Bayesian Statistics in CMC

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R&D Development, Biostatistics
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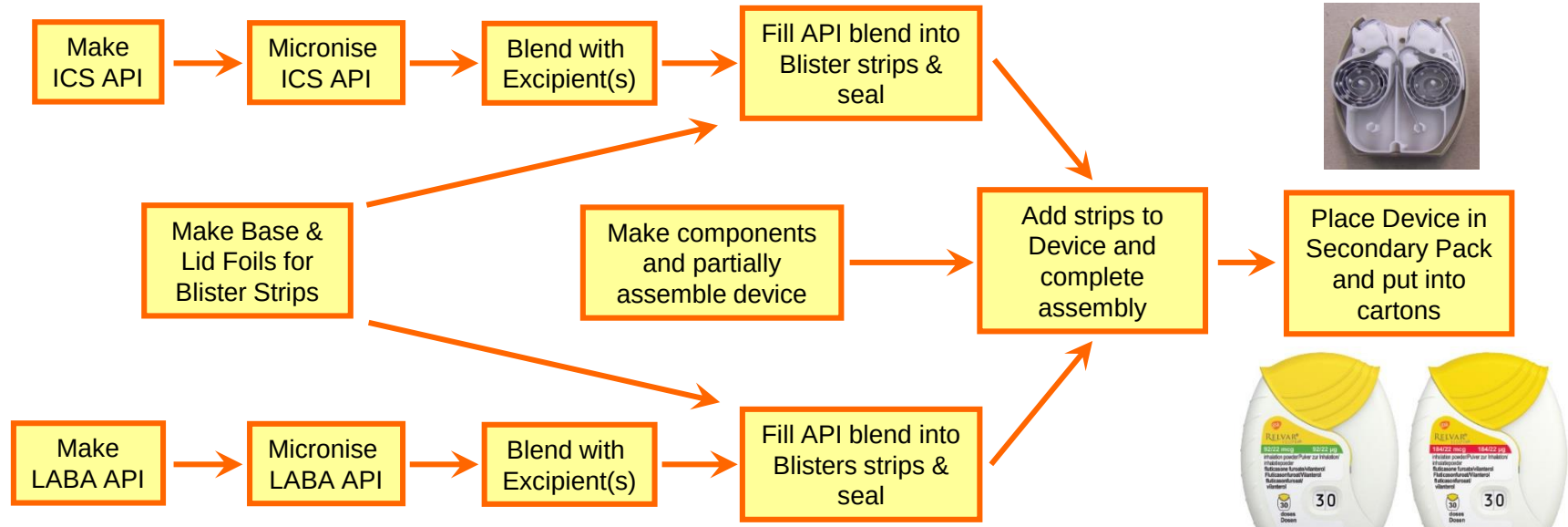
Transform data into knowledge by applying quantitative expertise to…

What is Chemistry Manufacturing and Controls (CMC)?

Example of manufacture of RELVAR ELLIPTA[1]



- Process Understanding
- Process Optimisation
- Process Transfer

- Method Development
- Method Validation
- Method Transfer

- Control Limits
- Sampling Protocols
- Quality Assurance Procedures

- Specifications

[1]RELVAR and ELLIPTA are trademarks owned by or licensed to the GSK group of companies

CMC Statistics in GSK, Pharma R&D

26 Statisticians globally

- Compounds across multiple therapeutic areas e.g. Respiratory, Infectious Diseases, Oncology
- Both small molecules and biopharmaceuticals
- Statistical Activities:
  - Consultancy, enablement and training for R&D scientists and engineers
  - Experimental Design
    - Factorial/Fractional Factorial, Response Surface, Screening, bespoke…
  - Data Modelling
    - Linear and Linear Mixed models (repeated measures and random effects)

Bayesian Analytical Biosimilarity

Supporting heading

With acknowledgements to:

EFSPI Working Group on Statistical methodology for comparative assessment of quality attributes in drug development:

Christophe Agut (Sanofi)
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Martina Kron (Abbvie)
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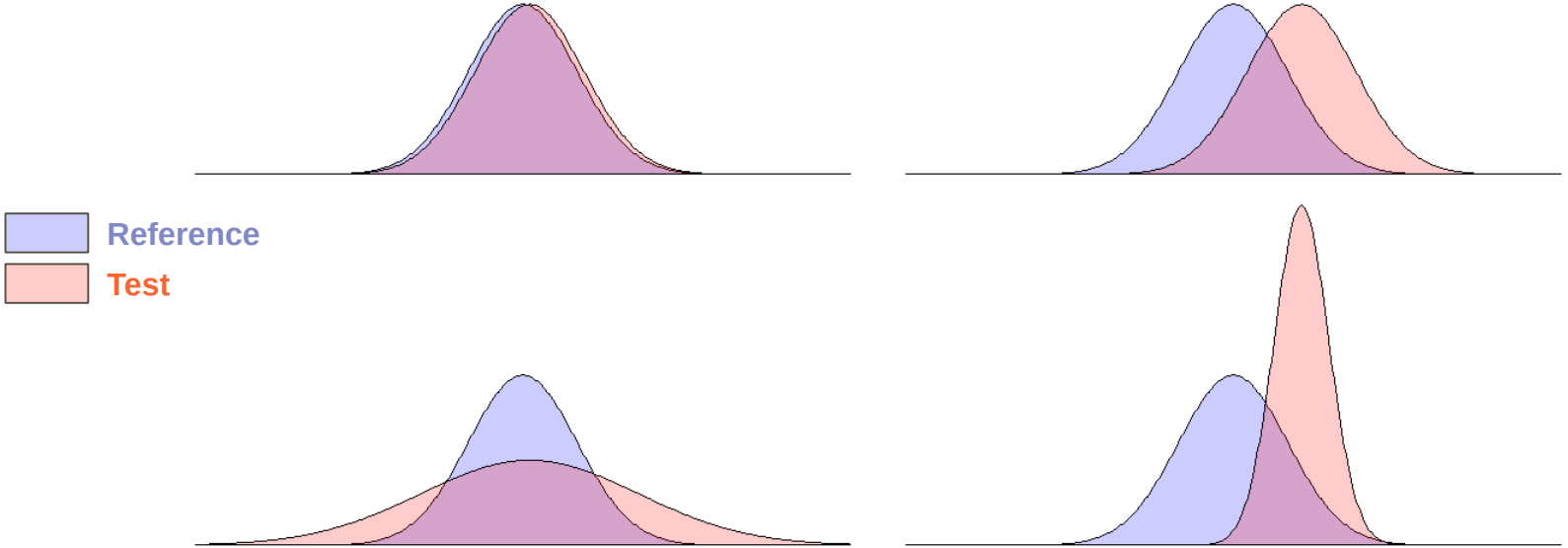
Jens Lamerz (Roche)
Timothy Mutsvari (Pharmalex)
Christian Seifert (Boehringer-Ingelheim)

Three Fundamental Requirements

1. Define what we mean by equivalence/comparability
2. Provide a well-defined decision procedure
3. Demonstrate the operating characteristics of the procedure
   - What is the probability of deciding in favour of equivalence/comparability?
   - What is the patient risk?
     - (Test product is deemed equivalent/comparable and a patient receives a bad lot from the Test product)
   - What is the producer risk?
     - (Test product is deemed not to be equivalent/comparable when it is)

What do we mean by equivalent/comparable?

