Small scale model justification: An industry position paper

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BioPhorum Development Group

Qualification of Small-Scale Models Workstream

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Presentation summary

- Qualification of small-scale models (QSSM)& Process Characterization Workstream
- Current regulatory guidance on QSSM
- "Justification of small-scale models: An industry perspective" whitepaper
  - Purpose & scope of the whitepaper
  - Terminologies (Qualification and Assessment)
  - Applications of the model
    - Special considerations for viral clearance support
  - Quality oversight
  - Design considerations
  - Study plan / protocol and execution
    - USP scale-down approaches
    - DSP scale-down approaches
    - Analytical set up and operators
    - Re-qualification
  - Data analysis and statistical methods
    - Advantages and disadvantages
    - Descriptive methods
    - Difference tests (eg t-test)
    - Equivalence tests (TOSTs)
    - Quality range methods
    - Multivariate analysis (MVA): PCA, PLS
- Case Study Sanofi
- Conclusions
- Acknowledgements

Justification of small-scale models: an industry perspective - BioPhorum

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Development Group 2022 Program – August 2022

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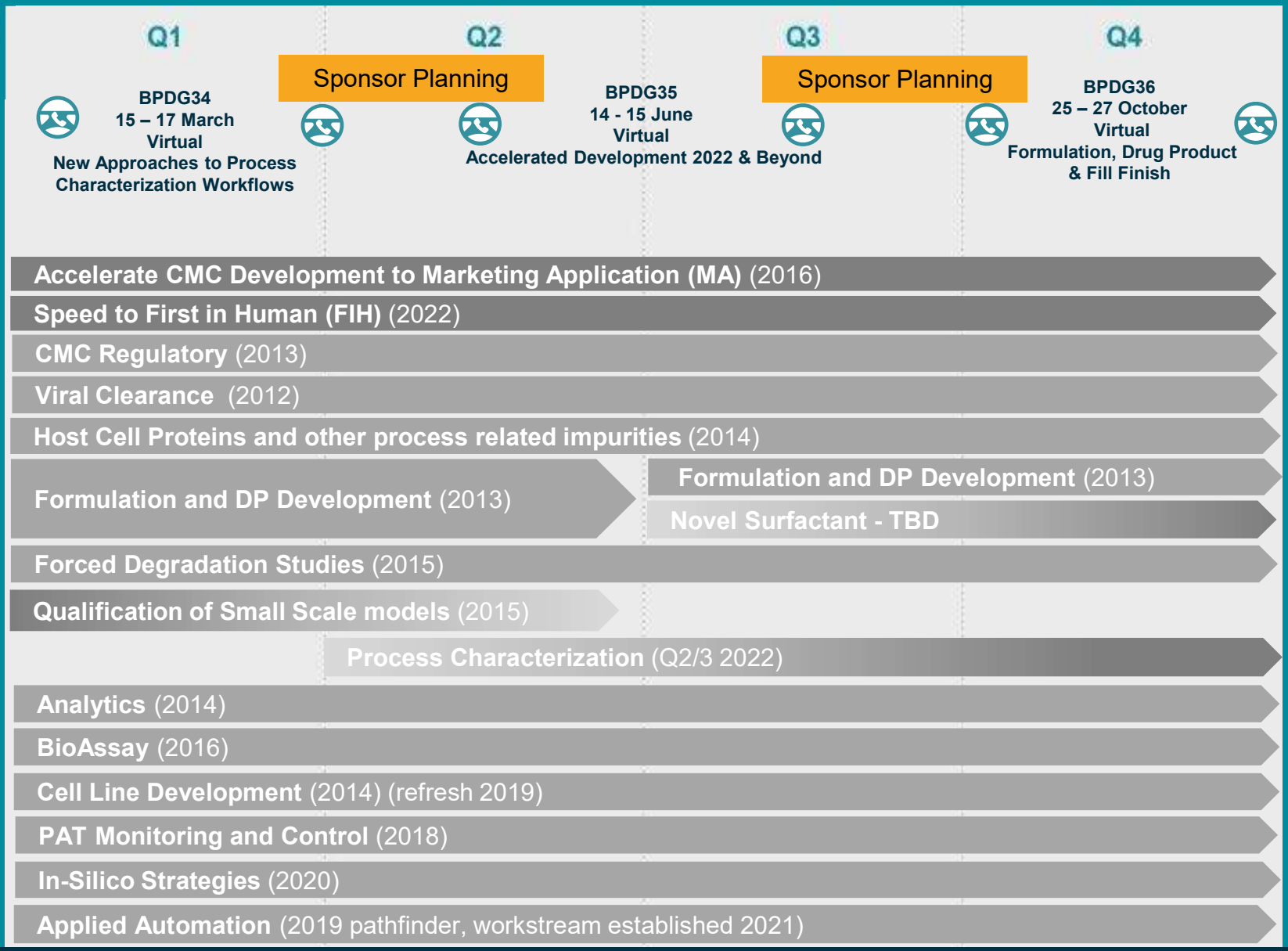
F2Fs
Emerging issues and direction setting



