Sandoz
Biopharmaceuticals

Performance characteristics of quality range methods and equivalence testing in the comparative assessment of quality attributes

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Agenda

1. Comparability and biosimilarity – from CMC guidances to statistics
2. Equivalence Criterion: Test population in reference population
3. Evaluating performance/operating characteristics against the equivalence criterion

Please note:

- *This presentation assumes data meeting all statistical assumptions*
  - *Case studies illustrating limitations due to real-life data were presented before*
- *Both manufacturing change comparability and biosimilarity are in scope of this presentation*
  - *differences only in sample sizes and level of prior knowledge*
- *Terminology:*
  - *Reference product: pre-change / reference biologic*
  - *Test product: post-change / biosimilar*

Comparability and biosimilarity

Comparability (ICH Q5E)

- Pre- and post-change product not necessarily identical, but **highly similar**
- Existing knowledge is sufficiently predictive to ensure that any **differences** have **no adverse impact upon safety or efficacy**

Biosimilarity (EMA/FDA)

- **Highly similar** quality profile, demonstrated by extensive comparability exercise[1]
- Any **differences** will have to be appropriately **justified** with regard to their **potential impact on safety and efficacy**[1]
- The biologic product is **highly similar** to the reference product notwithstanding **minor differences in clinically inactive components**[2]
- There are **no clinically meaningful differences** between the biologic product and the reference product in terms of safety, purity, and potency of the product[2]

1. EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance : quality issues (revision 1)
2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act;

Is ”Highly Similar” equivalent to ”Equivalent”?

comparable / biosimilar

↓

highly similar

↓ ?

equivalent

↓ ?

statistically equivalent

↓ ?

statistically equivalent for the means

Highly similar allows for differences if justified with respect to safety and efficacy

Merriam-Webster Dictionary
(Merriam-Webster.com, Apr 11th, 2017)
equivalent: one that is equal to another in status, achievement, or value
Equivalency: the state or fact of being exactly the same in number, amount, status, or quality

“Equivalent“ is stricter than “highly similar“

Using statistics – key considerations:

1. Relevant characteristic for comparison
2. Appropriate choice of statistical approach
3. Test parameters incl. equivalence margin / acceptance range
   - **Reference product (RP) based approach**
     - reference product defines acceptable quality
     - can be defined statistically
   - **Any other approaches feasible? No, not really**

Scientific considerations for comparability incl. biosimilarity

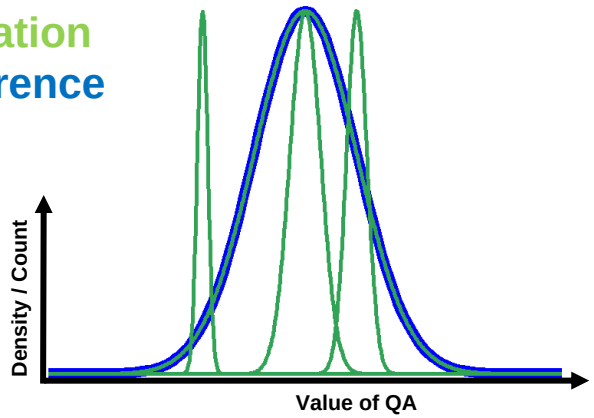
- Safety and efficacy within the reference product's variability have been demonstrated in clinical studies and by real-life experience with the reference product
- Every marketed batch from the reference product defines acceptable quality with respect to its quality characteristics
- A given quality characteristic of a reference product lot is acceptable for a test lot (e.g. biosimilar/post-change)

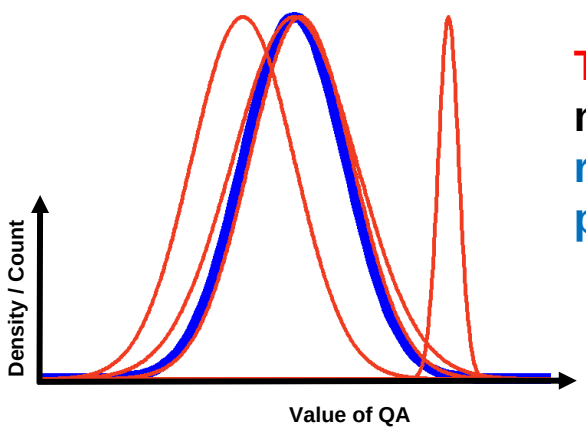
Mark McCamish & Gillian Woollett (2011) Worldwide experience with biosimilar development, mAbs, 3:2, 209-217, DOI: 10.4161/mabs.3.2.15005

Translating scientific considerations into a statistical criterion

- If the population of the test product is within the population of the reference product, all test lots are equivalent to reference lots on a batch level

