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Quality and Statistics: bringing two worlds together

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Disclaimer

The views expressed in this presentation are the presenter‘s personal views and not necessarily the views of BfArM or EMA

I am a statistician, not a quality expert

Introduction

- Quality experts have long experience in making comparability assessment of QAs
  - Comparability concept developed in 1990s for evaluation of manufacturing changes
  - Transferred to biosimilar concept in the 2000s
- More sophisticated ‘statistical’ methods were applied
- Increasing importance of the comparability exercise for totality of evidence of biosimilarity

  → Statisticians were increasingly involved
- Languages and traditions of quality experts and statisticians are different

Lost in translation

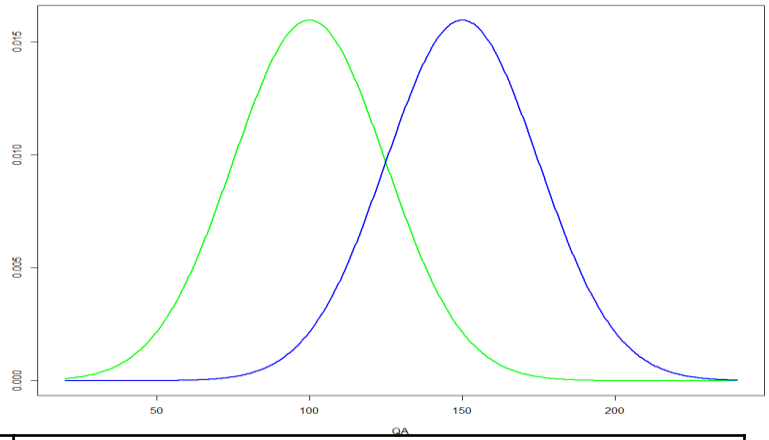
Mathematicians are a sort of Frenchmen; if you talk to them, they translate it into their own language, and then it is immediately something quite different.
(Johann Wolfgang von Goethe)

Quality tradition: Comparability ranges

- Comparability range = quantitative range established based on the measured quality attribute of reference medicinal product batches
  - Min-max, mean +/- X*SD, tolerance intervals
- Test batches should be included, differences justified

Reference range: mean ±3SD$_{ref}$

- How often (in %) will the mean ±3SD$_{ref}$ reference range contain all sampled test batches?



N_{test}=5	41.6%
N_{test}=10	25.0%
N_{test}=15	15.0%

- $N_{reference}$=30; SD_{test}=SD_{ref}=25

test product
reference product

Statistical tradition: equivalence testing

- Absence of relevant differences between two products
  - Quality: ‘Comparability‘
  - Statistics: ‘Equivalence‘
- Equivalence testing (of means)
  - demonstrating equivalence of parameter(s) describing test and reference distribution
  - First FDA draft GL (withdrawn)
  - Draft EMA RP: not explicitly recommended, but perceived in this way

Quality experts were unhappy…

- Misunderstandings of ‘equivalence‘ concept
  - Equivalence ≠ equal
- Equivalence testing of means is wrong concept
  - Fixed mean may not exist (shifts and drifts)
  - Equivalence of means is neither sufficient nor necessary for similarity – not center but range of reference distribution is important
  - No basis for justification of an equivalence margin

