4.13.3 Testing limits

In the side-by-side testing conducted, each test run includes a set of originator calibrators, a set (five levels including lower limit of quantification [LLOQ] and upper limit of quantification [ULOQ]) of originator quality control (QC) samples, a set of biosimilar calibrators, and a set (five levels including LLOQ and ULOQ) of biosimilar QC samples. The calibrators and the QCs for the originator and the biosimilar should first be evaluated separately. Each set of calibrators and their corresponding QCs should meet the predefined acceptance criteria. Once these predefined criteria have been fulfilled, the equivalency between the originator and the biosimilar can then be evaluated. More specifically, these are considered equivalent if the following conditions are met:

- The biosimilar QCs meet predefined acceptance criteria (e.g., ±20% bias [25% bias at LLOQ]) when evaluated against the originator calibration curve.
- The originator QCs meet predefined acceptance criteria (e.g., ±20% bias [25% bias at LLOQ]) when evaluated against the biosimilar calibration curve.
- The percentage difference from the mean between the originator QCs and the biosimilar QCs do not exceed ±20% (25% at LLOQ).

In addition, any trend in bias between the originator and the biosimilar should also be evaluated. The originator and the biosimilar may be considered equivalent if no significant bias or trend is detected. This will indicate that both are equally immunoreactive toward the assay reagents. The equivalency should be established during the initial phases of the method development, prior to evaluating other assay parameters (e.g., selectivity, dilutional linearity, and matrix effect).

If biological similarity cannot be established, two assays may be used: one for the measurement of an originator and one for a biosimilar, with appropriate scientific justification. In this case, all samples should be run in both assays. Robust statistical measures should be developed for meaningful comparison of data from two assays. Data interpretation and acceptance criteria will need to be addressed and documented prior to the sample analysis.

4.13.4 Impact of ADA on PK assessment

It is possible that the presence of ADA can have an effect on the PK evaluation. A further complicating factor is separating the effects of normal assay variability from ADA interference. Several factors should be kept in mind during the PK assay development and during the PK sample analysis.

For the PK method development, it is essential to understand the characteristics of the reagents used. For example, if the capture reagent used is the