Test population within reference population





Test population not within reference population

- "[...] ensuring that values of the attribute being tested for the proposed biosimilar tend to fall within the reference product distribution [...]"
  One of the three criteria for the suggested form of the equivalence margin in the FDA draft guidance "Statistical Approaches to Evaluate Analytical Similarity"
- 3 standard deviations is a good estimator of the actual population width
  "three-sigma rule of thumb", Cpk/PpK=1, Statistical Process Control (Nelson rule #1), FDA's tier 2 QAs

→ **3 sigma of the test population in 3 sigma of the reference population**

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Considered statistical approaches for the comparative assessment

Quality ranges / intervals	Assumptions	Statistical complexity	Considered implementation
Min-Max range	none	low	as is
x-sigma	normality (iid* data)**	moderate	3σ (coverage: 99.7%)
Tolerance intervals	normality (iid* data)**	moderate - high	coverage: 99% confidence: 90%
Inferential statistical methods	**allowing for a statistical quantification of uncertainty**		
Equivalence Test (for means)	normality **iid* data**	high	margin: $-1.5\sigma_R, 1.5\sigma_R$ confidence: 90%

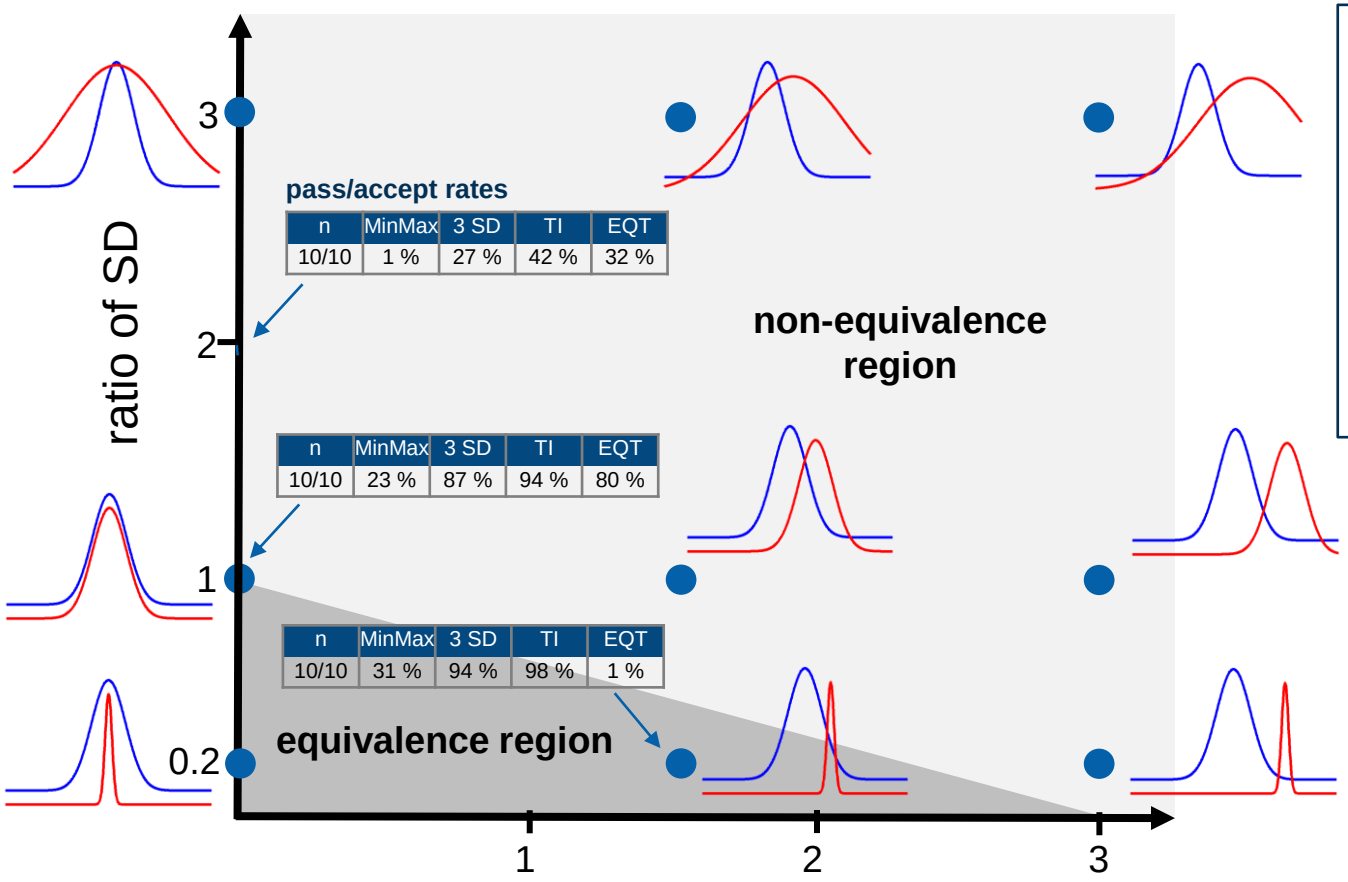
- NB: Major limitations for test interpretation may result from real-life CMC data not meeting the statistical assumptions

