strength, the quality, the purity, or the potency of the product as it relates to the safety or the effectiveness of the product.

Demonstrating that a proposed product is biosimilar to a reference product will be more complex than assessing the comparability of a product before and after the manufacturing changes made by the same manufacturer. This is because a manufacturer that modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. By contrast, the manufacturer of a proposed product is likely to have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, the FDA anticipates that more data and information will be needed to establish biosimilarity than would be necessary to establish that a manufacturer's postmanufacturing change product is comparable to the premanufacturing change product.

3.4.3 U.S.-licensed reference product and other comparators

The licensing of a proposed product under Section 351(k) of the PHSA requires that the sponsor demonstrate that the proposed product is biosimilar to a single reference product that has been previously licensed by FDA. In general, a sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. As a scientific matter, analytical studies and at least one clinical PK study and, if appropriate, at least one PD study intended to support a demonstration of biosimilarity for purposes of Section 351(k) of the PHSA must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed. However, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed comparator product to address, in part, the requirements of Section 351(k)(2)(A) of the PHSA. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. Sponsors are encouraged to discuss with the FDA during the development program their plans to provide an adequate scientific justification and a bridge to the U.S.-licensed reference product. A final decision on the adequacy of such justification and bridge will be made by the FDA during the review of the 351(k) application.