– We wish to demonstrate that a **proposed new process produces** lots of **Test** product that are (analytically) “equivalent/comparable” to those of a **Reference** product (both now and in the future).



When are the two distributions equivalent/comparable?

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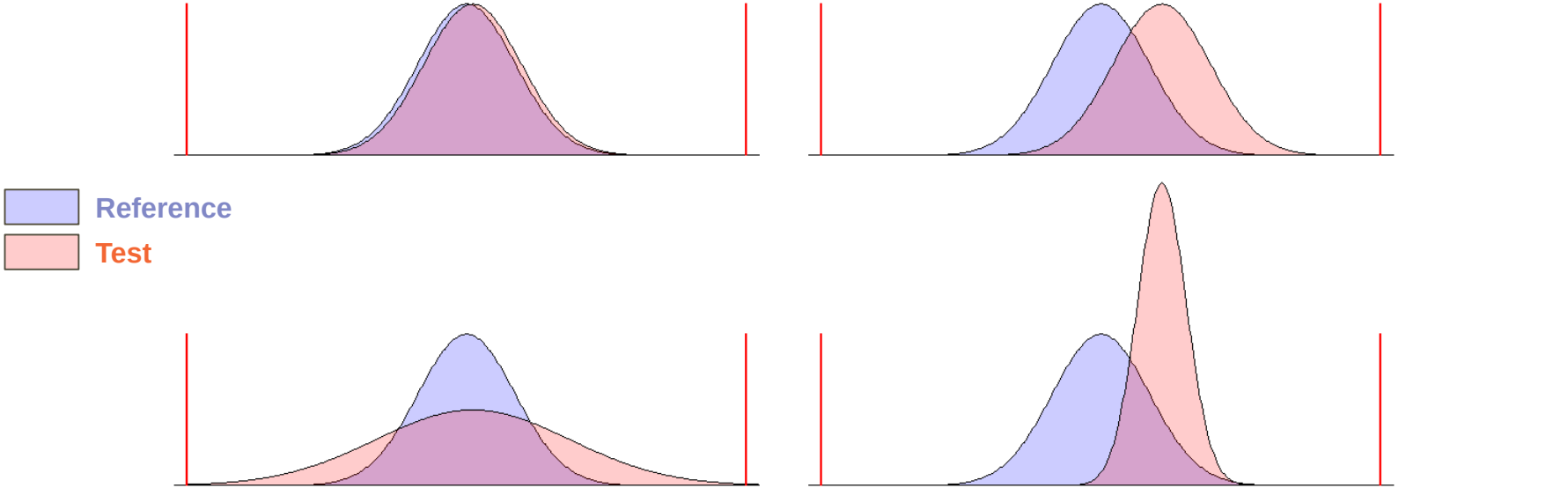

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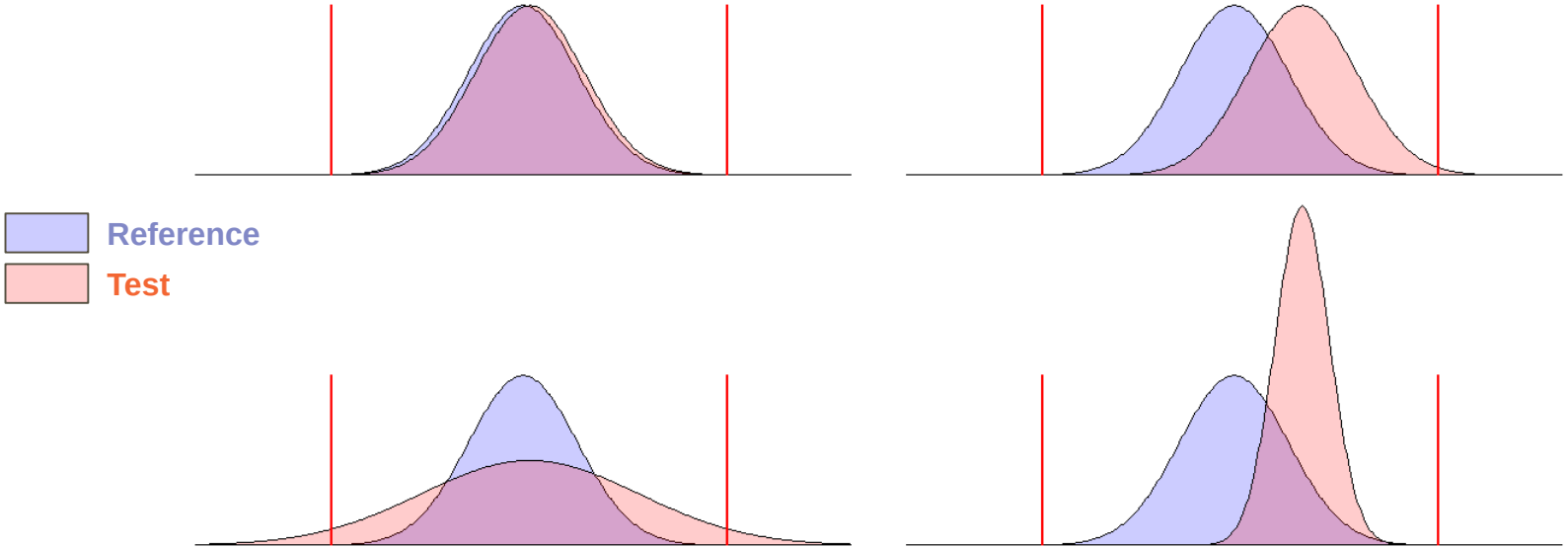
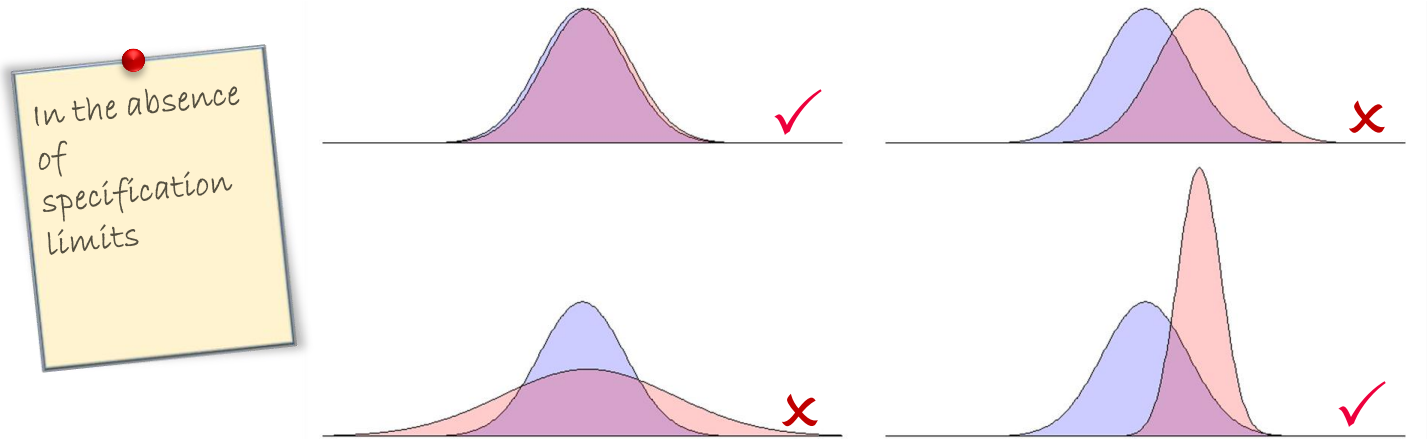


