



Statistically Derived MAD for TOST

A Combined Accuracy and Precision (CAP) Approach for PSD
Co-validation Studies

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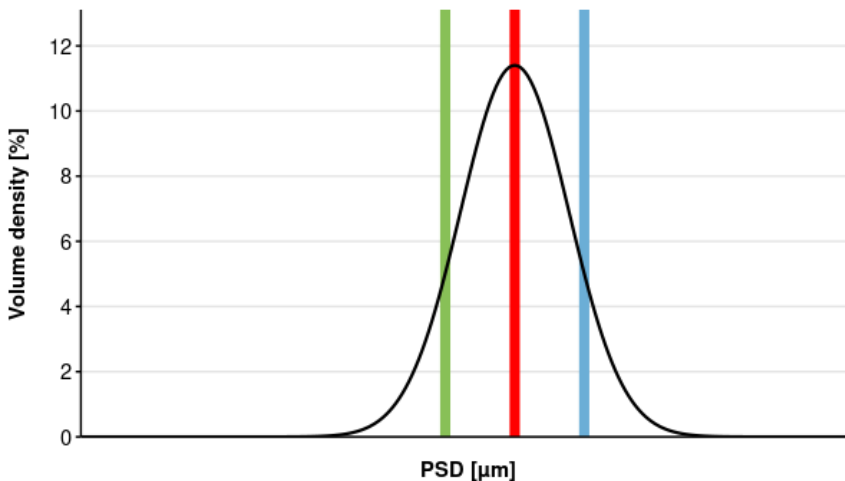
25/09/2026

Problem description

In PSD method validation, guidance documents are available for assessing repeatability

Some guidance documents are available for the validation of new PSD methods (**D10**, **D50** and **D90**).

USP <429> and EP 2.9.31 provides criteria to be used to evaluate **repeatability** for these 3 quantities.



PSD: Particle Size Distribution.

A PSD quantile **D** is defined as the value **X [μm]** such that **D%** of total volume is represented by particles with diameter smaller than **X**.

Problem description

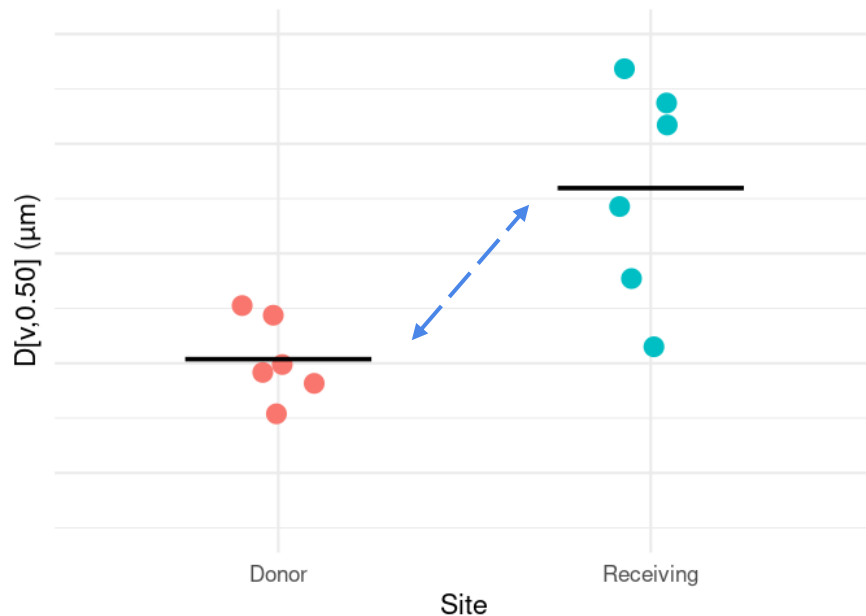
When a method is transferred, a co-validation study is performed to compare between-site average

If the method is **transferred** to a different manufacturing site, the difference between donor and receiving sites must be evaluated.



