

comparator product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed comparator product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. The complexity of the products, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. Additional factors that the FDA may consider regarding the extent of bridging data include, but are not limited to, the following:

- Whether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same;
- The route of administration of the U.S.-licensed reference product and non-U.S.-licensed comparator products;
- The design of the physicochemical and biological/functional assessments and the use of multiple orthogonal methods with adequate sensitivity to detect differences among the products;
- The scientific justification for the selection of the non-U.S.-licensed comparator lots used to establish the scientific bridge and how the selected lots relate to the material used in the nonclinical and clinical studies. The scientific bridge should include a sufficient number of lots of non-U.S.-licensed comparator product to capture adequately the variability in product quality attributes. When possible, the non-U.S.-licensed comparator lots used in the nonclinical or clinical studies should be included in the assessment performed to establish the analytical bridge.

Sponsors are encouraged to discuss with the FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by the FDA during the review of the 351(k) application.

At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

*Q. 1.9:* Is a clinical study to assess the potential of the biological product to delay cardiac repolarization (a QT/QTc study) or a