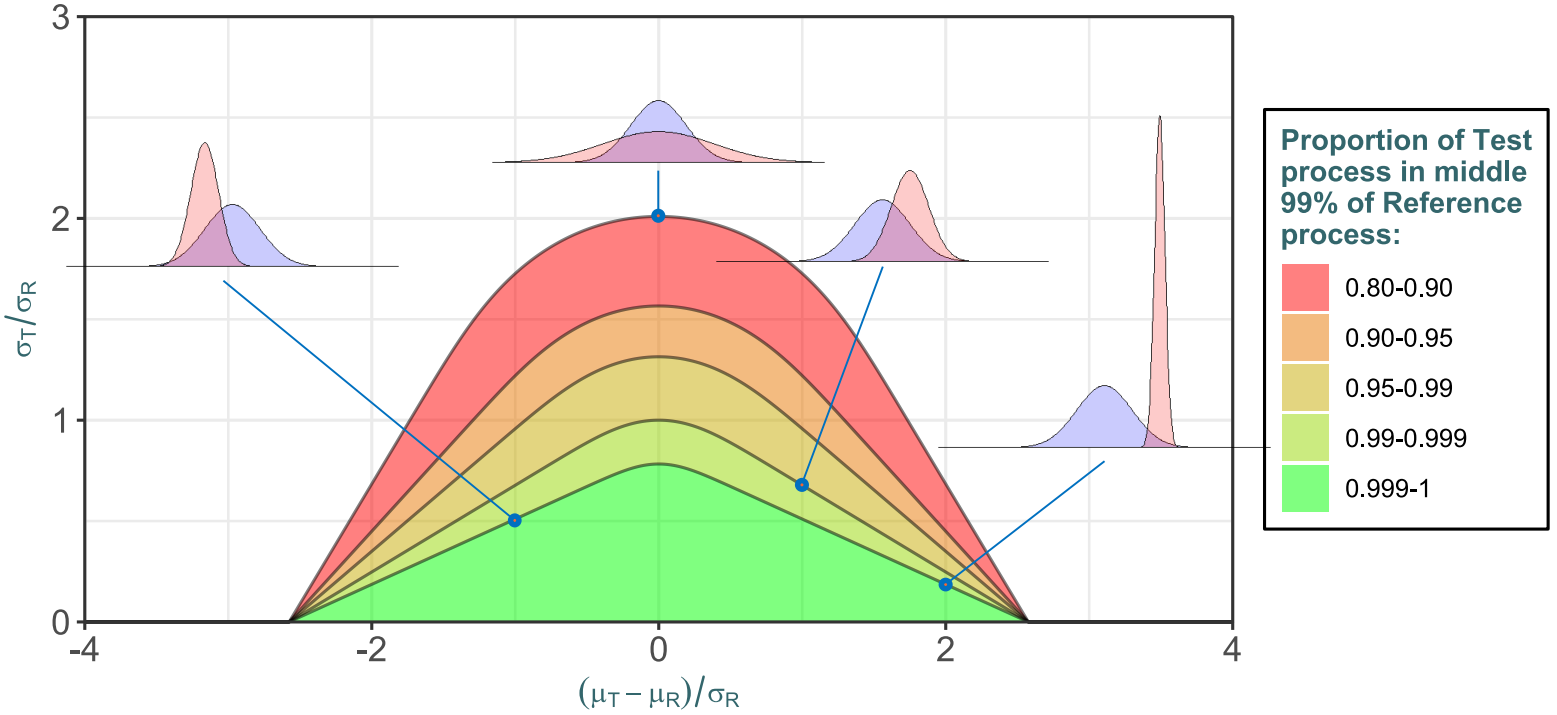
When are the two distributions equivalent/comparable?

A Definition of (Analytical) Biosimilarity

– The test product is analytically comparable (for a given attribute) to the **Reference** product if at least $P_T\%$ of all lots produced by the Test product process lie within the middle $P_R\%$ of the lots produced by the Reference product process.



