

9.2 Reference and biosimilar products

The FDA recommends that the analytical similarity evaluation begin with an understanding of the structural/physicochemical and functional attributes of the reference product. Based on information obtained about these attributes during development of the proposed biosimilar, the sponsor should develop an analytical similarity assessment plan (see Section 9.3.1). A key component of this plan is the description of lots available for similarity testing. The following factors should be considered when selecting lots to be used in the analytical similarity assessment:

- *Number of reference product lots*—To establish meaningful similarity acceptance criteria, sponsors should acquire a sufficient number of reference product lots. We recommend a minimum of 10 reference product lots be sampled. In cases where limited numbers of reference product lots are available (e.g., for certain orphan drugs), alternate analytical similarity assessments should be proposed and discussed with the FDA.
- *Number of biosimilar product lots*—To allow for meaningful comparisons, the FDA recommends a minimum of 10 biosimilar lots be included in the analytical similarity assessment.
- *Variability in reference product lots*—The reference product lots selected should represent the variability of the reference product. Lots with remaining expiry spanning the reference product shelf life should be selected. The date of the analytical testing as well as the product expiration date should be provided in the application. Expired reference product should not be included in the similarity assessment to avoid bias.
- *Accounting for reference product and biosimilar product lots*—Sponsors should account for all of the reference product lots available to them. A list should be provided in the application of all lots that were evaluated in any manner even if a particular lot was not used in the final similarity assessment. The list should include the disposition of each lot and the specific physicochemical, functional, animal, and clinical studies for which a lot was used. When a lot is specifically selected to be included in or excluded from certain studies, a justification should be provided. Similar information on every manufactured drug substance and drug product lot of the proposed biosimilar product should also be provided.
- *U.S.-licensed reference product and other comparators*—The analytical similarity acceptance criteria should be derived using data from an analysis of the U.S.-licensed reference product, and the similarity assessment should be based on a direct comparison of the proposed biosimilar product to the U.S.-licensed reference product. As a scientific matter, combining data from the U.S.-licensed reference product and comparator products approved outside of the United States to determine