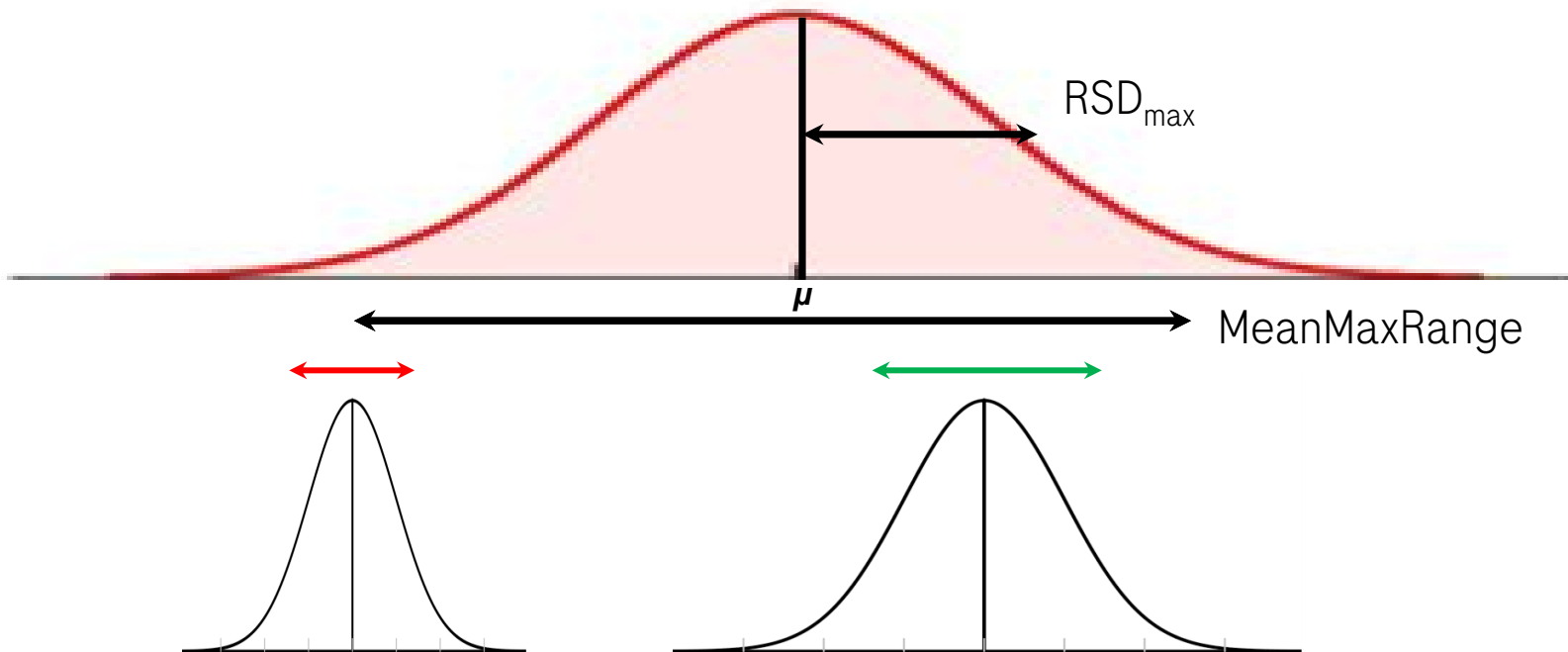
NO guidance available in this case

Donor site samples vs Receiving site samples



Combi Accuracy and Precision (CAP)

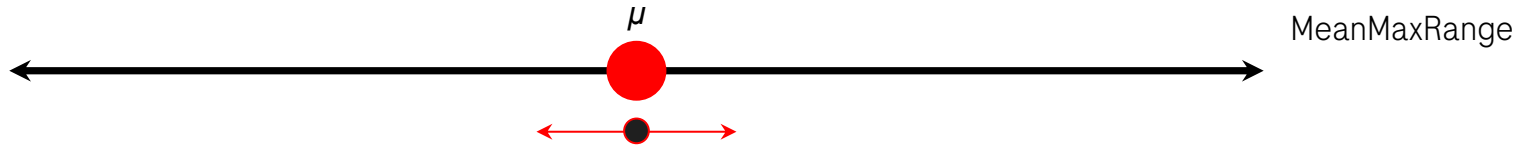
CAP provides the framework to evaluate acceptable combination of precision and accuracy



Note: μ is the donor site mean.