A Definition of (Analytical) Biosimilarity



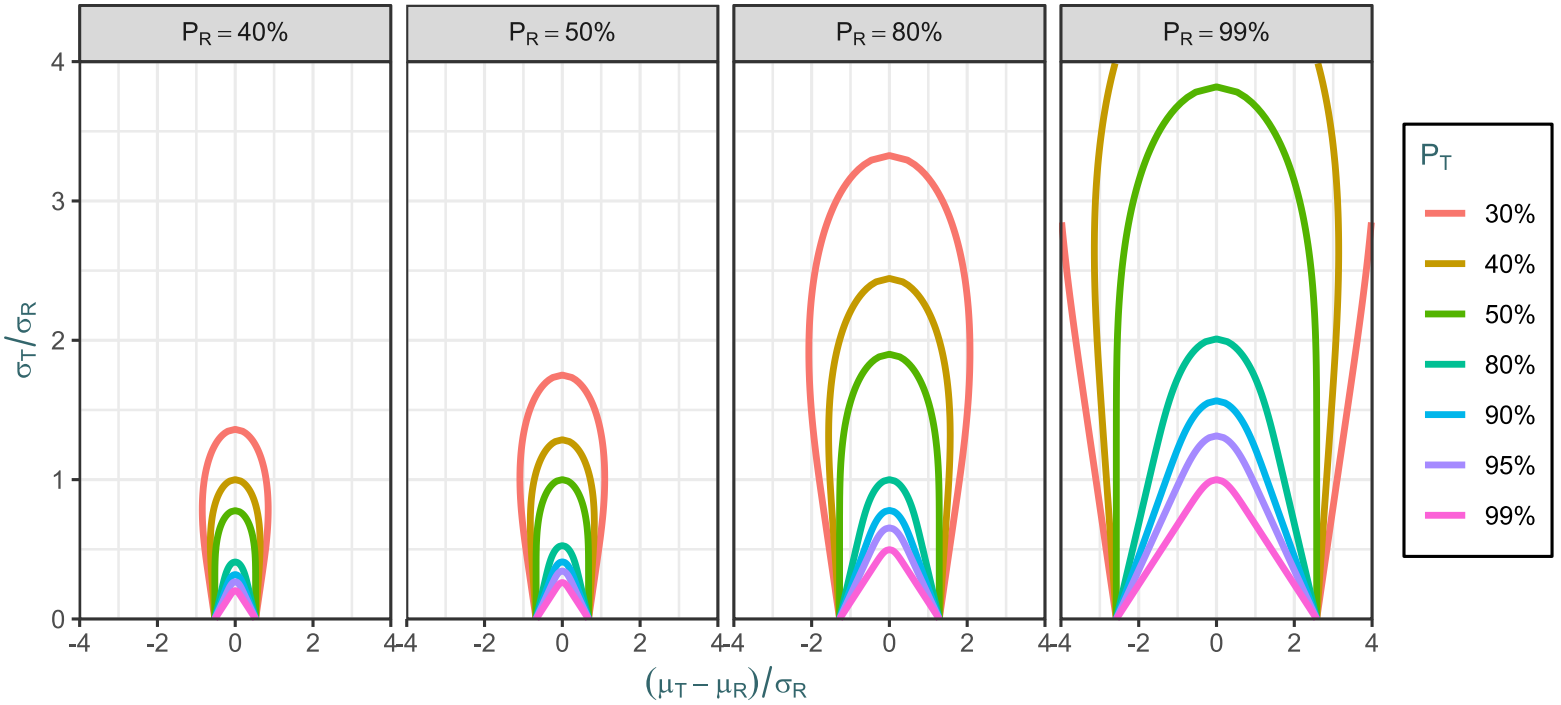
A Definition of (Analytical) Biosimilarity

– For normally distributed processes $N\left(\mu_T, \sigma_T^2\right), N\left(\mu_R, \sigma_R^2\right)$ comparability region only depends on difference in means and standard deviation relative to the Reference standard deviation:

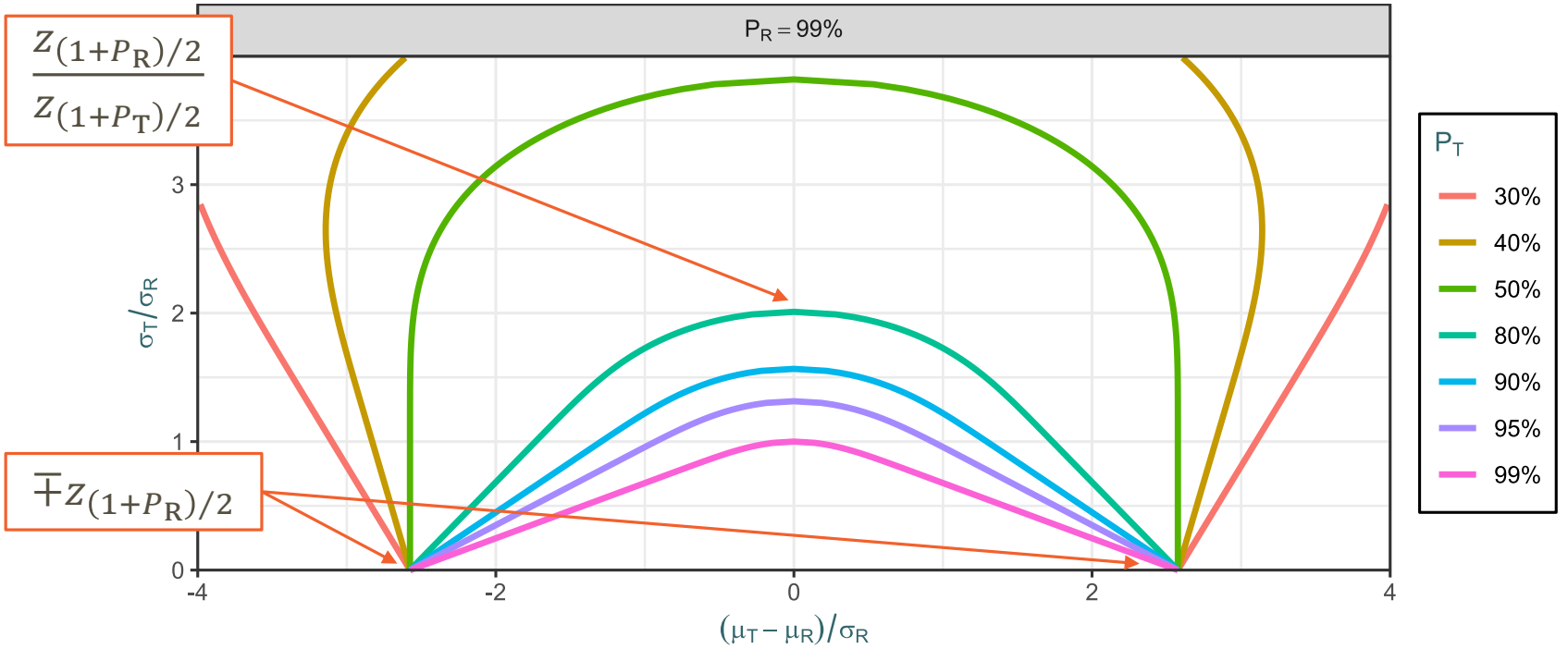
$$\mu_\Delta = \frac{\mu_T - \mu_R}{\sigma_R}; \rho = \frac{\sigma_T}{\sigma_R}$$

$$\left\{(\mu_\Delta, \rho) : \Phi\left[\frac{z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right] - \Phi\left[\frac{-z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right] \geq P_T\right\}$$

Impact of choice of P_T and P_R on Comparability Region



Comparability regions for $P_R = 99\%$



Posterior Probability of Biosimilarity

– In principle, calculating the posterior probability of Biosimilarity is easy:

1) Define an indicator function for Biosimilarity in terms of the unknown parameters:

$$B(\mu_\Delta, \rho) = \begin{cases} 1 & \Phi\left(\frac{z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right) - \Phi\left(\frac{-z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right) \geq P_T \\ 0 & \text{otherwise} \end{cases}$$