COMMUNITIES OF PRACTICE

Development Outsourcing

KEY LINKAGES

- Technology Roadmap
- Regulatory Governance
- Across Workstreams
- Accelerate CMC – Opportunity to leverage and “Bundle” workstream practices to recognize efficiencies in PD

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Current guidance on QSSM

SSMs are utilized to meet regulatory expectations of:

- ✓ Selection of an appropriate manufacturing process (ICH Q8(R2) Annex).
- ✓ Establishment of a control strategy, covering continuous process verification and lifecycle management (ICH Q8 (R2) & ICH Q10).
- ✓ Support of manufacturing process development and validation (ICH Q11 Step 4).

Some high-level regulatory guidelines exist

- ✓ Process Validation: General Principles and Practices (FDA, Jan 2011)
- ✓ EMA Guideline on Process Validation (EMA, Apr 2016)

Detailed guidance on current best practices for small-scale model development and qualification remains a gap.

This whitepaper provides an overview of current practices for the qualification and refinement of small-scale models (SSM) used in the development of biopharmaceutical drug substance manufacturing processes.

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Justification of small scale model publications and communication links

iMeet link
BioPhorum Website

Justification of small scale model publication

Summary Series Online Journals

Part 1: Implementation of Small-Scale Models for Biopharma Development (12 May)

Part 2: Planning Executing Small-Scale Model Qualification For Upstream Downstream Biopharma Processing (19 May)

Part 3: Statistical Methods For Comparing Small-Scale Models To At-Scale Biopharmaceutical Manufacturing (26 May)

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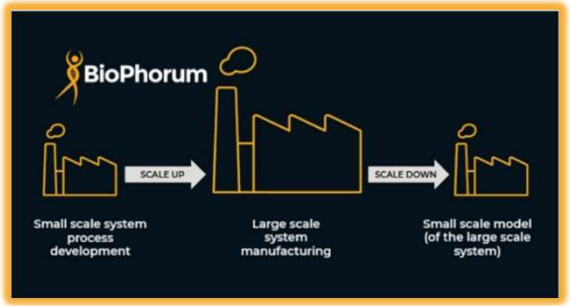
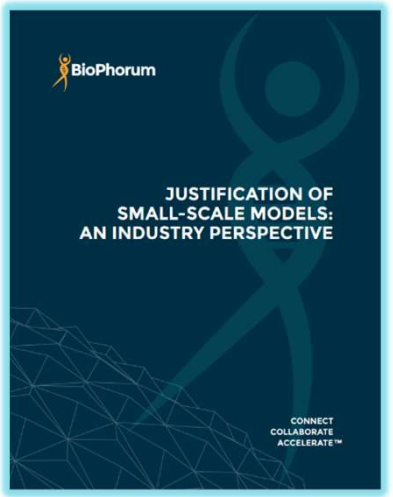
Post 1
Post 2
Post 3

Conferences

BPI East
ACS Fall
JBA Seminar





Purpose and scope of the whitepaper

Demonstration that a SSM is representative of the large-scale manufacturing system is important!

- Supports process validation
- Required by regulatory authorities

It is important to understand the degree to which these models represent the commercial process, including any limitations or differences that might exist

Aim is to provide options and tools for SSMQ:

- Design
- Execution
- Data analysis
- Justification of results

Case studies cover upstream and downstream unit operations

Topics closely related to process characterization are out of scope

Terminologies (Qualification and Assessment)