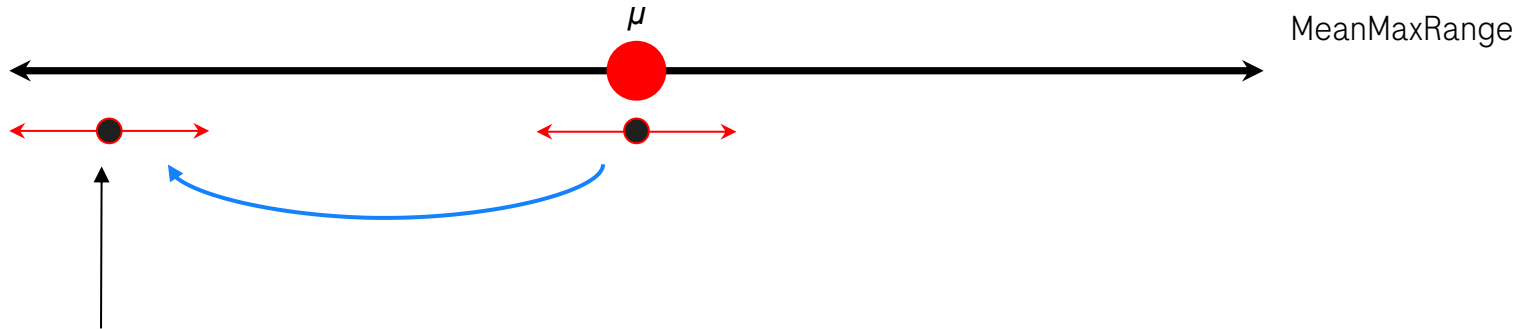
MAD derivation through CAP

The chosen MAD depends on how much bias is acceptable for the 95% CI of the reference mean



MAD derivation through CAP

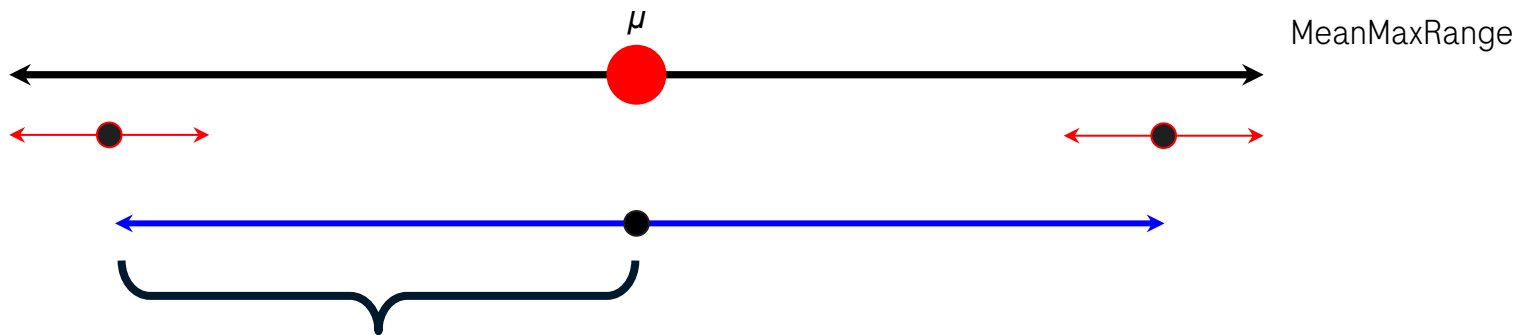
The chosen MAD depends on how much bias is acceptable for the 95% CI of the reference mean



Hypothetical new samples still with **Donor site precision**:
95% CI for the mean still within *MeanMaxRange*, hence acceptable.

MAD derivation through CAP

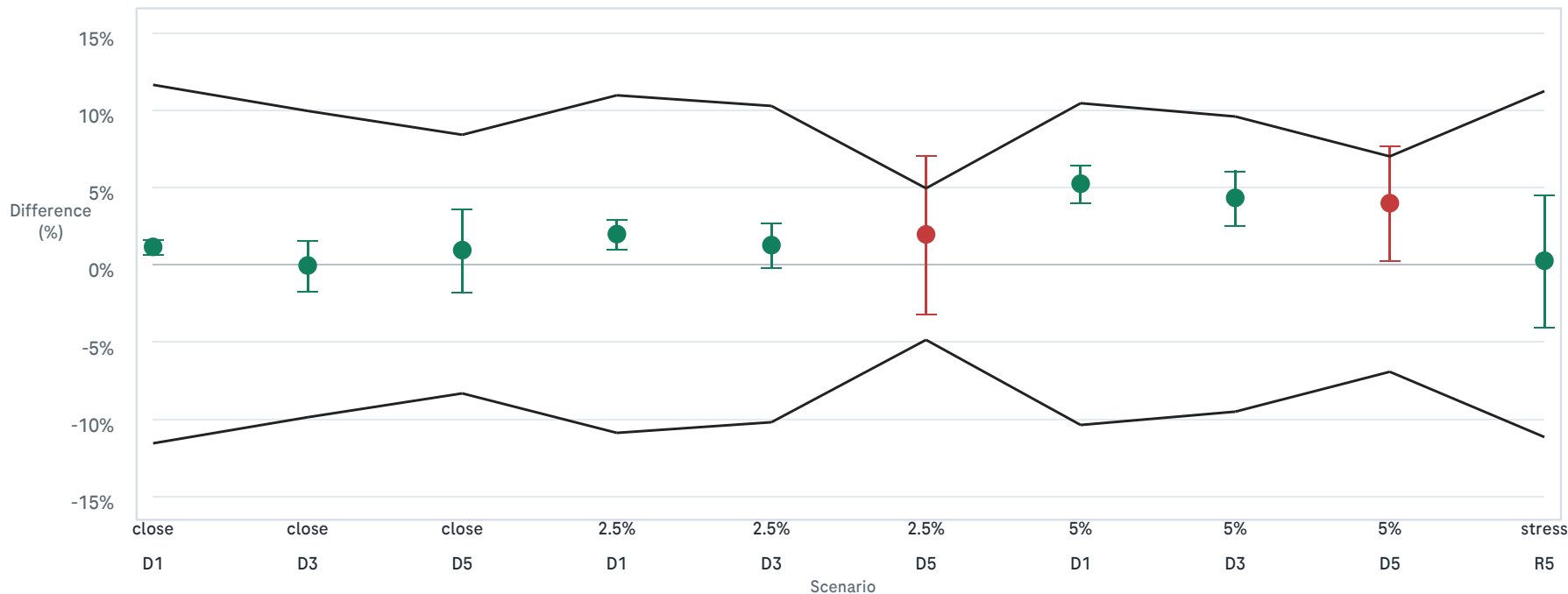
The chosen MAD depends on how much bias is acceptable for the 95% CI of the reference mean



