6.8.8 Lack of Full Analytical Characterization at the Start of the First in Human Clinical Trial

In vivo animal studies are sometimes performed to cover safety issues due to lack of appropriate analytical comparability data. Since fast development is key in many pharmaceutical companies, animal studies may be performed in order not to delay the start of clinical development. *In vivo* animal studies are sometimes used to reassure clinical investigators of the safety of the product. This may occur when the analytical comparability has not yet been performed, as ideally should be done to adequately characterize possible differences between both molecules and with a sufficient number of batches to enable a conclusion on safety from *in vitro* data alone. This "comfort factor" from first exposing animals before dosing humans is not based on a scientifically sound rationale and may even be misleading.

Even when the provided *in vitro* package of comparability data is considered appropriate by some regulators, it may be challenging for others or for clinical investigators or ethics committees to approve the start of biosimilar clinical trials in the absence of *in vivo* data. This could occur when dose escalation in the clinic is not possible (e.g., for biosimilars used in oncology where studies in healthy volunteers are not possible). In such cases, a direct dosing at the therapeutic dose in patients is needed, since an inefficient dose would ethically not be acceptable. To avoid program delays in these cases, companies may perform *in vivo* studies before submitting the clinical trial application to the different national competent authorities. However, when analytical and *in vitro* data do not raise concerns, additional *in vivo* animal studies are not considered needed.

6.9 CURRENT PRACTICE

The provided *in vitro* package in a nonclinical dossier for submission of a marketing authorization can be variable, depending on the complexity of the molecule. This information is publicly available in the European Public Assessment Reports (EPARs) published on the EMA website (EPARs of EMA). In this section, we describe the nonclinical study programs of the approved marketing authorization applications of all biosimilar products registered in the EU until October 1, 2015, which includes the nonclinical study programs of twelve different biosimilar molecules. The *in vitro* results are summarized in Table 6.3.

The nonclinical study programs of the approved, rejected, and withdrawn EU biosimilars up to October 1, 2013, have also been recently reviewed by van Meer et al. (2015a).

For the very first biosimilars that were approved in Europe, the two somatropin biosimilars, *in vitro* comparability assays were not performed. However, these products were developed before the legal framework for biosimilars existed in Europe. A year later two different erythropoietin biosimilar molecules were approved in the EU; here, *in vitro* comparability assays were included, consisting of receptor binding and biological activity assessment. Also, the *in vitro* studies to support filgrastim developments included a bioassay and a receptor binding assay for the four different filgrastim biosimilar developments.