need for animal studies in these cases. See the discussion in the paragraph above on the pharmacokinetics for cases where a nonclinical *in vivo* study would be justified to compare the PK behavior of biosimilar and reference product in animals first. Also, if excipients are introduced for which there is no or little experience with the intended clinical route of administration, local tolerance may need to be evaluated. If other *in vivo* studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies (EMA, 2015a).

When the formulation includes a completely new excipient, or when the intended route of administration is new for a known excipient, additional nonclinical data are needed in accordance with relevant guidance. In case insufficient information is available, toxicology studies may also be required (van Aerts et al., 2014).

6.8.4 Unexpected Toxicity

The value of extensive use of nonhuman primates in routine safety studies of mAbs has been questioned, as the toxicity of these products is characterized as usually related to on-target effects, so-called exaggerated pharmacology (van Meer et al., 2013). Most adverse events related to biologicals in general are linked to exaggerated pharmacology. For biosimilars, exaggerated pharmacology is a predictable type of toxicity that the innovator has established for the reference product. When the *in vitro* pharmacological activity of the biosimilar has been shown to be comparable, there is no need to confirm these properties in a less sensitive animal model. Moreover, given the clinical experience with the reference product, the clinical relevance of exaggerated pharmacology observed in animals is already known.

Another type of adverse event is one that is not related pharmacologically and in which variable terminology is used, such as unexpected toxicity, off-target toxicity, and nonspecific toxicity. As specified in ICH S6, this type of toxicity needs to be investigated for new biologicals. In rare cases, unexpected toxicity may be encountered in animal studies during the development of new biologicals. For biosimilars, however, off-target toxicity may be regarded as a predictable type of toxicity, since this has already been established for the reference product.

Nevertheless, some concern has been voiced about whether new off-target toxicities that have not been observed with the reference product could occur with a biosimilar. In the EMA workshop discussions on biosimilar development, no examples of off-target toxicity of biosimilars were presented in the EMA mAbs workshop (EMA, 2011). In addition, unexpected toxicity by postchange products was discussed, and it was stated that following changes to the production process of an already marketed biological, unexpected toxicity was never encountered in animal studies. The examples of unexpected toxicity presented were scarce and concerned rather new biologicals that were still in development (EMA, 2011). The well-known case of pure red cell aplasia (PRCA) following the use of inferior erythropoietin is often mentioned in connection with the biosimilar discussion. As explained later in this chapter, this example is not a reason to perform additional *in vivo* studies.