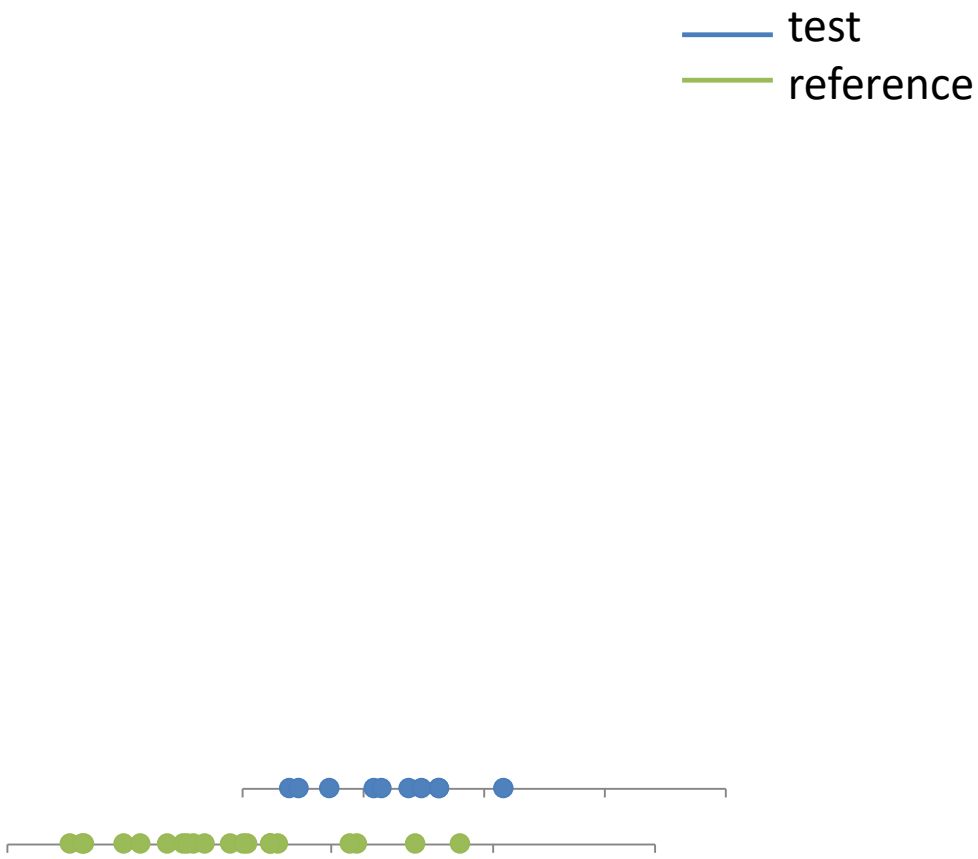
Looking for common basis

- Both sides have good arguments that simple concepts of the other side may have serious limitations
- What is the basis for coming together?
  - Achieve a common understanding of the question to be answered
  - Understand the properties of statistical approaches to answer it
  - Achieve a common understanding what role statistics can/should play for totality of evidence

What is the question?

- Overall aim: demonstration that test and reference product are comparable
  - EMA GL: The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the reference medicinal product chosen by the applicant are similar
- Traditional comparability assessment: strong focus on test batches at hand

Descriptive analysis



What is the question?

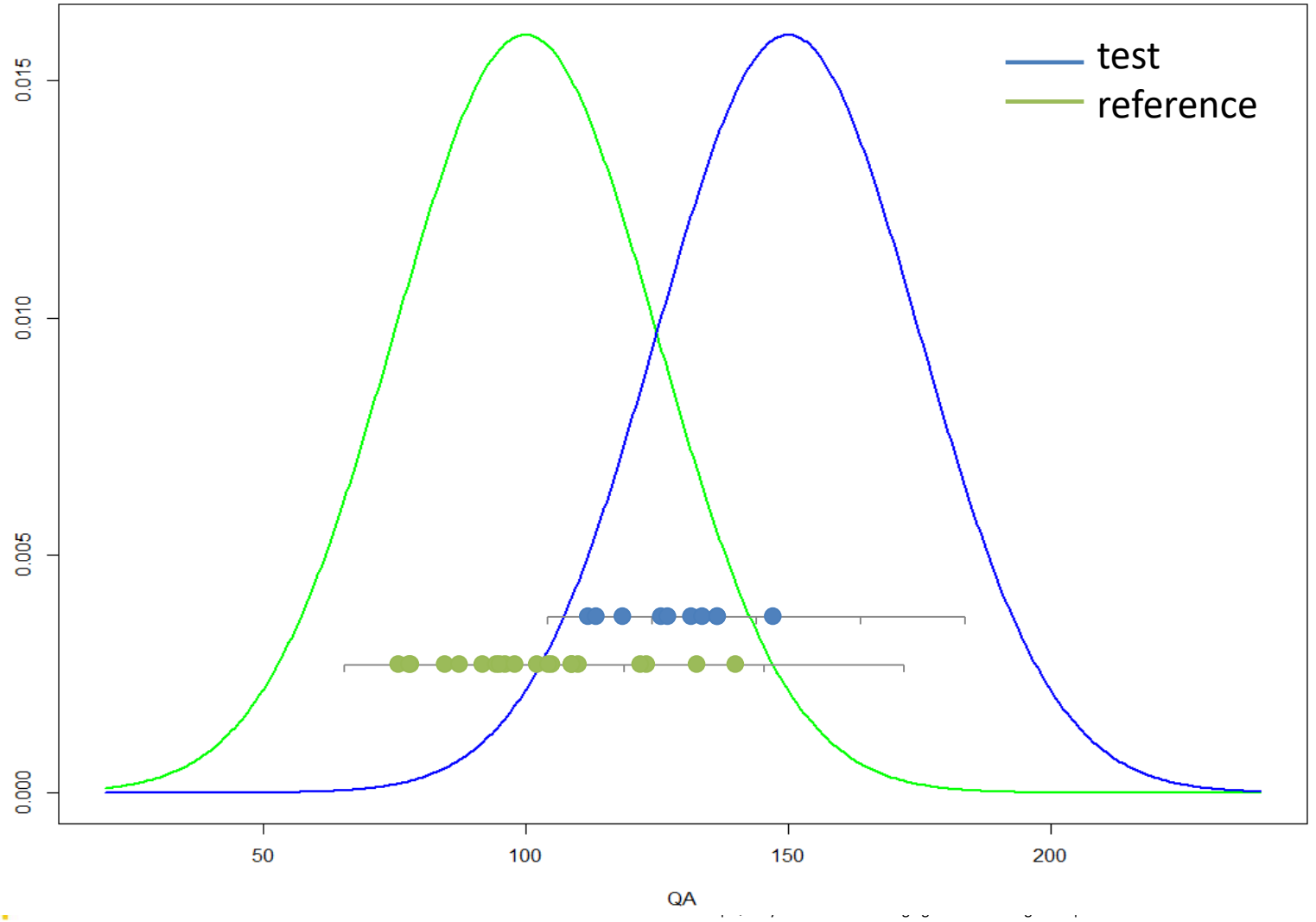
- Overall aim: demonstration that test and reference product are comparable
- Traditional similarity assessment: strong focus on batches at hand