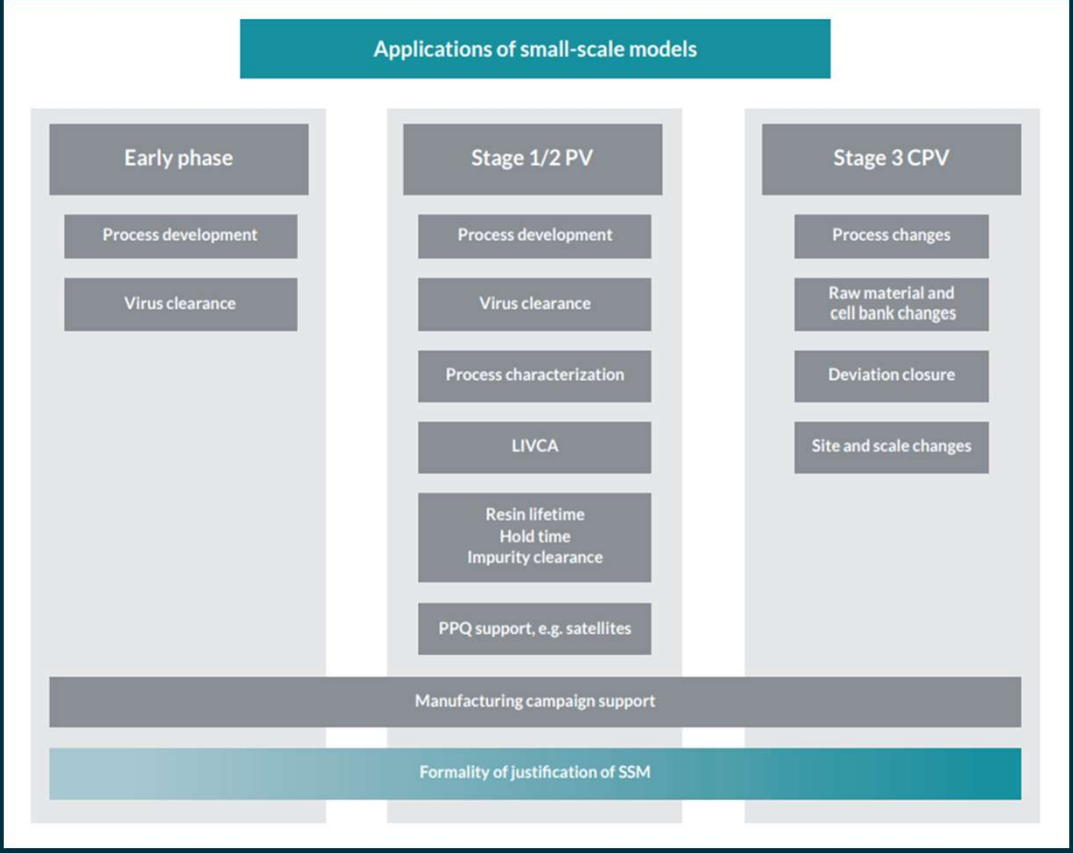
Small-scale models are any scale *smaller than the full-scale commercial process.*

*'*Small-scale models are important tools in the development and evaluation of biopharmaceutical manufacturing processes. During process evaluation, small-scale models enable evaluation of input material and parameter variability to an extent that may not be feasible at manufacturing scale. A small-scale model must be designed and executed, and ultimately justified, as an appropriate representation of the manufacturing process'. (EMA)

Small-scale model qualification (SSMQ) is a formal procedure to justify representative behavior of a small-scale model (SSM) in comparison to manufacturing scale. The requirements for each SSMQ (e.g. scientific justifications, required data, statistical assessments, etc.) are based on multiple aspects (e.g. SSM / process experience, SSM / process complexity, intended use of the SSM, etc.) and may thus differ between companies and between products.

Small-scale model assessment is an effort to justify representative behavior of a small-scale model (SSM) in comparison to manufacturing scale. Small-scale model qualification is a more rigorous form of small-scale justification.

