No specific ICH guideline covers biosimilars. However, a more global consideration of the 3Rs principles where the nonclinical development of biosimilars is concerned would be welcomed. However, there is currently no plan for development of an ICH guideline on biosimilars.

6.8 FREQUENT CONCERNS WITH RESPECT TO OMITTING *IN VIVO* STUDIES

In the publication by van Aerts et al. (2014), the regulatory strategy that helped to shape the new guidance to favor a risk-based approach that could lead to biosimilars entering the clinic without conducting any animal study is explained in detail. We refer to this publication for an explanation of the strategy, substantiated with numerous case examples. The following paragraphs review the most essential elements with respect to the frequent concerns to omitting *in vivo* studies.

6.8.1 Need to Establish Biological Activity in IU in Pharmacopoeial *In Vivo* Bioassays

Pharmacopoeial bioassays with potency determination in animals exist for some biologicals. Such assays are employed to express the biological activity of the product in international units (IUs). However, there may be considerable variability in these *in vivo* assays, which limits their use in a comparability exercise (Mulders et al., 1999; Zimmermann et al., 2011). Therefore, the results are not expected to contribute significantly to establishing biosimilarity.

For poorly characterized products where the active substance is extracted from a biological matrix, this approach to express biological activity in IU based on *in vivo* potency appears sensible, but these products may not be developed as biosimilars.

Whereas, for well-characterized products such as recombinant proteins, *in vitro* alternatives to the pharmacopoeial *in vivo* assays may be available, and the biological activity expressed in µg comparing the biosimilar and the reference product based on *in vitro* assays could be employed.

6.8.2 Establish Pharmacokinetics before Administration to Humans

Quality attributes, such as the presence of the binding target, whether this target is soluble or not, and the mechanism of clearance (e.g., receptor-complex mediated or not) may affect the PK behavior of a biological. In the case of mAbs, PK properties are also mediated by Fc-dependent mechanisms, and differences in glycosylation patterns of an mAb may influence Fc receptor binding. Although several functional aspects of the impact of a difference in glycosylation can be evaluated *in vitro* (as discussed in the paragraph in this chapter on product-related differences), the PK behavior cannot be covered by *in vitro* methods. However, comparative PK assessment in animals would require large numbers of animals, and both immunogenicity issues and species differences may limit the relevance of animal data with regard to PK in humans.