This is the **MAD** value
we propose to use

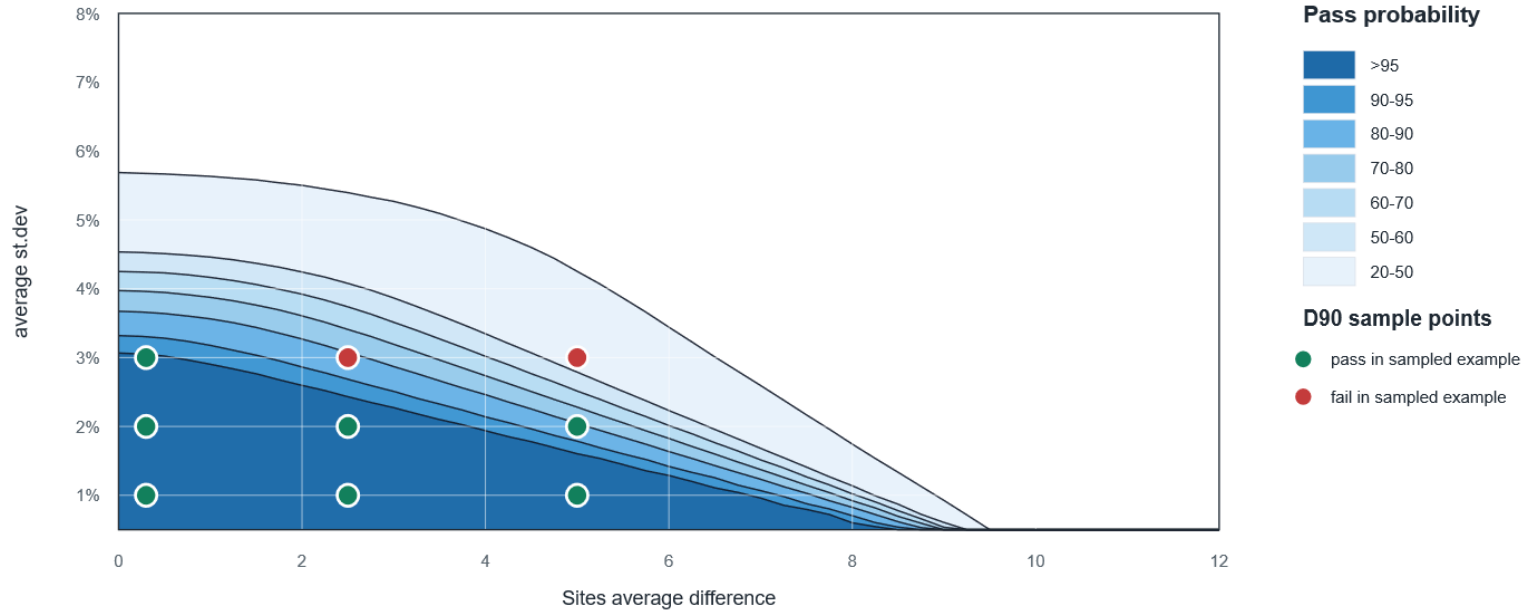
Application on synthetic data: D90

D90 synthetic scenario with reference mean 100 nm: guidance RSDmax is 15%



Power analysis

Colored points show the D90 example conditions, while background shows TOST pass-probability regions



Doing now what patients need next