

an attribute and the performance of the drug product (see ICH Q8 (R2)) suitable attributes (e.g., potency).

An extensive analytical characterization may also reveal differences between the reference product and the proposed product, especially when using analytical techniques capable of discriminating qualitative or quantitative differences in product attributes. Emphasis should be placed on developing orthogonal quantitative methods to distinguish any differences in product attributes. Based on the results of analytical studies assessing functional and physicochemical characteristics, including, for example, HOS, PTMs, and impurity and degradation profiles, the sponsor may have an appropriate scientific basis for a selective and targeted approach to subsequent animal and/or clinical studies to support a demonstration of biosimilarity. It may be useful to compare differences in the quality attributes of the proposed product with those of the reference product using a meaningful fingerprint-like analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods. Enhanced approaches in manufacturing science, as discussed in ICH Q8(R2), may facilitate production processes that can better match a reference product's fingerprint. Such a strategy could further quantify the overall similarity between two molecules and may lead to additional bases for a more selective and targeted approach to subsequent animal and/or clinical studies.

The type, the nature, and the extent of any differences between the proposed product and the reference product, introduced by design or observed from the comprehensive analytical characterization of multiple manufacturing lots, should be clearly described and discussed. The discussion should include identification and comparison of relevant quality attributes from product characterization, as this is an important factor in assessing whether the proposed product is highly similar to the reference product. The potential clinical effects of observed structural and functional differences between the two products should be evaluated and supported by animal or clinical studies, if necessary.

The type and the extent of animal or clinical studies that are needed to demonstrate biosimilarity of the proposed product can be influenced by several factors, especially the ability to discern differences between the proposed product and the reference product and their potential effect on safety, purity, and potency. For example, factors such as the ability to robustly characterize the proposed product or the reference product (e.g., lack of suitable or sufficiently discriminative analytical techniques) or the availability of a relevant drug substance derived from the reference product could affect the nature and the extent of subsequent animal or clinical studies.

In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. Under certain circumstances, a sponsor may use