Applications of small-scale models

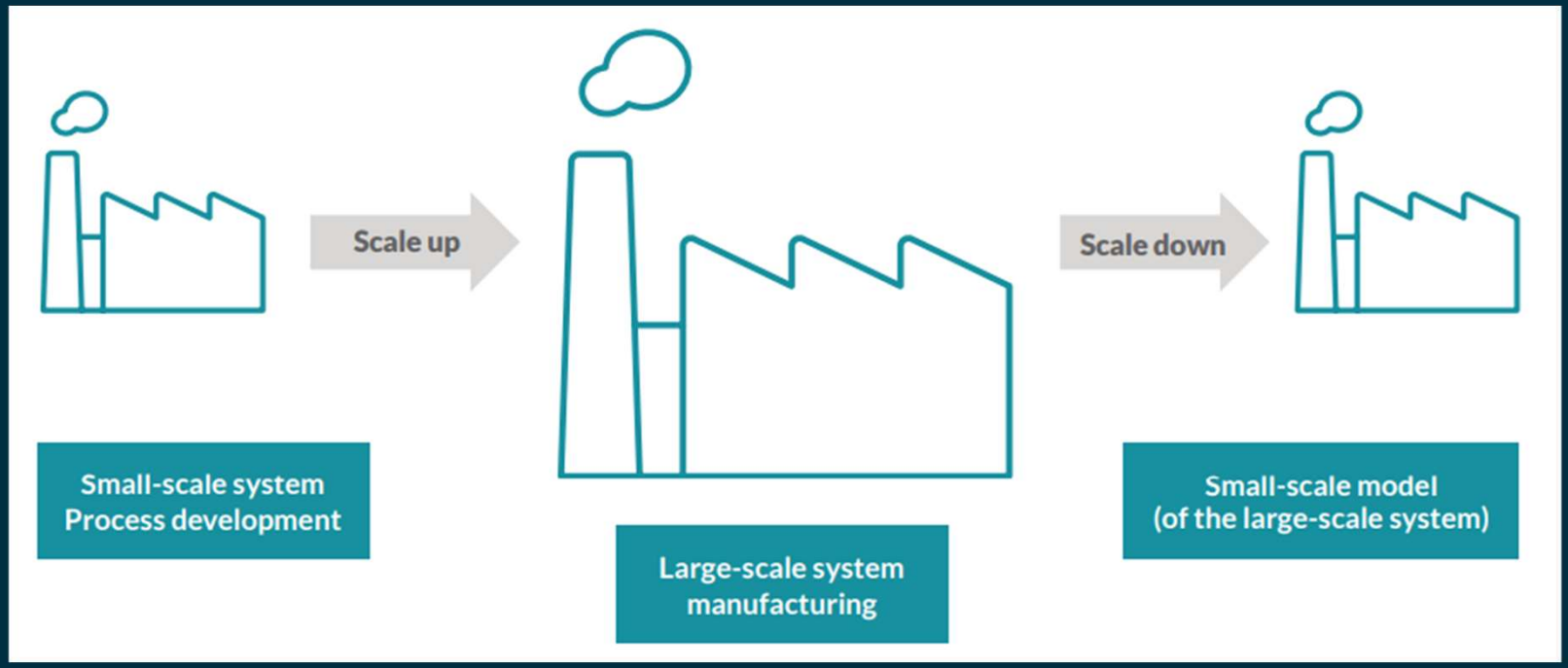


PV: Process Validation, CPV: Continued Process Verification, LIVCA: Limit of In Vitro Cell Age

- SSMs can be applied across the product development lifecycle
- Formality with which representativeness of model is justified increases with maturity of product development
- Qualified SSMs are heavily used during Stage 1 and Stage 2 Process Validation (e.g., for Process Characterization studies)
- Qualified SSMs are often used to support post-approval changes and deviation investigations

Design considerations

- Small-scale system vs. large-scale system
- Risk-based design for small-scale model justification
- Assessment and qualification of small-scale models
- Number of runs needed
- Acceptance criteria and evaluation criteria
- Use of statistical methods



USP Scale-down approaches

Legend

Pre-culture | Large-scale batch | Small-scale batch

Satellite Approach (paired):

- Small-scale batch is inoculated with N-1 or N bioreactor at-scale
- Isolates the scale dependent differences from random variability
- Good to detect potential differences between scales
- Requires synchronized experimental timing with at-scale

Non-Satellite Approach (unpaired):

- Does not require inoculum transfer
- SSM seed train is passively qualified
- Uncoupled from large scale runs
- Execution is less complex (e.g. use DoE center points)
- Capability to detect potential differences is lower

Data analysis and statistical methods

When performing a SSMQ, most companies employ a statistical evaluation of the behavior of the small-scale when compared to the manufacturing scale

Outcomes of some statistical methods are binary: '**comparable**' or '**not comparable**', but these outcomes must be evaluated by SMEs in the totality of evidence which often include qualitative evaluations

These methods (if statistics are used) should be adapted for satellite approach (small-scale batches paired with manufacturing-scale batch) or non satellite approach (unpaired batches). And they are applied to each product attribute separately, except for Multivariate Analysis.

Data analysis and statistical methods

- Different types used and the advantages and disadvantages of each methods will be discussed

- Types of methods used
  - Descriptive
  - Inferential
  - Combined descriptive & inferential

Descriptive statistical methods

These methods consider only the samples as there is no inference to the unknown population of at-scale and small-scale batches, but they are extremely useful to both SMEs and health authorities in making a qualification assessment.

Examples

- ✓Scatter plots
- ✓Bland-Altman plots (for satellite)
- ✓Tables listing the number of data points (N), min, mean, median, max and standard deviation(SD) by scale or of the differences (for satellite)
- ✓Observed average difference D, D=mean of SSM data – mean of at-scale data

Inferential methods

Difference tests

Inferential statistical procedures that test the null hypothesis (e.g.mean of SSM = mean of at-scale for the t-test) against an alternative hypothesis (e.g. mean of SSM ≠ mean of at-scale) and which have a p-value computed and used to decide whether the data is consistent with the null hypothesis or not.

Examples

- ✓t-test is used to compare the means between scales
- ✓F-test, or Levene or Brown-Forsythe tests, are used to compare the variances between scales.

These procedures offer a simple implementation and conclusion, but they have 3 major drawbacks, from which the equivalence test does not suffer (next slides).

Inferential methods

Equivalence tests

Two one-sided t-tests (TOST)

Test that focuses on determining if the differences between the means of the at-scale and small-scale batches is small, or of no practical difference

If **$-\theta \leq$ mean of SSM – mean of at-scale $\leq \theta$** the scales are deemed equivalent, with θ called the equivalence margin.

Disadvantages of t-test & advantages of the TOST are discussed on subsequent slides

Disadvantages of T-Test

Assumes what it intends to establish (i.e. the equivalence of small and large scales)

Does not consider what constitutes a practically-meaningful difference

Incentivizes small N and noisy data instead of more/better quality data

Inferential method : TOST advantages over t-test

First, equivalency is not the assumed state of nature (null hypothesis), it is the alternative state of nature (alternative hypothesis), so the state of nature the evaluation intends to establish (in rejecting the null hypothesis).