  → Descriptive analysis (=describing what we observe)

  → possible conclusion: biosimilar developer was able to produce batches with comparable quality
- Is this sufficient for drawing conclusion on comparability of test and reference **product**?
  - Product is more than limited number of batches

  → Inferential conclusion: what is observed (batches) is used for a conclusions about an 'underlying truth' (product) that cannot be (completely) observed

Inferential question



What is ‘inferential‘?

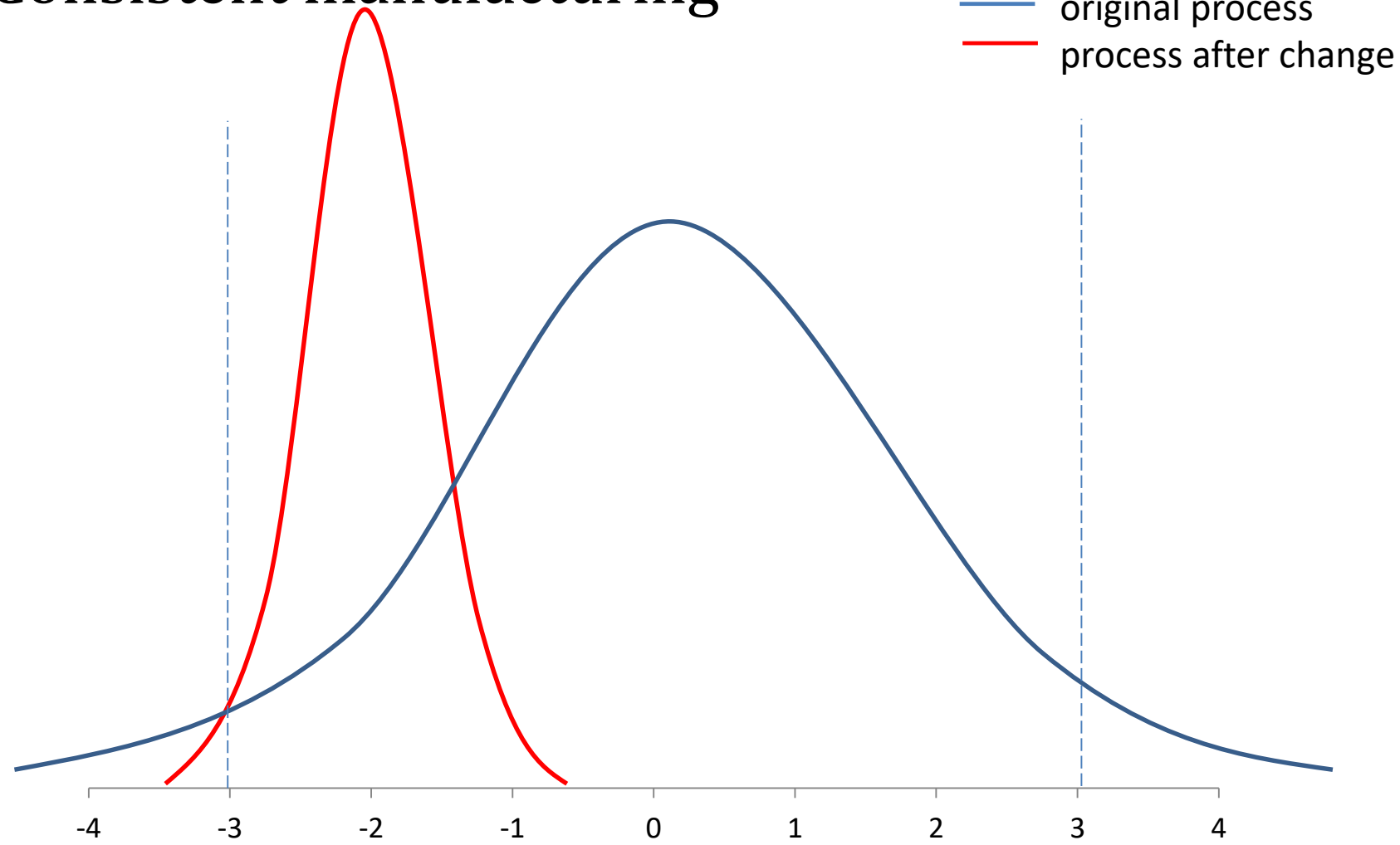
- Important learning from EMA workshop: understanding of term ‘inferential‘
  - Analysis being ‘descriptive‘ or ‘inferential‘ does not depend on applied method/similarity criterion but on conclusion that is drawn