* independent and identically distributed data: no shifts, trends, outliers
** only necessary to draw inferential-like conclusion as drawn later in this presentation

Operating characteristics: Quantification of uncertainty

- From a pure statistical point of view
  - inferential statistics can quantify uncertainty
    - e.g. false positive rate alpha restricted to 5%, power for a give sample size & deviation from H_0
  - uncertainty cannot be quantified for range methods
    - TI‘s confidence is not an uncertainty estimation for the testing procedure
- From a combined scientific & statistical point of view
  - it‘s possible quantify the uncertainty based on a clear scientific hypothesis about acceptable quality (= equivalence criterion)
  - works for inferential methods and range methods
  - can identify false accepts (false positives) and false rejects (false negatives)

Comparing two normal populations: Test vs reference



Pass/accept rate

= n_{pass}/n_{sim}; n_{sim}=1000

Equivalence Test:

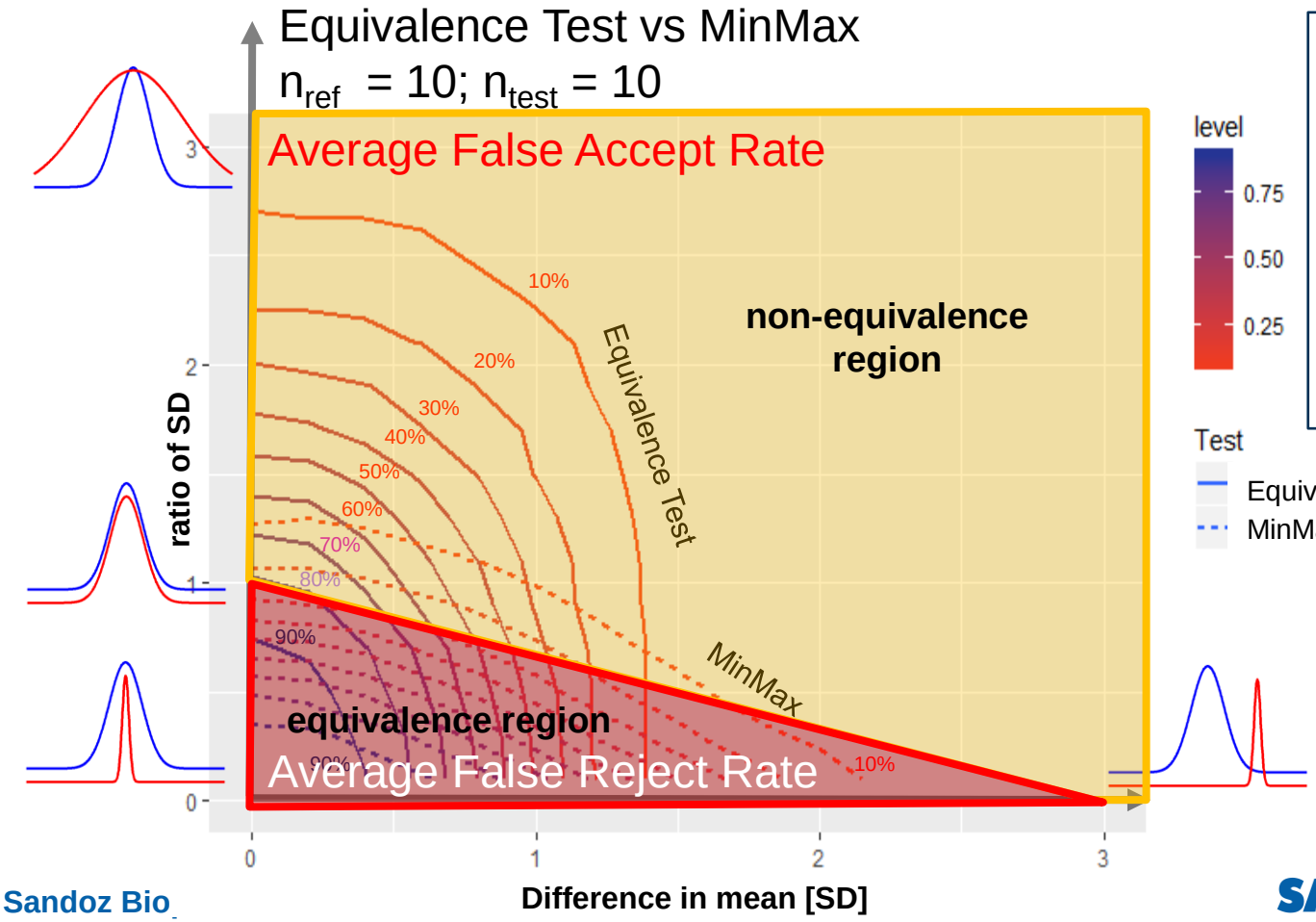
- type I error prob. 5%
- equiv. margin 1.5 σ_{ref} (sample)

