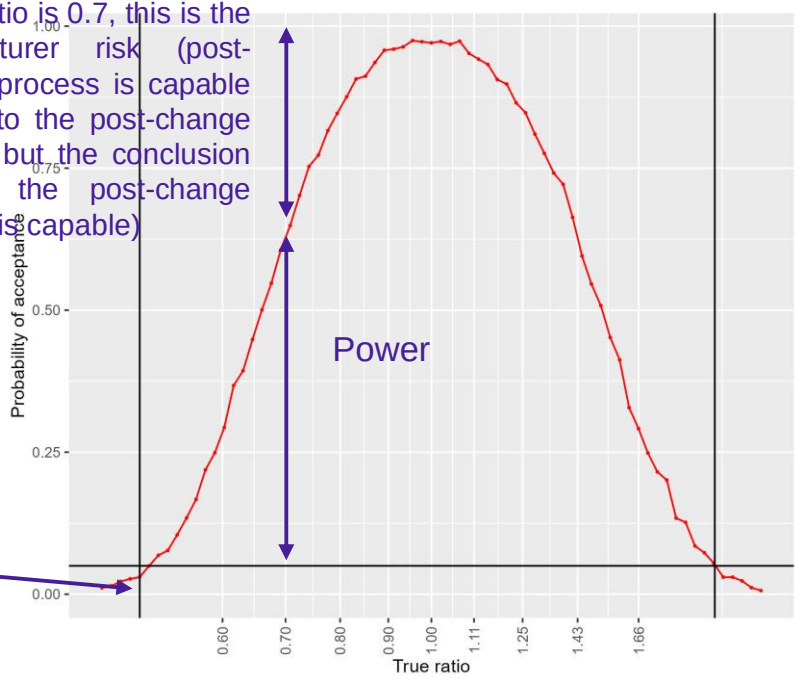
Powering: Example of operating curve characteristics

Plot looks similar but

1. x-axis is the true ratio (not estimated ratio)
2. y-axis is the probability of acceptance (not capability)
3. Black vertical bars are the acceptance criteria of the TOST
4. Plot can be obtained for any sample size (number of donors, number of measurements, etc.)

Post-change process to be accepted as comparable because the ratio is between acceptance criteria

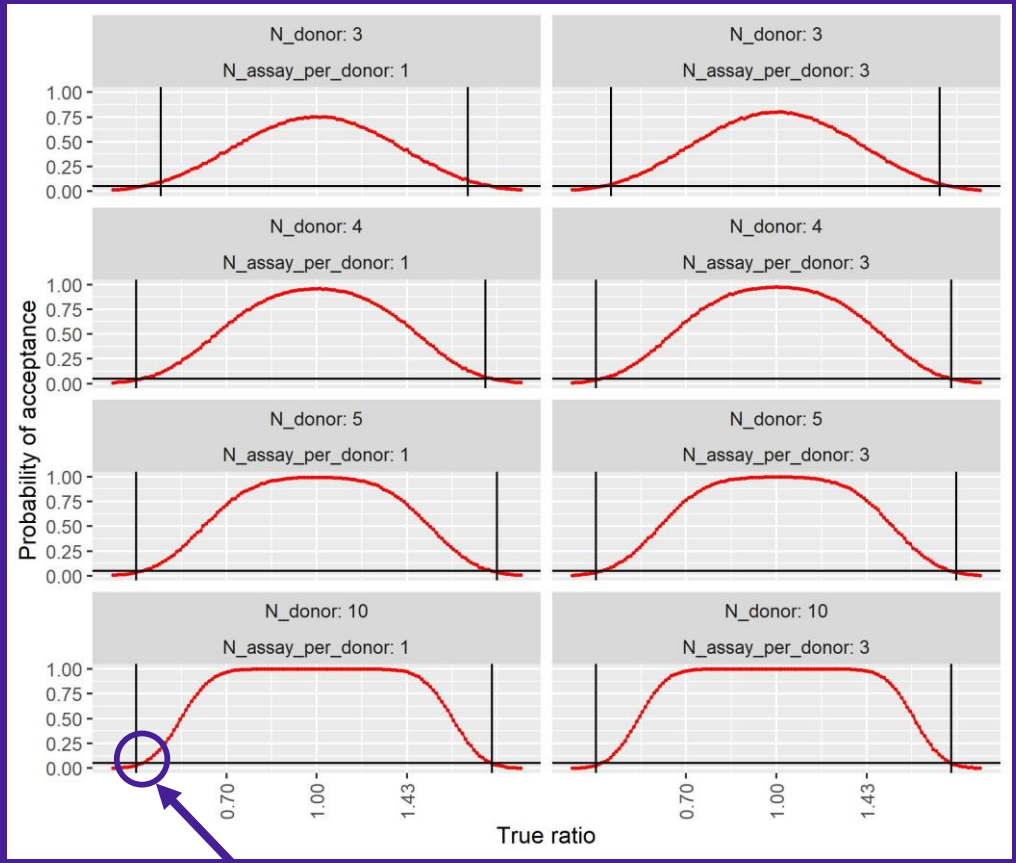
If true ratio is 0.7, this is the manufacturer risk (post-change process is capable relative to the post-change process but the conclusion is that the post-change process is capable)



If true ratio is below lower acceptance criteria, this is the patient risk (post-change process not capable relative to the pre-change process but the conclusion is that the post-change process is capable)

Results of operating curves

1. X axis is the hypothesized ratio
2. Y axis is the probability of acceptance
3. Vertical lines are criteria on the CI on the ratio
4. When the sample size or the number of measurements per donor increases, probability of acceptance are steeper
5. Curves cross the criteria at 5% probability of acceptance in all scenarios
   - Criteria is on the CI
   - X axis is not the CI. This is the assumed mean ratio. It is not possible to assume a true CI
   - 90% CI is used. On the lower end, 5% of CI will not contain the true ratio. This is why the curve crosses at 5% probability



Conclusions

- We derived a criteria that:
  - That Is consistent with FDA request for a TOST
  - That ensures capability of the new process

- Bayesian approach:
  - Bayesian statistics allows us to derive future capability given actual data
  - Back calculation allows us to derive acceptance limits that control risk

- Method needs to be benchmarked against other criteria justification
  - k-sigma
  - Clinically relevant difference between pre- and post-change process

Thank you

The stat team
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