  → Making conclusion about product going beyond batches at hand = inferential
- Similarity exercise being inferential unavoidable?
  - Manufacturing control system in place

What is a “product“?

- “The product is the process“?
    - Process can change over time
- Product = all material produced by consistent manufacturing process
- Consistent manufacturing process:
    - Process that is allowed to vary (randomly and systematically) but is controlled to stay within acceptable limits

Consistent manufacturing



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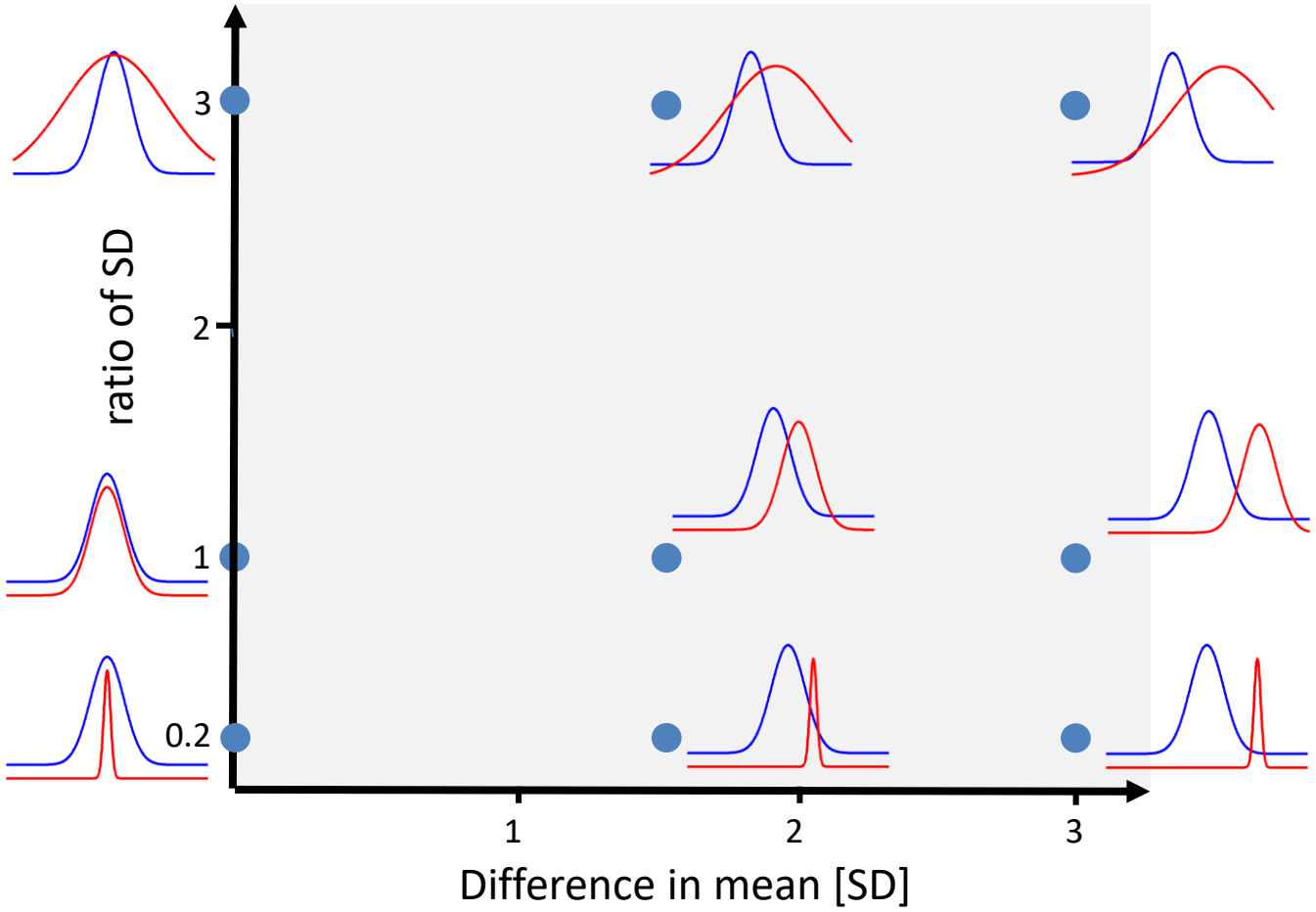
Importance of operating characteristics