MinMax/3SD/TI

- complete test sample within MinMax/3SD/TI based on reference sample

Comparing two normal populations: Test vs reference

Contour plot of test's pass/accept rates



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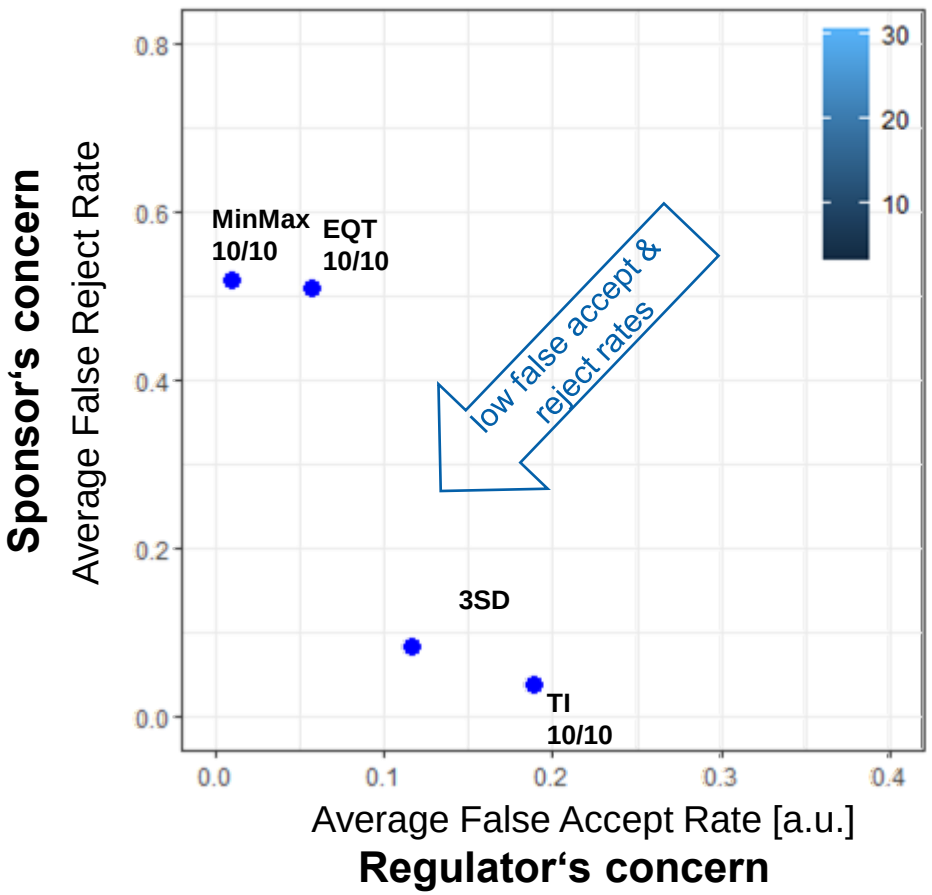
Evaluating different test´s operating characteristics

Average false accept rates & average false reject rates



- Compare tests e.g. for given sample sizes (n_{ref} & n_{test})
- Most desirable: low false rejects and low false accepts
- Evaluate the impact of sample size (n_{ref} & n_{test})
  - Examples:
    - n_{test} 4,6,8,..,30 for n_{ref}=10
    - n_{ref} 4,6,8,...,30 for n_{test}=10