Second, the equivalence margin is determined prior to data collection, bolstering the integrity of the procedure,(e.g. use of historical at-scale data not involved in the TOST).

Third, if the means are truly equivalent, the chance of the TOST rejecting the null hypothesis increases with sample size.

Quality range (QR) methods

Statistical procedures that consider both the mean and the variability of the at-scale samples to assess comparability of small-scale samples.

- The Quality Ranges are calculated on at-scale data as reference.
- The comparability is claimed when all small-scale values, or a certain proportion, are inside the QRs
- The advantage of the QRs is a graphical visualization of all individual values for both the at-scale and SSM samples, making the outcome easy to determine.
- The disadvantage is wide QRs that lead to false assumption of the comparability when at-scale samples size is limited.

Examples

Normal distributed data

✓ sigma intervals (e.g. mean of at-scale+/-3*standard deviation of at-scale)

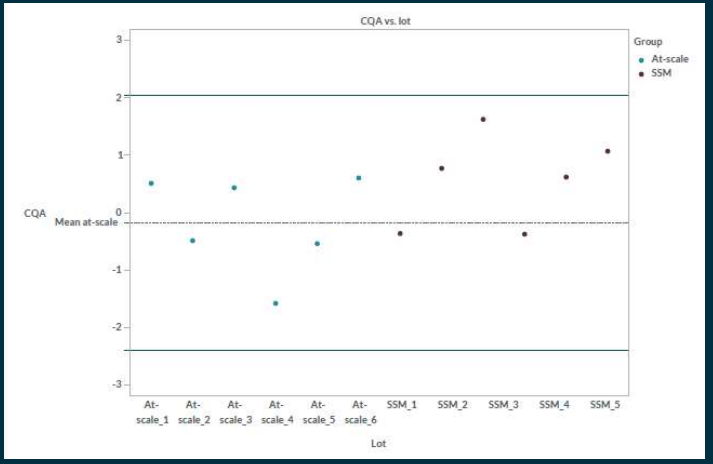
✓ prediction intervals

✓ tolerance intervals

Distribution-free data intervals

✓ smooth curve percentile

✓ Min-Max



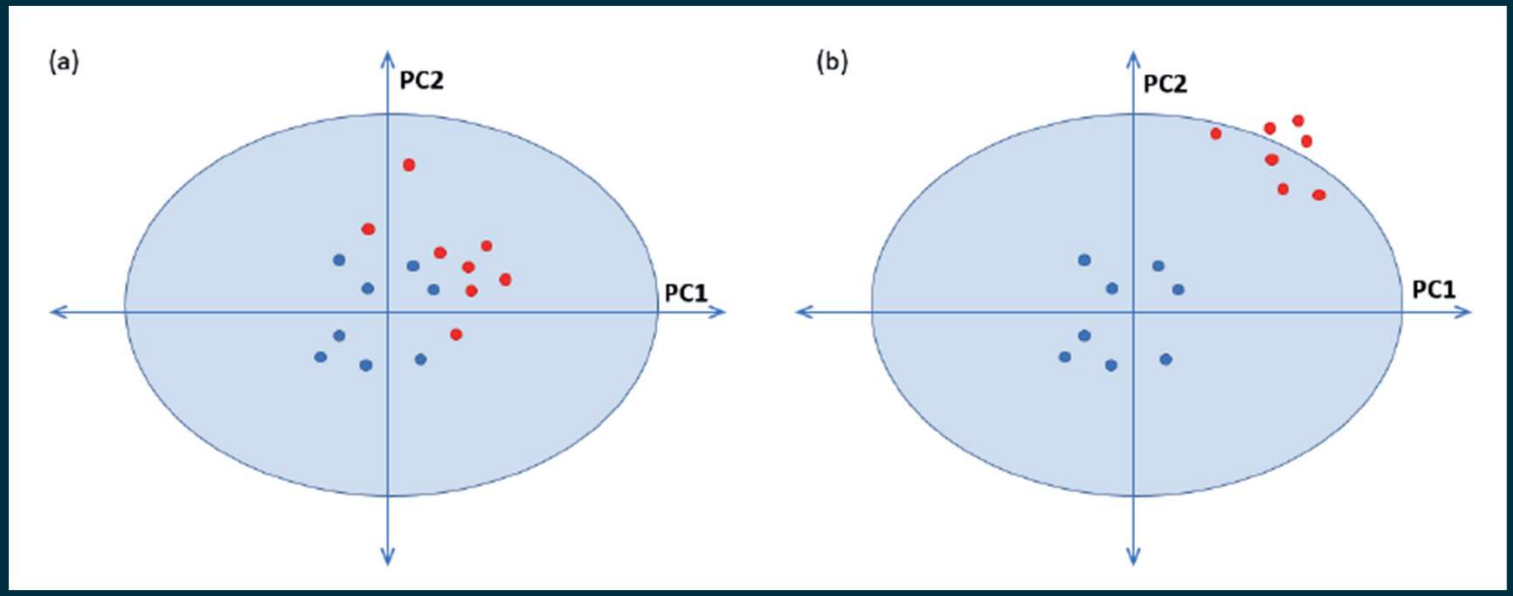
Multivariate analysis (MVA)

MVA is a set of statistical tools used for the simultaneous analysis of multiple variables and that consider the correlation among the entire set of variables to be used for comparability testing.