- Several criteria/methods to decide on similarity of products – how to compare?
- No criterion will make ‘right’ or ‘wrong’ decisions in all situations
- Understanding operating characteristics of a decision criterion is key
    - Probability to conclude similarity for non-similar products
    - Probability to conclude similarity for similar products

Framework for comparing OCs of similarity criteria

- Defining range of relevant underlying scenarios
    - Underlying distributions for products to be compared
- Quantitative definition of true similarity
- Sample size (number of test and reference batches)
- Summary measure(s) to describe OCs

Framework: Range of scenarios of interest



modified from Stangler, 2018

Framework: Definition of true comparability

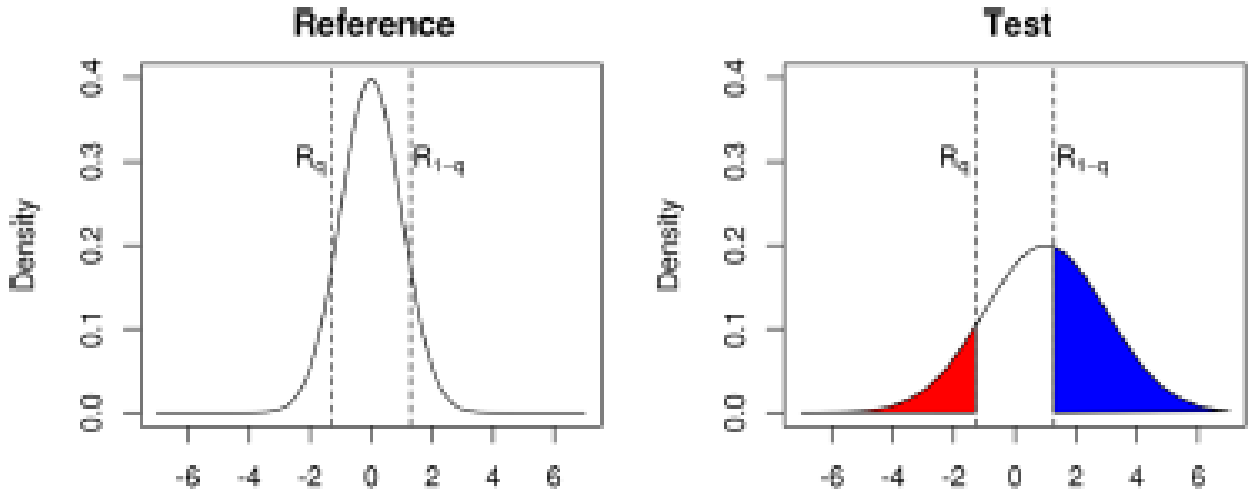
- Inferential decision on comparability requires quantitative definition of ‘true comparability‘