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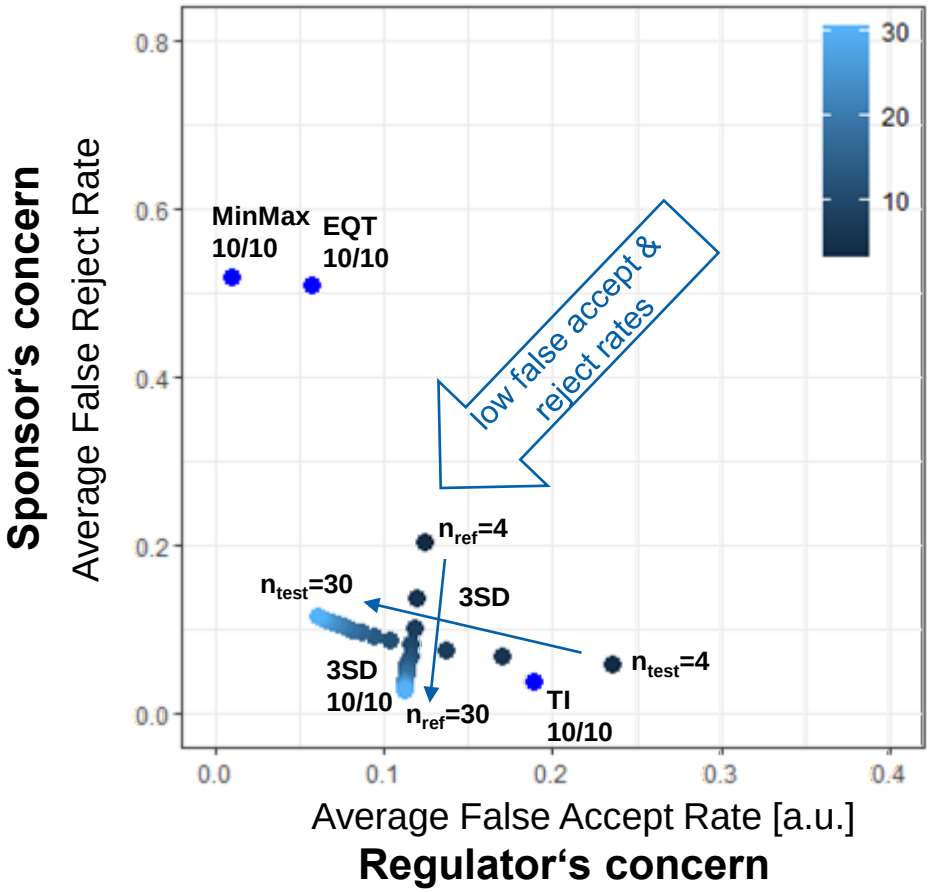

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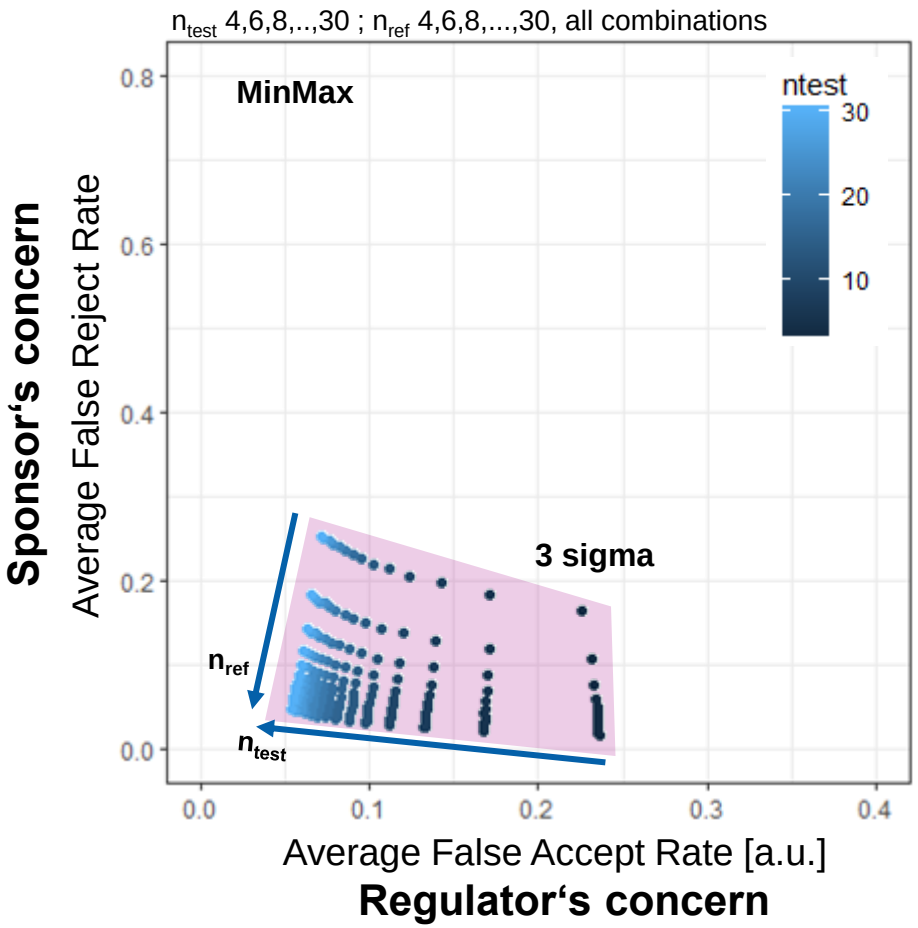

- 3 sigma
  - relatively low av. false reject rates
  - increasing sample sizes decrease error rates
- Tolerance Intervals (TI)
  - low samples (test & ref) increase only av. false accept rates (but not av. false reject rates)
- MinMax
  - lowest average (av.) false accept rates but high av. false reject rates
- Equivalence Test (EQT)
  - high av. false reject rates
  - av. false accept rates increase with sample size
- Significant av. false reject rates for all approaches (& aggravated by multiplicity)
- For samples n ≥ 10, all quality range methods exhibit av. false accept rates not higher that those seen for the EQT

