

be unique to biosimilar development requirement since scale change can significantly alter the product characteristics. The 505(j) or 505(b)(2) applicants may choose a smaller scale for the development, and this choice is not available to biosimilar developers, notwithstanding any justified scaling that is fully justifiable. To comply with this requirement, the to-be-commercial process should lot at representative scale and will have same unit operations and critical raw materials used for toxicology, clinical, and commercial lots; the site of manufacturing should be the same as used for the clinical lots, and analytical data are accumulated for similarity assessment over development life cycle.

Much vagueness exists in the literature regarding the method of demonstrating analytical similarity; it is not a one-time side-by-side testing of the reference product and the biosimilar product using a limited number of obvious tests. It involves accumulating knowledge of reference products of different ages on the market to understand the range and the variability of the originator manufacturing process. Knowledge about any comparability protocols conducted by the originator is very useful in understanding the nature of these processes. Know that the FDA and the EMA allow manufacturers to change their process including change of host cells, change of manufacturing sites, and change in specification and purity profiles over the life of the product. In the United States, this is called, *comparability protocol*. This is allowed because the manufacturer has an in-depth and keen understanding of the product and the process, an experience that the biosimilar product developer is missing.

The specification of what constitutes similarity is established ahead of the analytical testing exercise. Results for each attribute are evaluated against its predefined similarity assessment criteria, and the predefined similarity evaluation criteria are established based on two general approaches:

- Nonstatistically derived similarity evaluation criteria: Similarity is met when all test lots meet the predefined evaluation criteria established based on knowledge of reference products and instrument and assay capabilities.
- Statistically derived similarity assessment criteria: Similarity is assessed using statistical equivalence testing when the data are deemed best evaluated by comparing differences in the means between the two products.

Any attribute failing the similarity criteria should be subjected to impact assessment using a risk-based approach. Confidence in analytical similarity can be built upon increasing rigor and objectivity that may lead to following outcomes:

- Extensive analytical testing shows that CQAs fail to meet similarity criteria and are likely to impact safety and efficacy. In such case, apply impact assessment for all analytical differences based on the magnitude of the difference and the