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TITLE: Statistically Derived MAD for TOST: A Combined Accuracy and Precision Approach for PSD Co-validation Studies

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ABSTRACT: Within the Synthetic Molecules (SM) drug development process, robust methods to evaluate Particle Size Distribution (PSD) for drug substances are essential. When manufacturing occurs across multiple sites, these analytical methods must be transferred effectively.
The Two One-Sided t-Test (TOST) is the standard statistical framework for assessing site-to-site comparability. However, its application requires a Maximum Allowable Distance (MAD) to be predefined and justified. While available guidance documents provide clear limits for repeatability, specific thresholds for site-to-site comparison are lacking. Consequently, a MAD is typically established based on expert judgment, which can be difficult to defend during regulatory review.
We propose a novel methodology for deriving statistically justifiable MAD values by leveraging the Combined Accuracy and Precision (CAP) framework from ICH Q2(R2). The CAP approach evaluates the joint contributions of accuracy and precision to the total variability of a quantity of interest, defined here as the 90% confidence interval of the difference between site means.
Our approach reverses the CAP logic: starting from the regulatory bound on method repeatability, we partition the accuracy and precision contributions to total variability. By subtracting the reference site's method precision, this process allows derives an acceptance limit for the site-to-site difference of means. This value is subsequently utilized as the MAD for the TOST, ensuring the MAD is directly linked to the established regulatory acceptance criteria for repeatability.
We demonstrate an application of this technique using synthetic datasets to illustrate its performance and limitations across various scenarios. Finally, we provide a comparative analysis of this approach against other methods commonly employed by analytical scientists to assess site-to-site comparability.

BRIEF SPEAKER BIO: Michele Firmo is a Statistician within the PTE Statistics and Data Science group at Roche, where he specializes in providing statistical support for the process development and optimization of Synthetic Molecules. He previously held a similar role at Lonza, focusing on statistical applications for Large Molecules development.
Michele holds an MSc in Mathematics from the Università Cattolica del Sacro Cuore (IT) and a PhD in Applied Statistics from the University of Bath (UK).