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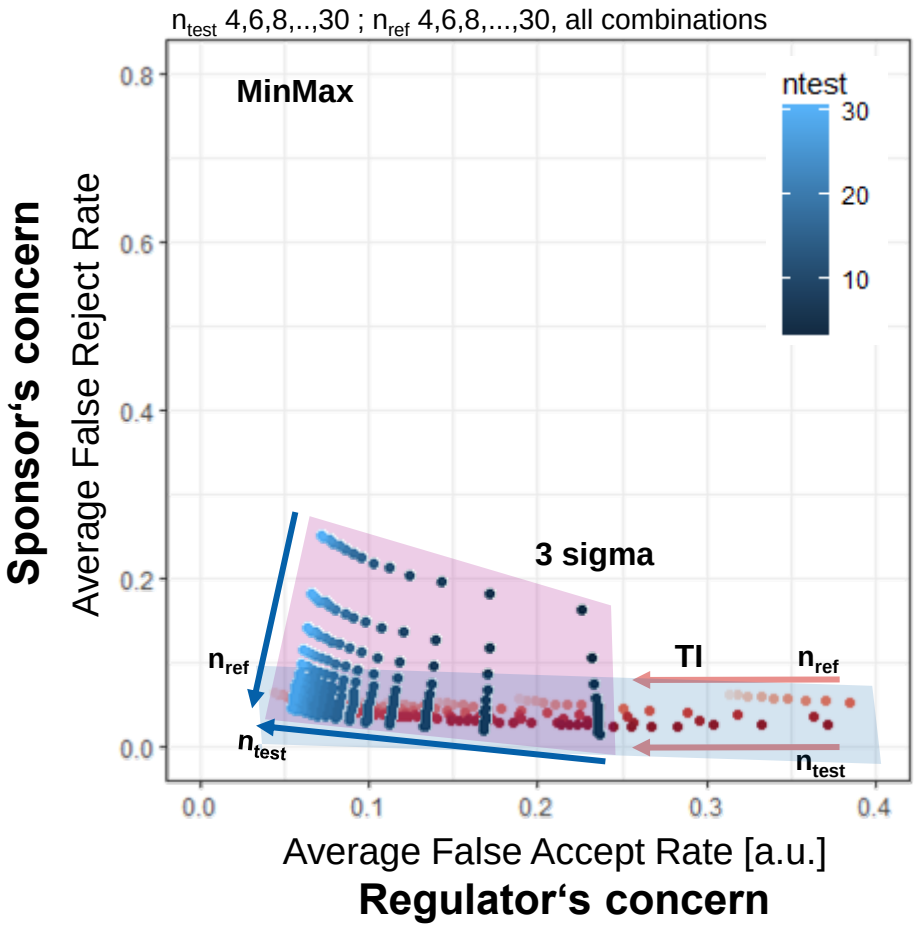

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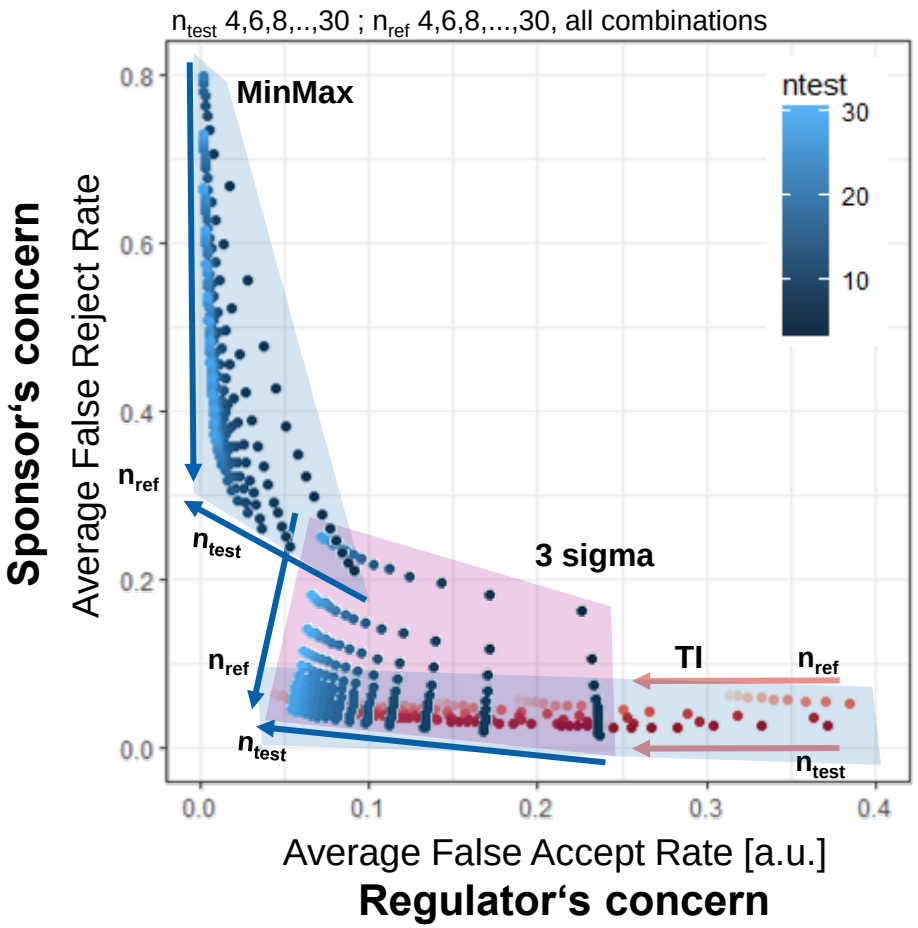