2) "Integrate" this over the unknown parameters weighted by the joint posterior density:

$$P(\text{Biosimilarity}|\text{Data}) = \int_{\sigma_R, \sigma_T, \mu_T, \mu_R} B\left(\frac{\mu_T - \mu_R}{\sigma_R}, \frac{\sigma_T}{\sigma_R}\right) P\left(\mu_T, \mu_R, \sigma_T, \sigma_R|\text{Data}\right)$$

Posterior Probability of Biosimilarity

(Independent Samples from Test and Reference Processes)

Using Jeffreys' Prior: $P(\mu_T, \sigma_T, \mu_R, \sigma_R) = \sigma_T^{-1} \times \sigma_R^{-1}$

Posterior:

$$P\left(\mu_T, \mu_R, \sigma_T, \sigma_R | \text{Data}\right) = P\left(\mu_T, \sigma_T | \bar{X}_T, s_T, N_T\right) \times P\left(\mu_R, \sigma_R | \bar{X}_R, s_R, N_R\right)$$

$$(\mu_T|\sigma_T) \sim N\left(\bar{X}_T, \sigma_T^2/N_T\right); \quad (\sigma_T^2) \sim \Gamma^{-1}\left((N_T-1)/2, (N_T-1)s_T^2/2\right)$$

$$(\mu_R|\sigma_R) \sim N\left(\bar{X}_R, \sigma_R^2/N_R\right); \quad (\sigma_R^2) \sim \Gamma^{-1}\left((N_R-1)/2, (N_R-1)s_R^2/2\right)$$

Posterior Probability of Biosimilarity

– With a bit of effort it's possible to show that

$$P(\text{Biosimilarity}|\text{Data}) = \int_{\sigma_R,\sigma_T,\mu_T,\mu_R} B\left(\frac{\mu_T-\mu_R}{\sigma_R}, \frac{\sigma_T}{\sigma_R}\right) P\left(\mu_T,\mu_R,\sigma_T,\sigma_R|\text{Data}\right)$$

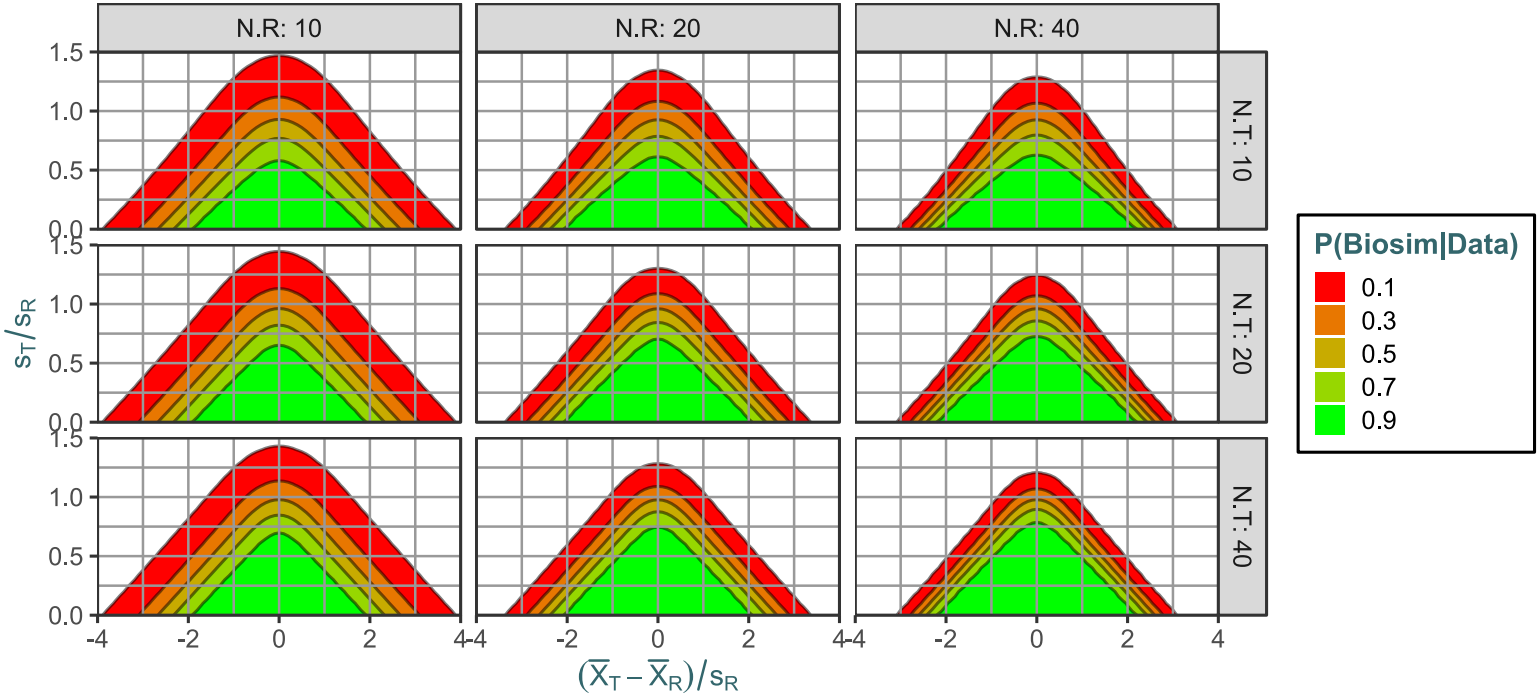
can be re-written as a double integral over two Γ^{-1} random variates

– Value only depends on:

$$(\bar{X}_T - \bar{X}_R)/s_R; \quad s_T/s_R; \quad N_T; \quad N_R.$$

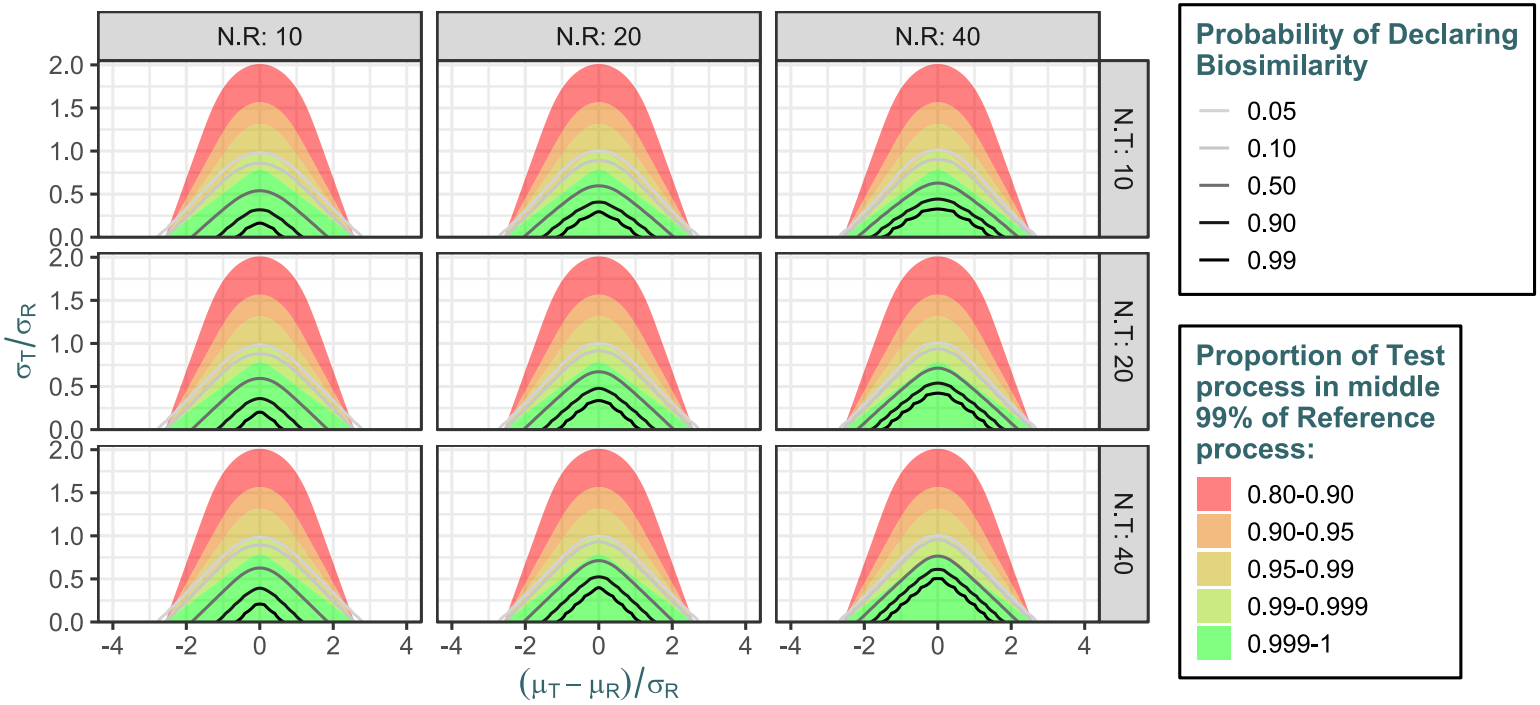
Posterior Probability of Biosimilarity

Biosimilarity based on $P_T = P_R = 99\%$



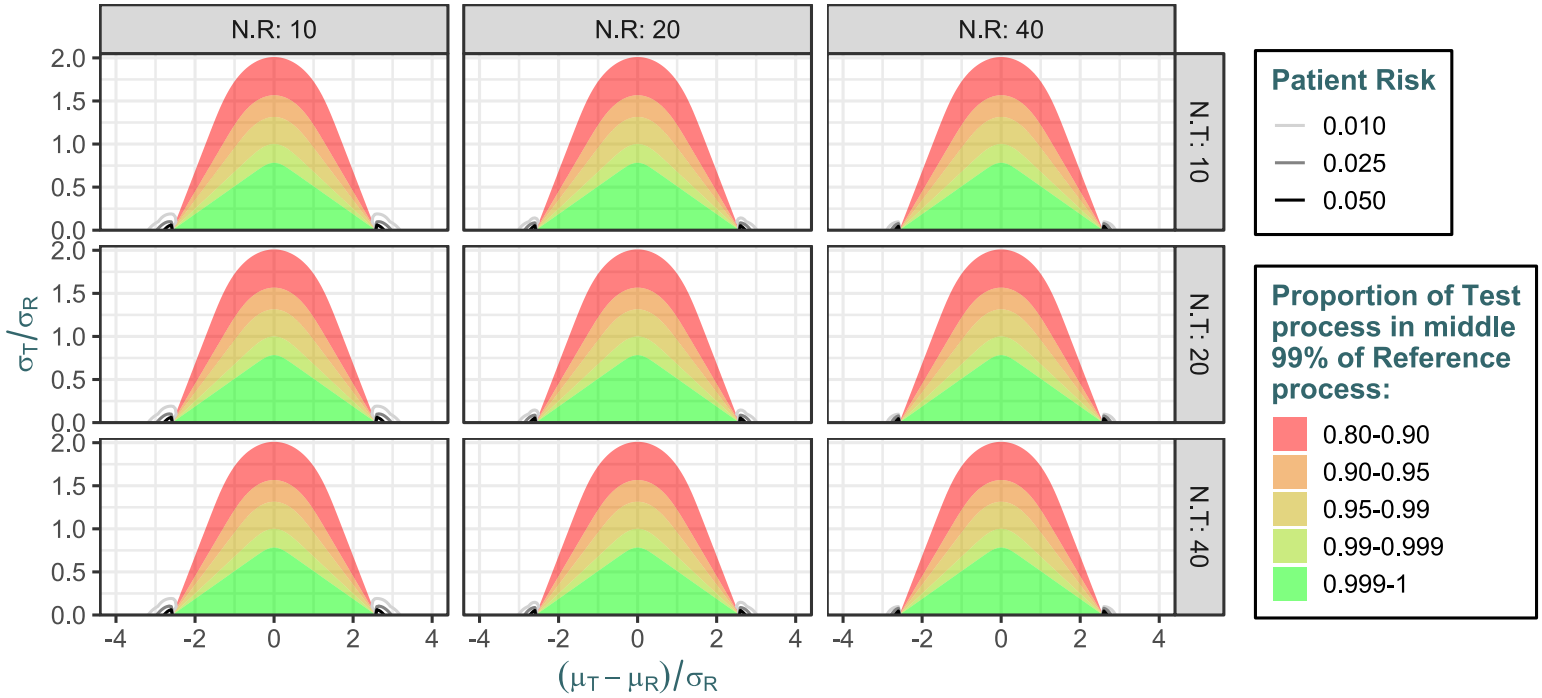
Operating Characteristic based on P(Biosim|Data) > 0.9

Biosimilarity based on $P_T = P_R = 99\%$



Patient Risk[1]