→Concept of comparability needs to be translated in quantitative terms

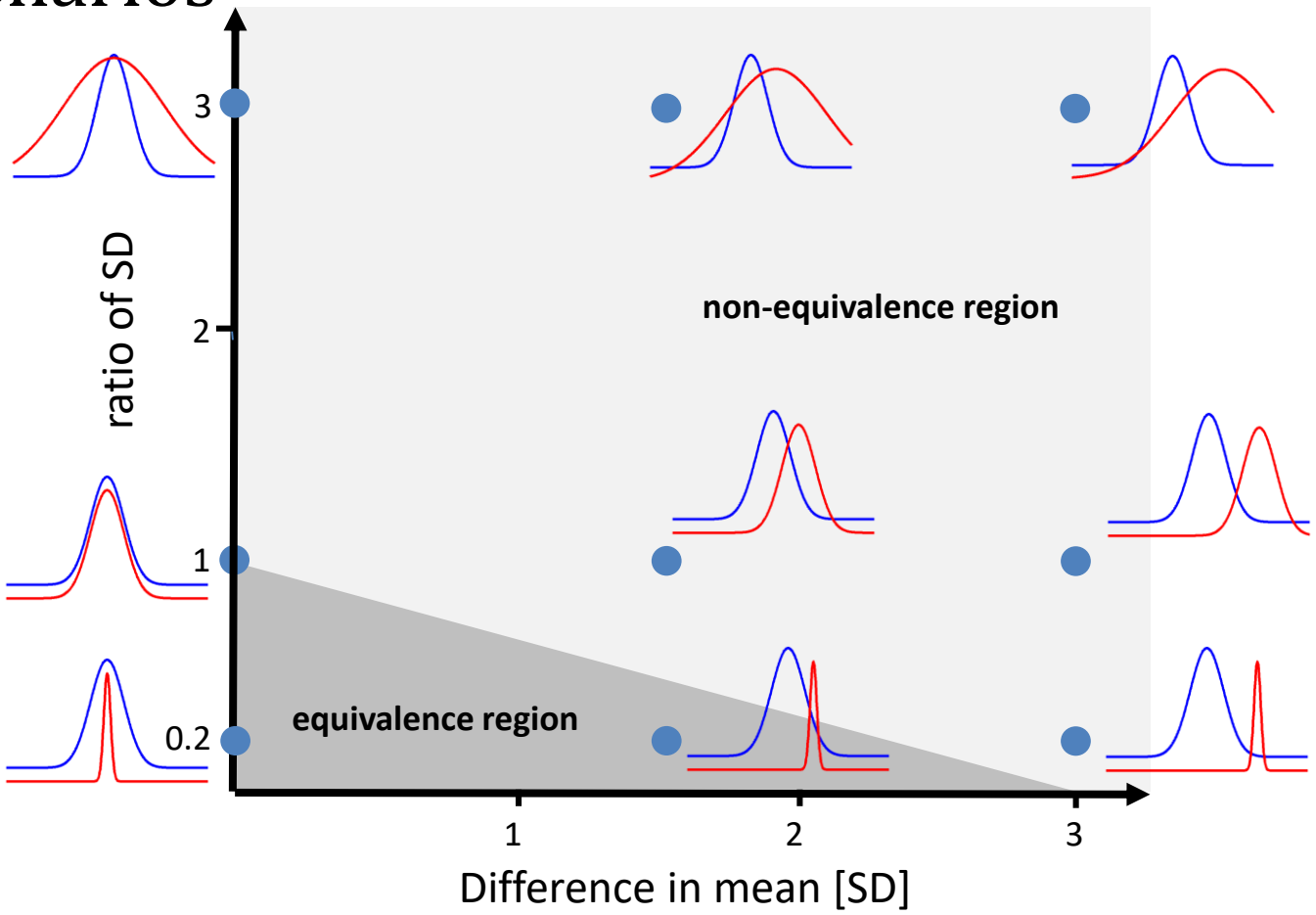
- Translation will never be perfect
  - Simplifying assumptions needed
  - ‘Statistical comparability‘ is not necessarily the same as ‘comparable’ in quality GLs

Proposals for formalisation

- Similarity of distribution parameters (mean, SD)
- "Population within population"
  - $Mean_{Test}$ +/- X*SD_{Test} within $Mean_{Ref}$ +/- X*SD_{Ref} (Stangler, 2018)
  - Tail criterion: $2q - (P(X_T < R_q)+P(X_T>R_{1-q})) \geq c$ (Mielke et al., 2019)