- Examples include Principal Component Analysis (PCA) and Partial Least Squares (PLS)

PCA Example

- Model developed based on large-scale data set (blue), then small-scale data (red) projected onto the resulting two-dimensional space
- This score scatter plot can be used to identify patterns of offset between the data sets or excursions of batches that exceed the 95% Hotelling's T2 tolerance ellipse.



Advantages: Considers multiple time-course variables simultaneously across batches
Disadvantages: Requires compilation of diverse process data (i.e., growth, titer, PQ)

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Comparison of different approaches in using Operating Characteristics (OC) curves

Examples, focus on usual Quality Ranges (QR)

Normal distributed data :

- ✓ sigma intervals (e.g. mean of at-scale+/-3*standard deviation of at-scale)
- ✓ prediction intervals (PI) with 95% confidence level of at-scale
- ✓ tolerance intervals (TI) with 99% coverage and 95% confidence levels of at-scale

% of SSM batches included in QR ≥ 90% to conclude to comparability

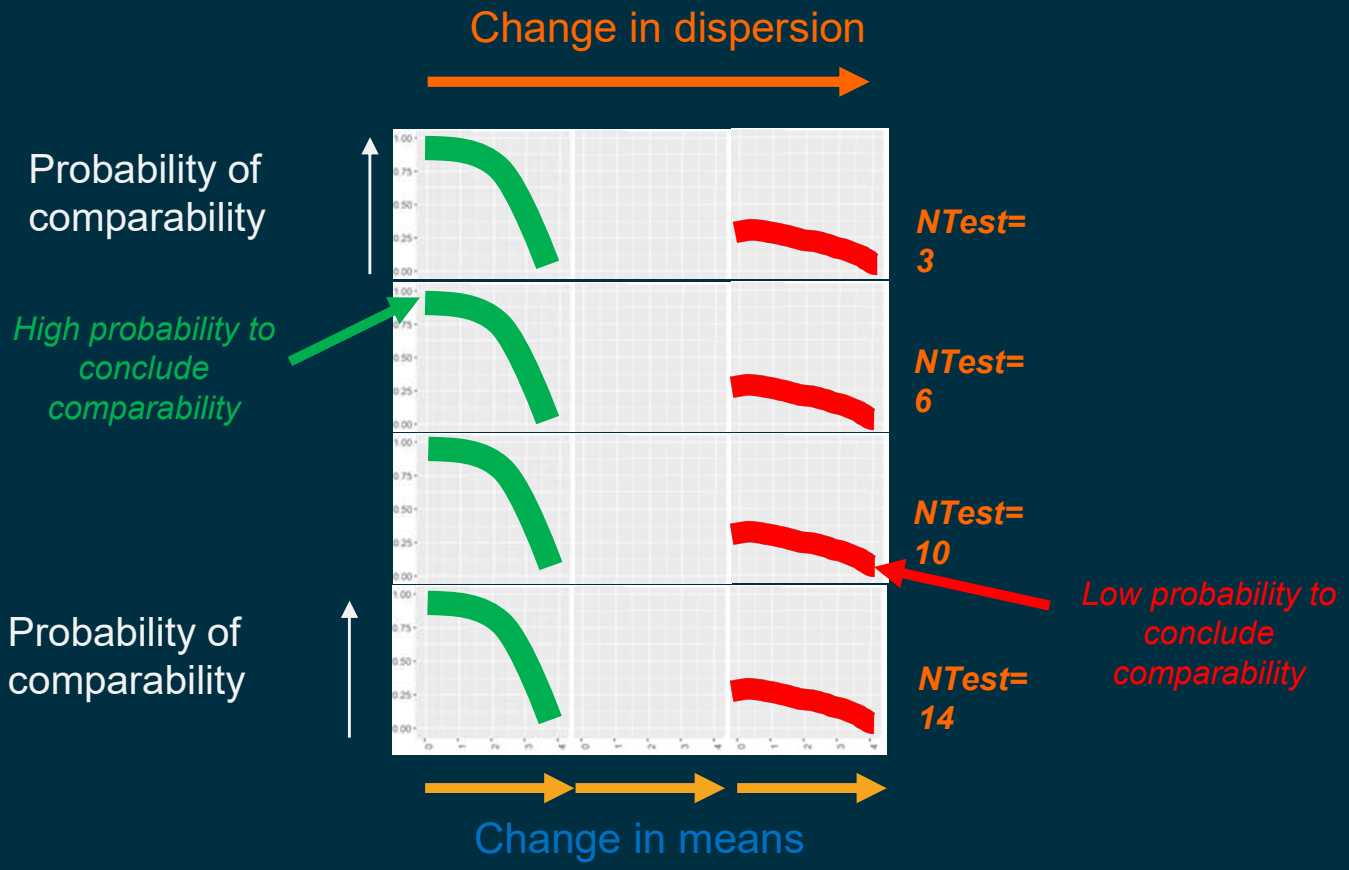
Simulation principles to investigate the probability to be comparable :

