

in the case of adalimumab. However, the FDA may require matching attributes that may not appear clinically meaningful. For most of the product-related components, where these match the originator, the discussion is not needed but if process-related impurities are found that are not present in the originator product, these may be clinically meaningful and will likely require complete identification and toxicology evaluation in some instances. The developer can make a good case by analyzing a large number of originator lots to avoid getting caught with observations that might be clinically meaningful.

2.2.5.9 Fingerprint-like similarity

The FDA has established four tiers of biosimilarity assessment: not similar, similar, highly similar, and fingerprint-like similar. The minimum entry level to be a biosimilar is highly similar, a vocabulary that is now also used by EMA. However, it is possible to develop fingerprint-like similarity that will further reduce the burden of proof on the sponsor to conduct any phase III trials. While the FDA has not provided specific guidance on what would constitute a fingerprint-like similarity, the scientific view of this assessment is known. Generally, a comparison of HOS using such standard techniques as ultraviolet, fluorescence, circular dichroism, Fourier transform infrared spectroscopy, size-exclusion chromatography, static and dynamic light scatterings, differential scanning calorimetry, area under the curve (AUC), and other similar techniques will not be considered providing fingerprint-like similarity assessment. While these techniques might provide sufficient characterization of the HOS, variability in the HOS as it might happen during use is not made evident by these techniques. There are two ways of escalating the evaluation. One is by using an orthogonal approach where the HOS is modified through thermodynamic stress applied to induce a change and then studied if similar changes take place in the originator and the biosimilar candidate product. Some of the stresses recommended include pH, ionic strength, temperature, agitation, freezing/thawing, concentration change, variations in surfactants, use of columbic forces, and magnetic field. All of these are proposed by the author and is a subject of several pending U.S. patents (e.g., United States Patent and Trademark Office Application No. 20140356968; inventor, Niazi).

Another approach to establishing fingerprint-like similarity involves using biophysical tools that can provide information with much higher spatial and temporal resolutions. Examples include hydrogen/deuterium exchange mass spectrometry, small-angle x-ray scattering, and nuclear magnetic resonance. The higher resolution of current instrumentation continues to make existing instruments more valuable. A good example is the increased sensitivity of mass spectrometry by a million times over the past decade; the higher utility of AUC using the program SEDFIT is another good example of improved instrumentation; the use of Orbitrap mass spectrometry further exemplifies the kind of studies that might qualify a biosimilar product to be labeled as fingerprint-like similar.