Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the product (i.e., no species in which the biologic activity of the product mimics the human response). For a detailed discussion about demonstrating species relevance, see the criteria described in ICH S6(R1). However, there may be some instances when animal data from a pharmacologically nonresponsive species (including rodents) may be useful to support clinical studies with a proposed product that has not been previously tested in human subjects, for example, comparative PK and systemic tolerability studies. If animal toxicity studies are not warranted based on an acceptable scientific justification, additional comparative in vitro testing (using human cells or tissues when appropriate) is encouraged. Data derived using human cells can provide valuable comparative information between the proposed product and the reference product regarding potential clinical effects, particularly in situations where there are no animal species available for safety testing.

In general, nonclinical safety pharmacology, reproductive and developmental toxicities, and carcinogenicity studies are not warranted when the proposed product and the reference product have been demonstrated to be highly similar through extensive structural and functional characterizations and animal toxicity studies (if such studies were conducted).

3.4.5.3.2 Inclusion of animal PK and PD measures Under certain circumstances, a single-dose study in animals comparing the proposed product and the reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity. Specifically, sponsors can use results from animal studies to support the degree of similarity based on the PK and PD profiles of the proposed product and the reference product. PK and PD measures can also be incorporated into a single animal toxicity study, where appropriate. Animal PK and PD assessments will not negate the need for human PK and PD studies.

3.4.5.3.3 Interpreting animal immunogenicity results Animal immunogenicity assessments are conducted to assist in the interpretation of the animal study results and generally do not predict potential immune responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, a measurement of antitherapeutic protein antibody responses in animals may provide useful information. Additionally, differences observed in animal immunogenicity assessments may reflect potential structural or functional differences between the two products not captured by other analytical methods.

3.4.5.4 Clinical studies—General considerations The sponsor of a proposed product must include in its submission to the FDA information