Parameters	Value
Number of simulations	10000
Distribution of batches	Normal (position, dispersion²)
Tested numbers of simulated 'at-scale' batches	3 or 10;
Tested numbers of simulated 'small-scale' batches	3; 6; 10; 14;
position parameter of the simulated 'at-scale' batches	5
dispersion parameter of the simulated 'at-scale' batches	2
position parameter of the simulated 'small-scale' batches	5; 6; 7; 8; 9
dispersion parameter of the simulated 'small-scale' batches	2; 3; 4

Comparison of different approaches in using Operating Characteristics (OC) curves

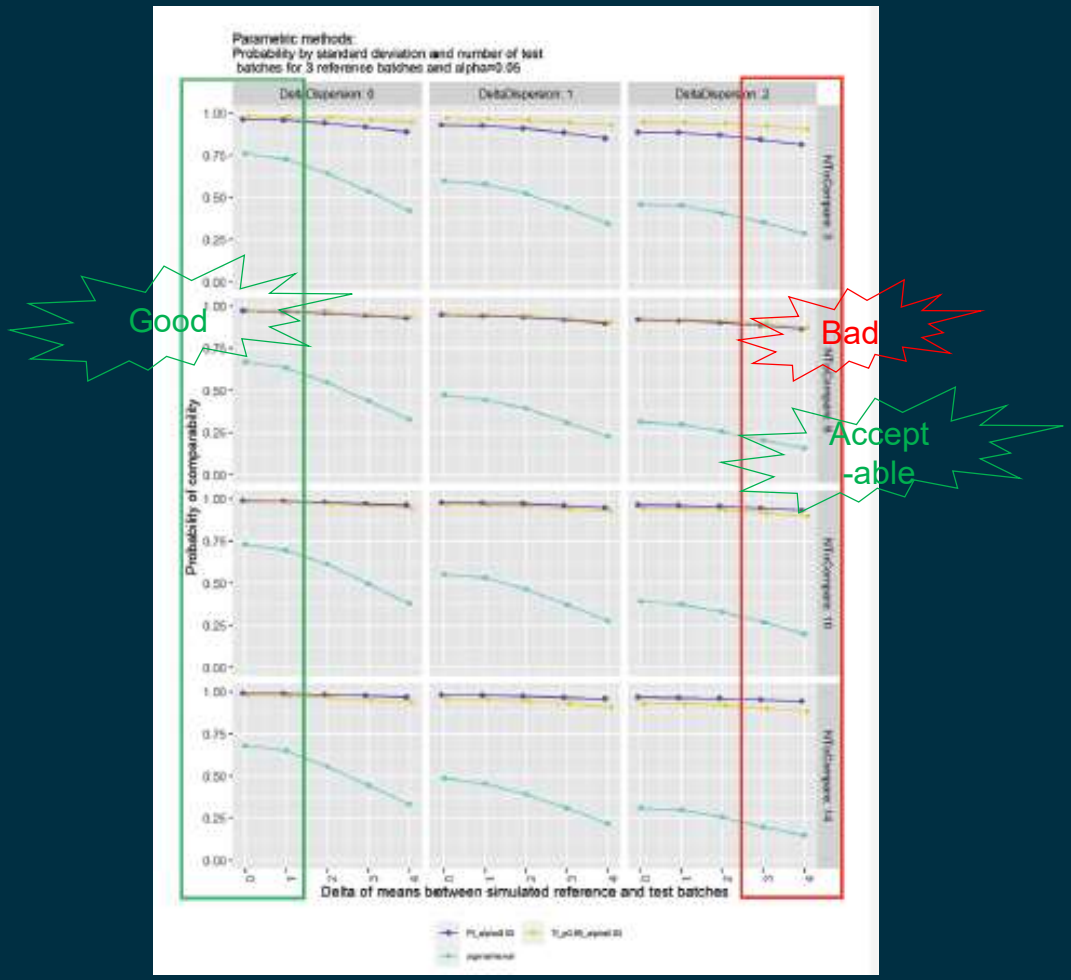
Explanation of the graphics

✓ For a fixed number of reference values, 3 or 10 :



Comparison of different approaches in using Operating Characteristics (OC) curves