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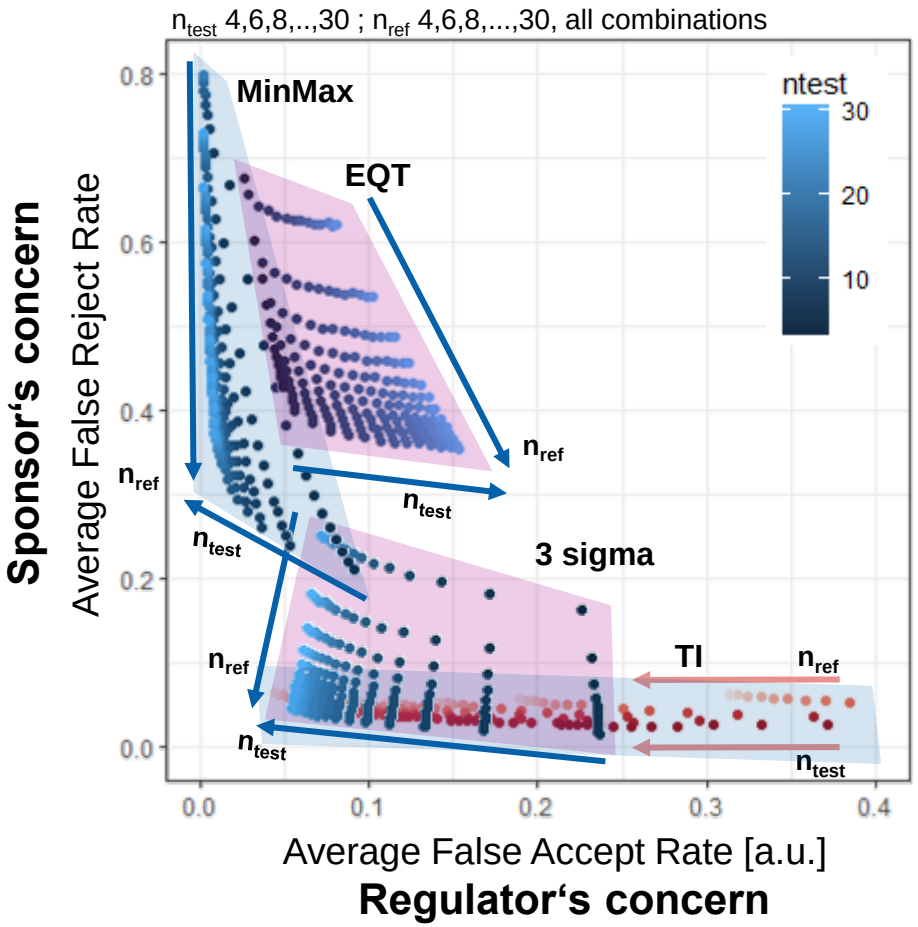