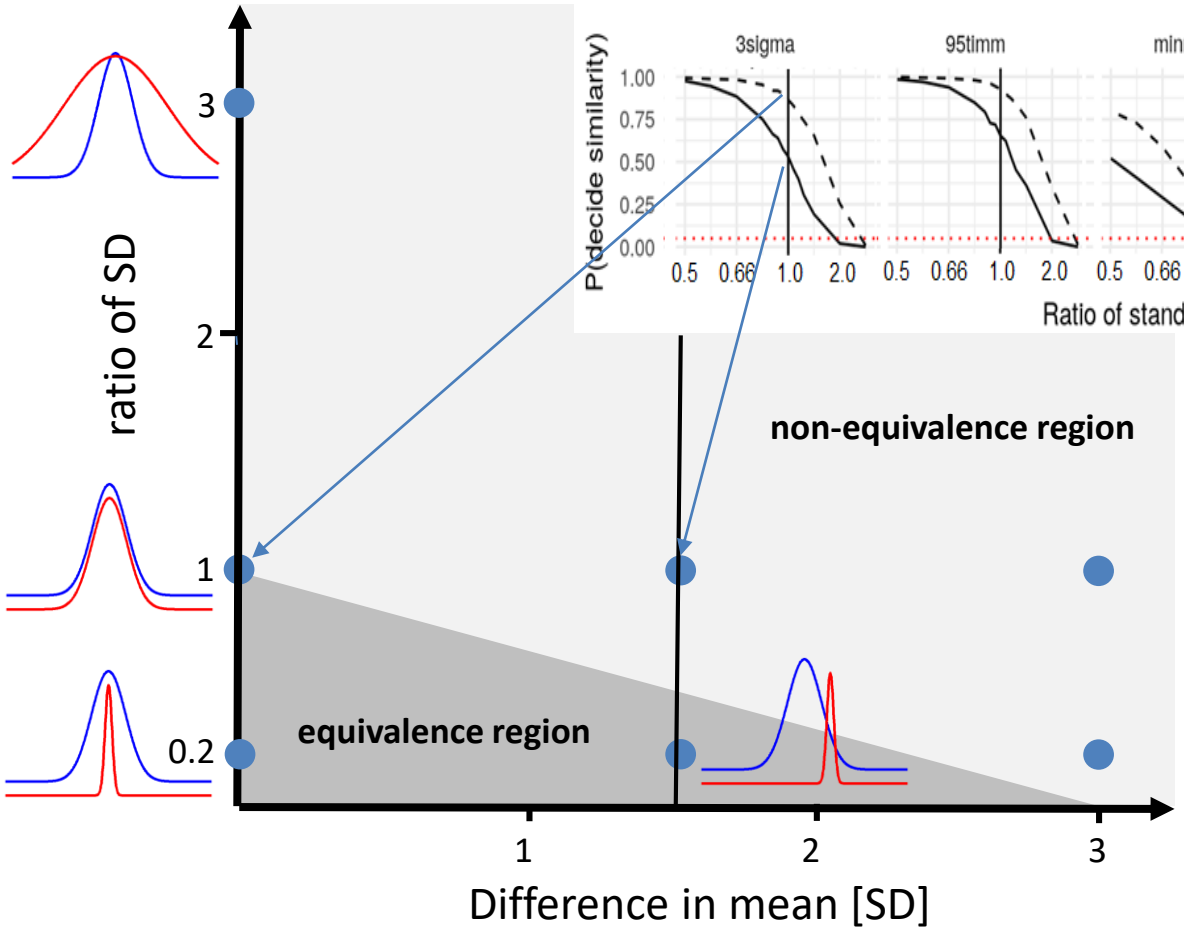


“True“ comparability for relevant scenarios



modified from Stangler, 2018

Comparing OCs



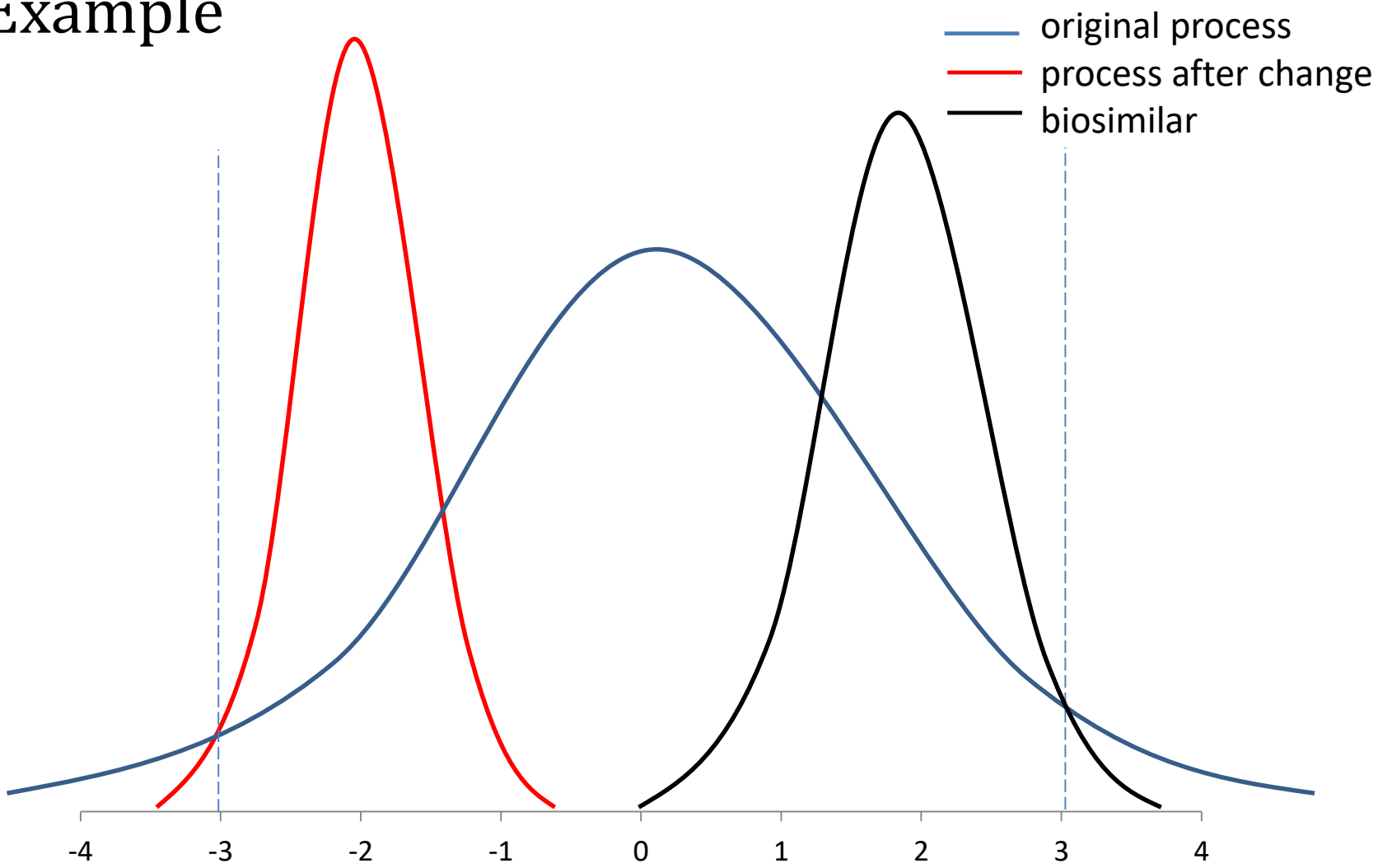
From: Klinglmueller, 2018

Shifts and drifts: what is truly comparable?

- So far: relevant scenarios assume ONE underlying NORMAL distribution for test and reference
- Starting point: Quality experts insist that mean and variance can vary over time

→ Shifts and drifts in reference (and in test) add to complexity

Example



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Shifts and drifts: operating characteristics

- Shifts and drifts may not be detectable from the data
- Shifts and drifts will influence operating characteristics
- How many shifts/drifts?
    - Any shift adds 1-2 distribution parameters
- Number of batches sampled before/after shift?
- Possible to define meaningful restrictions?

Role of statistics

- Overall aim: making decision on similarity
  - Based on totality of evidence
  - Statistical methods contribute to totality of evidence
  - Statistical decision should not be a pass/fail criterion
- But what role could statistics actually play?
- What are the consequences of passing/failing
  - Passing: statistical decision reliable for accepting similarity, for reducing non-clinical/clinical data requirements?
  - Failing: What kind of justification can be accepted to accept similarity in spite of failing, when are additional data required?

Summary

- Continued collaboration of quality experts and statisticians required
- Improve understanding of question
- Develop frameworks for comparing OCs of similarity criteria
- Agree on role of statistics for descision making

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Thank you very much for your attention!

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Inferential question