3.6.2 Scope

The scientific advice from the FDA heavily dwells on analytical studies that are relevant to assessing whether the proposed product and a reference product are highly similar to support a demonstration of biosimilarity. Although the FDA guidance specifically applies to therapeutic protein products, the general scientific principles may be informative for the development of other protein products, such as in vivo protein diagnostic products. If the reference product or the proposed product cannot be adequately characterized with state-of-the-art technology as recommended by this guidance, the application may not be appropriate for submission under Section 351(k) of the PHSA. The FDA recommends that the sponsor consult the FDA for guidance on the proper submission pathway.

The FDA provides detailed guidance for additional chemistry, manufacturing, and controls (CMC) information that are relevant to assessing whether the proposed product and the reference product are highly similar. All product applications should contain a complete and thorough CMC section that provides the necessary and appropriate information (e.g., characterization, adventitious agent safety, process controls, and specifications) for the product to be adequately reviewed. The FDA encourages early interactions to discuss specific CMC issues that may arise for a sponsor's proposed product. For CMC requirements for submission of a marketing application, sponsors should consult current regulations and see the guidance for industry *Submission on Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA–Derived Product or a Monoclonal Antibody Product for In-Vivo Use*, as well as other applicable FDA guidance documents.

The use of the terms *product-related substances* and *product-* and *process-related impurities* is consistent with their use and meaning in the ICH guidance for industry Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

In addition to comparative analytical studies, an assessment of whether a proposed product is biosimilar to a reference product will include animal studies (including the assessment of toxicity) and a clinical study or studies (including the assessment of immunogenicity and PK and/or PD).

3.6.3 General principles

Advances in analytical sciences (both physicochemical and biological) enable some protein products to be extensively characterized in terms of their physicochemical and biological properties. These analytical procedures have improved the ability to identify and characterize not only the desired product but also the product-related substances and the product- and process-related impurities. Advances in manufacturing science and production methods, as well as advances in analytical