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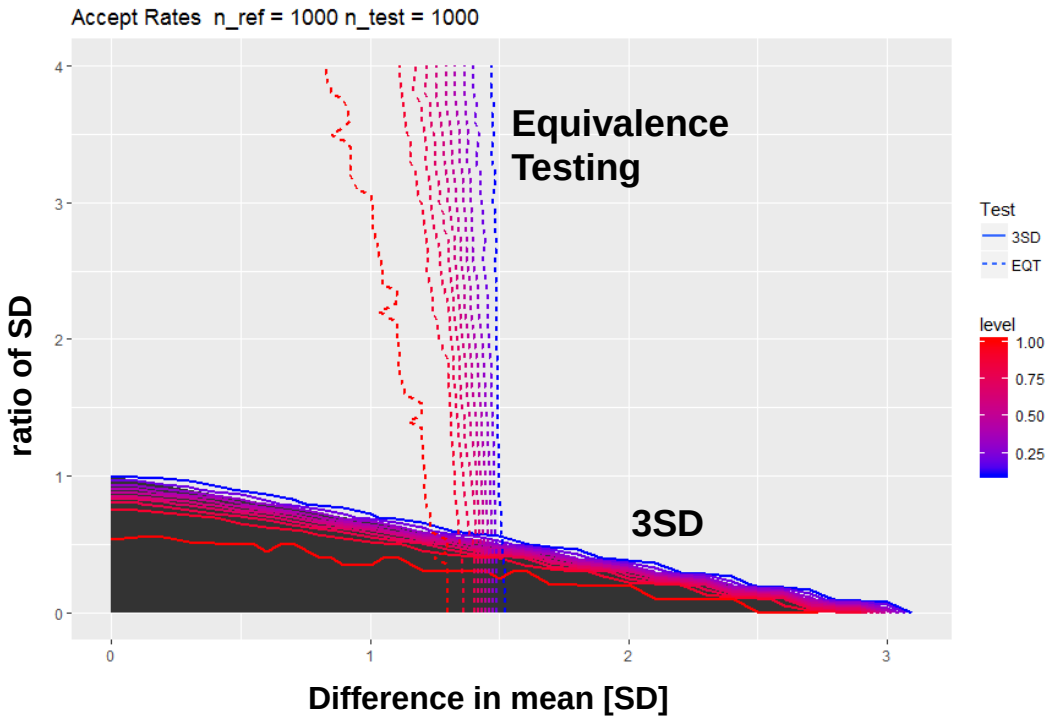
Different scientific hypotheses for quality ranges vs equivalence testing

illustrated by large test and reference sample sizes

- The average false accept rate of the equivalence test increases with sample size
- Equivalence testing is the wrong tool to control a population in a population
  - EQT controls the mean to be within the equivalence margin
  - EQT does not control the variance (ratio of SD)
    - variance is a minor matter for equivalence testing for the mean
    - done decreasingly well for larger sample sizes



Multiplicity implications for overall average success rates

Testing more than one quality attribute: Overall success rates for truly equivalent products

$n_{ref} = 10$, $n_{test} = 10$

# of QA	Min Max	3SD	TI	EQT
1	48.0%	92.0%	96.0%	49.0%
3	11.1%	77.9%	88.5%	11.8%
10	0.1%	43.4%	66.5%	0.1%
20	0.0%	18.9%	44.2%	0.0%

$n_{ref} = 30$, $n_{test} = 10$

# of QA	Min Max	3SD	TI	EQT
1	71.8%	97.1%	95.8%	62.2%
3	37.0%	91.4%	87.9%	24.1%
10	3.6%	74.1%	65.1%	0.9%
20	0.1%	54.9%	42.4%	0.0%

Success rates < 50% colored red for illustration purposes only. 50 % should not be considered a reasonable success rate.

- Significant multiplicity issues due to high statistical uncertainty
  - MinMax and EQT have already for a single QA very low average success rates
- From the evaluated approaches, 3 sigma is certainly not perfect but the test of choice for any larger number of quality attributes
- In any case, false alarms are very likely and should not be overrated

Statistical conclusions

- Low sample sizes in comparability / biosimilar settings create considerable uncertainty (aggravated by multiplicity)
- Increasing sample size can have surprising and undesirable consequences
  - e.g. increase in false accept rate with test sample size for equivalence testing
- Test performance depends on scientific hypothesis
  - range methods better suited than EQT to test for „population in population“
- Typically trade-off between false accepts and false reject
  - exception EQT – which is just worse since not aligned with scientific hypothesis
- Sample sizes are of key importance
  - Scientific expectation: larger sample sizes should primarily improve the conclusion
  - for Biosimilars, consider to include representative small scale studies, where possible, to have more lots (e.g. at least 10)

Conclusions

- The presented framework allows to evaluate operating characteristics of statistical approaches
  - against a clear scientific hypothesis of equivalency (population in population)
  - other test proposals can be easily evaluated
  - equally applicable for manufacturing change comparability and biosimilarity
- Any remaining benefit from inferential vs non-inferential methods?
  - with a clear scientific hypothesis, uncertainty can be equally well estimated for non-inferential and inferential methods
- Statistics cannot be a pass/fail criterion due to
  - very limited sample size which leads to a high uncertainty
  - „Comparability" (highly similar) is less strict than statistical equivalence
  - the fulfillment of the assumptions for statistical inference is unclear
- How to find the right balance between false accept and false reject error rates?
  - depends on risk profile (e.g. QA risk in tiered approach, prior knowledge in context of a manufacturing change); multiplicity (testing of more than one quality attribute)
- Unless a complex test has clear benefits – go for simplicity (KISS*: keep it simple, stupid)