TITLE: Comparability with Statistical Rigor in Manufacturing Development

AUTHOR: Bill Pikounis *-J&J*

ABSTRACT:

Demonstrating that new manufacturing sites for capacity, new measurement analytic methods, and other changes are sufficiently comparable to existing sites, methods, and product, respectively, is a critical business need for therapies. In July 2023 the FDA released a first draft version of "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" to solidify communications between manufacturers and regulatory officials, and to help build mutually agreeable manufacturing quality frameworks for the frontier modalities of cell and gene medicines. The guidance includes a substantial statistics section that includes the phrase "we recommend that you consult with a statistician" for design and analysis of comparability studies.

Design and analysis approaches acceptable to health authorities for manufacturing comparability are analogous to long-established concepts of equivalence and cross-validation in clinical development. In recent sponsor-health authority review periods, requirements independently arose for more rigorous assessment of comparability of manufacturing scale changes in cell therapy components. Because of limited sample sizes previously approved in protocols, "comparability equivalence margins" (CEM) were requested to be determined for statistical assessment with 90% Confidence Intervals, akin to standard two one-sided (TOST) procedures. Collecting new data to increase the sample size and statistical assurance to justify comparability was not a feasible option under timelines. Solution-oriented negotiations led to the novel use of commercial retest data, and a proposed strategy based on Bayesian models was developed to approximate pre-change reference distributions to determine CEMs retrospectively and carryout formal equivalence testing without collecting new data. This strategy was accepted.