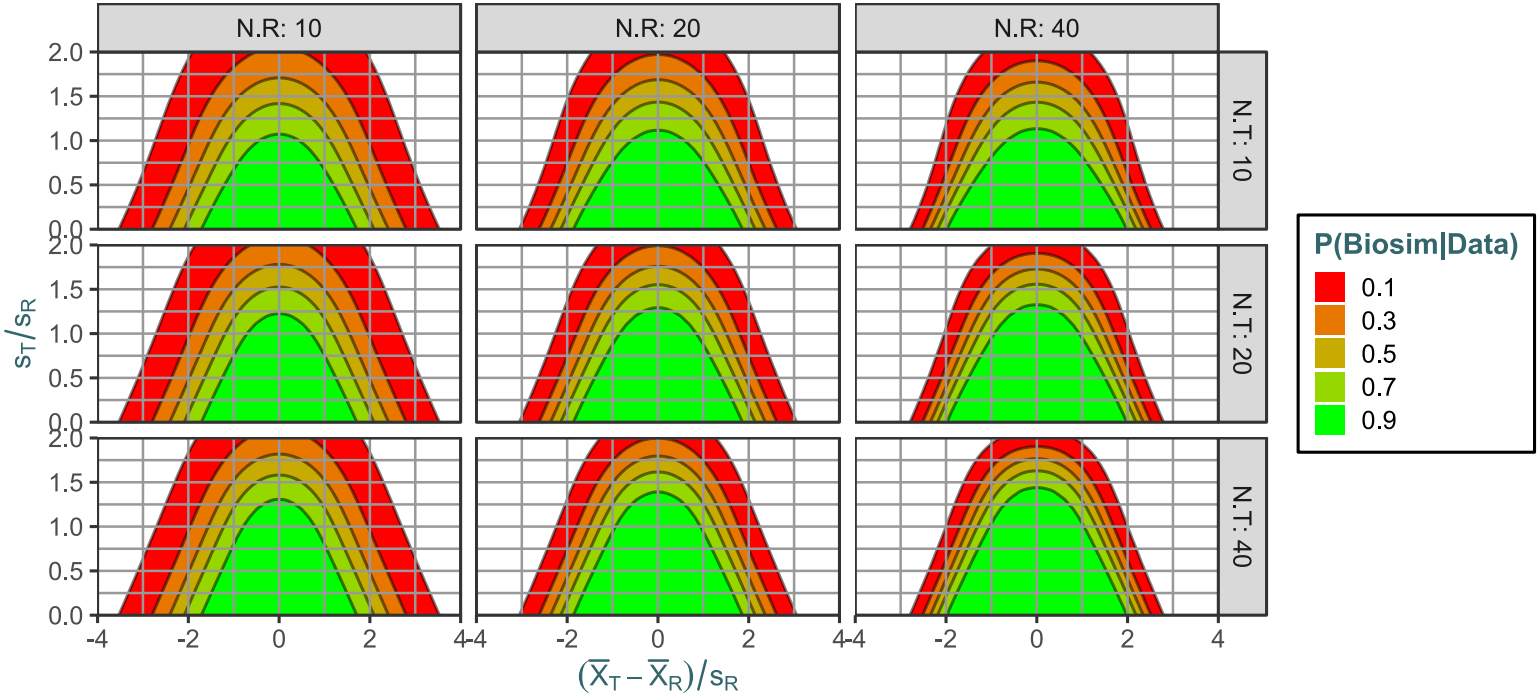
Biosimilarity based on $P_T = P_R = 99\%$ and P(Biosim|Data) > 0.90



[1]Declare Test Biosimilar and patient receives Test lot outside middle **99%** of Reference process

Posterior Probability of Biosimilarity

Biosimilarity based on P_T = 80% P_R = 98%



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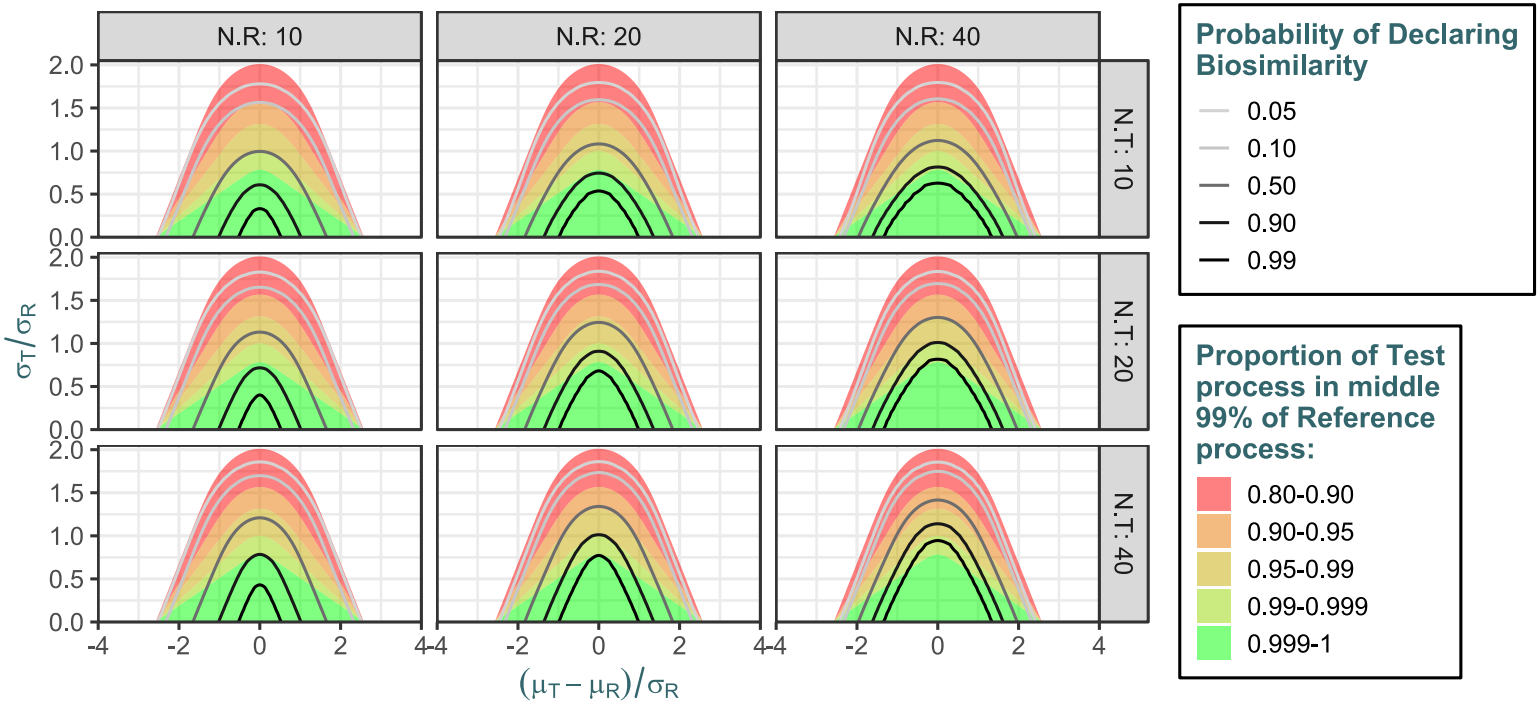
Biosimilarity based on P_T = 80% P_R = 98%



