in equivalence tests, a smaller sample size and/or more variance in the collected data will lessen the chance of demonstrating similarity.

5.2.2.5 Pharmaceutical Development

As set out above, the concepts of critical quality attributes (CQAs) or QTPP exposed in ICH Q8(R2) *Pharmaceutical Development* (ICH, 2009) appear to be valuable tools for identifying the meaningful target acceptance criteria for biosimilars. Likewise, the risk management principles described in ICH Q9 *Quality Risk Management* may help define comparability criteria and assist in the evaluation and management of inevitable differences between the biosimilar and its reference (ICH, 2005b; Schiestl, 2009). However, it is generally recognized that the design space largely depends on a particular manufacturing process. ICH Q8 and ICH Q9 are applicable to biosimilars but primarily for their own development in the same way as for the originators (Kresse, 2009).

5.2.2.6 Specifications

As mentioned in guidelines (ICH, 1999; WHO, 2013), specifications are not aimed at fully characterizing the drug substance and the drug product but, instead at verifying their routine quality and consistency. Biosimilars do not differ from other medicinal products in this regard. Where applicable, their specification and limits are required to comply with pharmacopoeial prescriptions. Having said that, we find that compliance with compendial standards is generally regarded as a minimum set of requirements, additional test parameters being usually required.

As for any biotechnological and biological products, the establishment of specifications for biosimilars is guided by the principles laid down in ICH Q6B (ICH, 1999). In line with these principles, the establishment of a specification is a global process and is not simply based on the range of the quality attributes of the reference but instead on the manufacturer's experience on a sufficient number of lots and upon a full data package, encompassing manufacturing process, analytical procedure, stability, characterization, and preclinical and clinical studies.

As mentioned earlier, the manufacturing processes of a biosimilar and its reference are different. Accordingly, a number of tests and acceptance criteria will be customized for a given biosimilar and established on their own, without referring to the originator. This is typically the case for specifications addressing the manufacturing process consistency and its control (e.g., uniformity of dosage units, residual humidity, visible and subvisible particles) or the process-related impurities (e.g., Host Cell Proteins, residual DNA, media component).

Analytical procedures are also developed and validated by the manufacturer of the biosimilar, regardless of the methods used by the reference manufacturer.

In contrast, the stability studies needed to set up the specification are to be conducted on the biosimilar but not independently from the reference. For instance, it makes sense to conduct accelerated and stress stability studies in parallel on both the biosimilar and its reference in order to establish their degradation profiles which, in turn, will reverberate on the specifications.

Similarly, the characterization of the biosimilar, since it is closely related to the comparability exercise, is not an exercise conducted independently from the