products in terms of safety, purity, and potency. In this example, because some excipients may affect the ability to characterize products, a sponsor should provide evidence that the excipients used in the reference product will not affect the capacity to characterize and compare the products.

Clinically meaningful differences could include a difference in the expected range of safety, purity, or potency of the proposed product and the reference product. By contrast, slight differences in rates of occurrence of certain adverse events between the two products would ordinarily not be considered clinically meaningful differences.

3.4.5 Demonstrating biosimilarity

This section discusses scientific considerations in the stepwise approach to developing data and information needed to support a demonstration of biosimilarity. To demonstrate biosimilarity, a sponsor must provide sufficient data and information to show that the proposed product and the reference product are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency. The type and the amount of analyses and testings that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

3.4.5.1 Structural analyses The PHSA requires that a 351(k) application include information demonstrating biosimilarity based on data derived from, among other things, analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, unless the FDA determines that an element is unnecessary in a 351(k) application. The FDA expects that, first, a sponsor will extensively characterize the proposed product and the reference product with state-of-the-art technology because the extensive characterization of both products serves as the foundation for a demonstration of biosimilarity. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications such as N- or C-terminal truncations that are not expected to change the product performance may be justified and should be explained by the sponsor. Additionally, sponsors should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structures; PTMs; and biological activities) to demonstrate that the proposed product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. The more comprehensive and robust the comparative structural and functional characterizations are, the stronger the scientific justification for a selective and targeted approach to animal and/or clinical testing.