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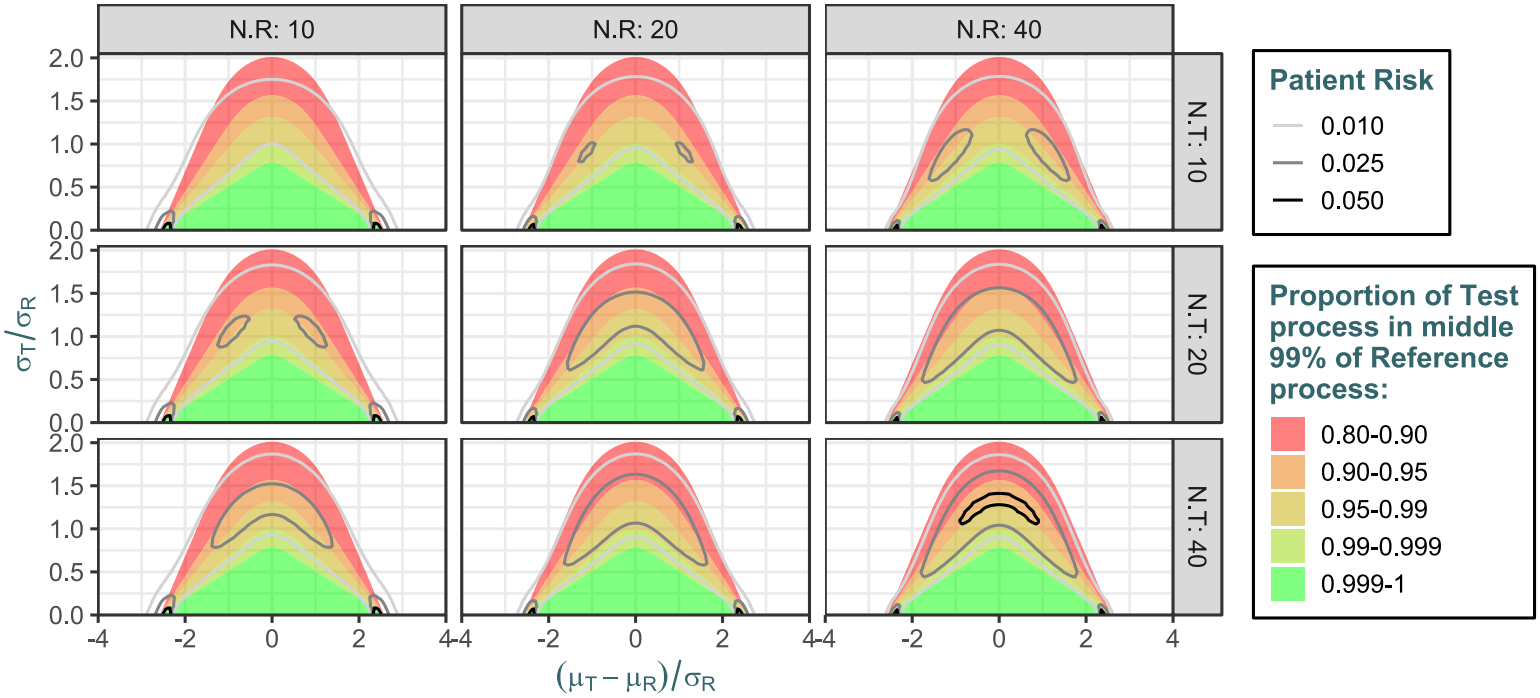

[1]Declare Test Biosimilar and patient receives Test lot outside middle **98**% of Reference process

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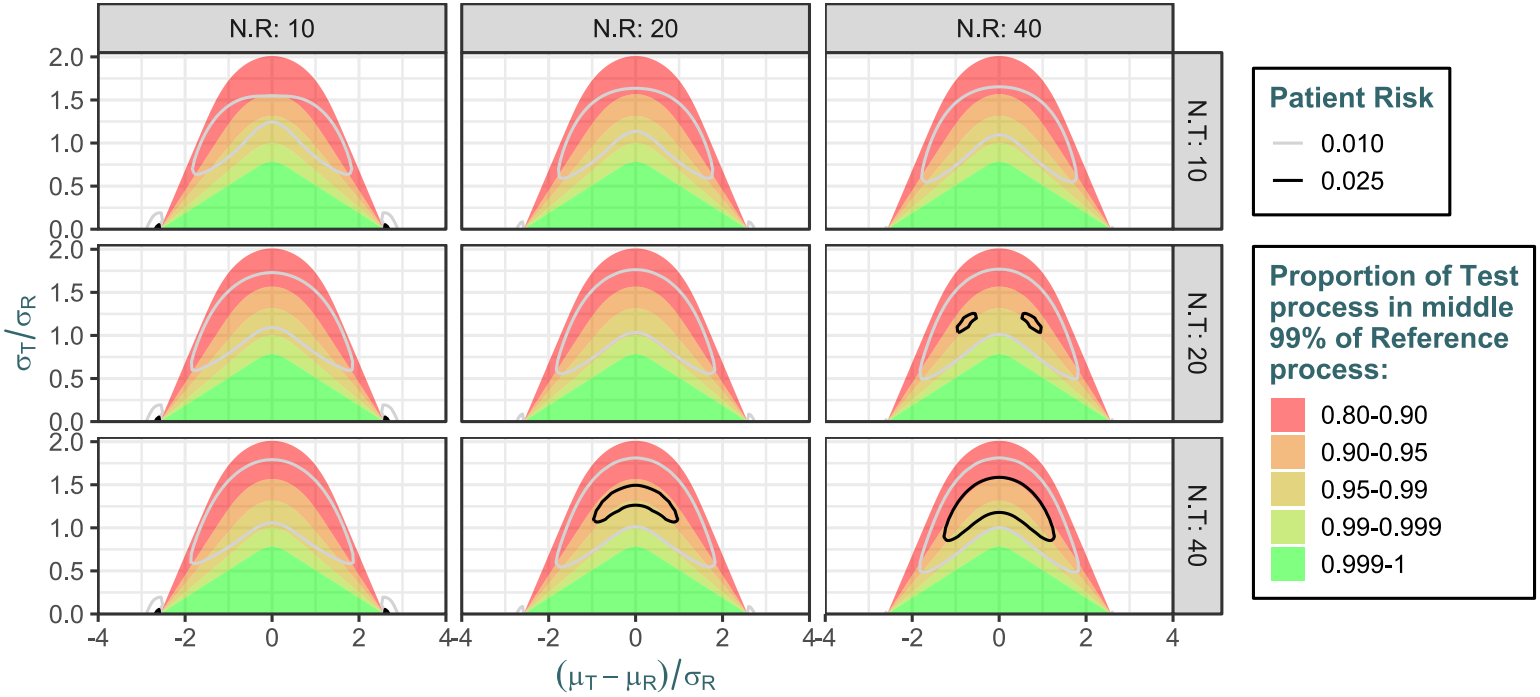
Biosimilarity based on P_T = 80% P_R = 98% and P(Biosim|Data) > 0.90



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