Simulation with 3 reference values



Conclusion for 3 reference values

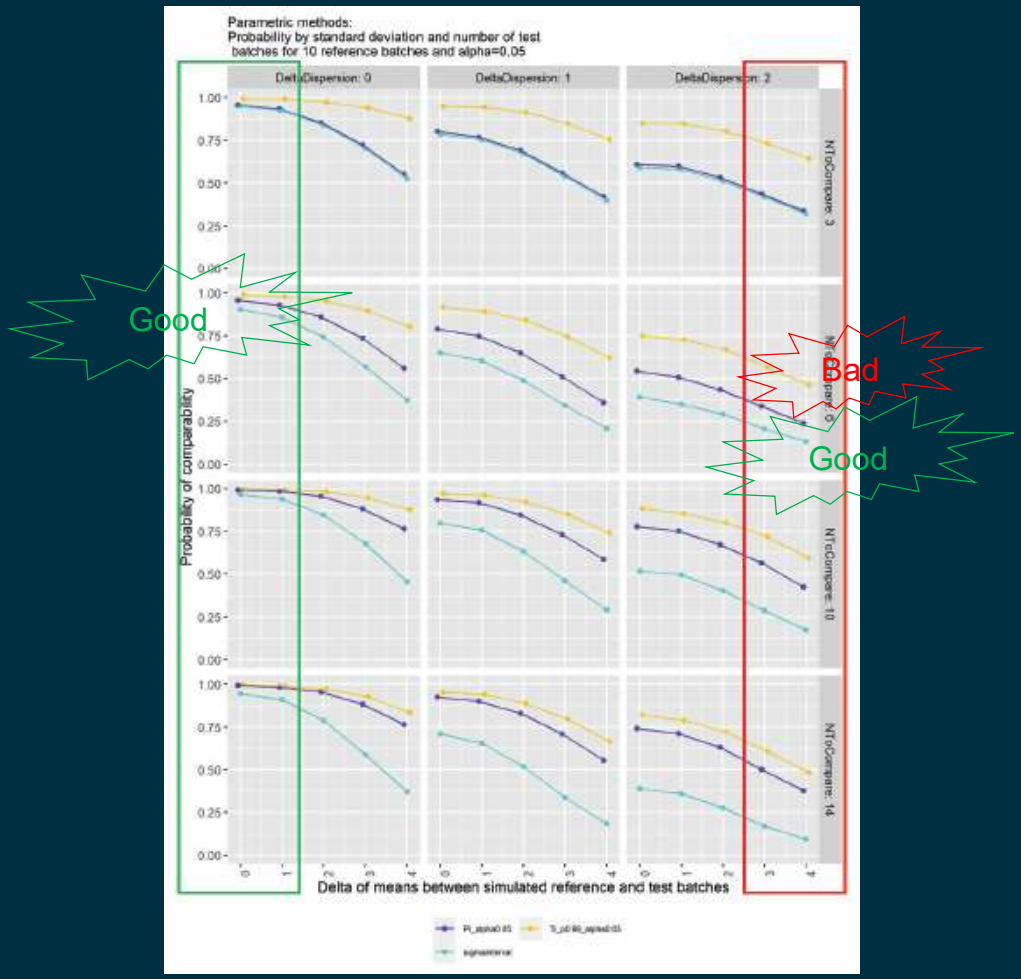
The probability of concluding to comparability when it's expected (*green square*) is higher for the TI 99%/95% and the PI 95% than for the 3-sigma QR.

But conversely the probability of concluding to comparability is high for TI 99%/95% and the PI 95% when the small-scale data are different from the at-scale data (*red square*) for 3 at scale data, what is not expected.

It's better to choose 3-sigma QR if very few at-scale data are available to avoid erroneous conclusions about comparability.

Comparison of different approaches in using Operating Characteristics (OC) curves

Simulation with 10 reference values



Conclusion for 10 reference values

The probability of concluding to comparability when it's expected (*green square*) is high, what is expected, for the TI 99%/95%, the PI 95% and for the 3-sigma QR.

In case of discrepancy between small-scale and at-scale data (*red square*),the probability of concluding to comparability is low, what is expected, for the PI 95% if the number of small-scale batches is smaller than the number of at-scale batches and for the 3-sigma QR in every cases.

But this probability remains high for TI 99%/95% (*red square*), what is not expected.

Comparison of different approaches in using Operating Characteristics (OC) curves

Simulation conclusion

It’s important to choose the appropriate QR and its coverage and/or confidence levels based on the at-scale and, small-scale samples size and on at-scale distribution.

This is to avoid concluding wrongly to comparability (example of TI 99%/95% for small sample size and for normal distribution) or rejecting wrongly the comparability.

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- A small-scale model is a lab or pilot scale system (a group of equipment) that represents a manufacturing scale system
- All small-scale models need to be justified, some need to be qualified, using a risk-based approach
- Data from large scale are usually used to set criteria / references
- To qualify the small-scale model is to demonstrate comparability of the small-scale population and the large-scale population
  - In terms of outputs (CQAs, step yield, etc.)
  - Using sample runs taken from both scales
- "The devil is in the details" – consider which approach to take, case by case, when designing the study
- In all cases, have sound scientific rationale for the approach, and document them - so sponsor is confident to defend the study when questioned by regulatory agencies

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