In reporting other attributes like bioassay as Tier 1, a different number of lots were used as reported in the Briefing Document, to analyze protein content, indicating that not all tests were conducted on the same lots. This is against the suggestions by the FDA that all similarity testing be done on all lots. This may be a subject of discussion with the FDA. One reason why a different number of lots for different tests may be admissible may have to do with the degree of variability in the test method and assays used. Generally, the FDA will want you to increase the number of test lots or improve the method of analysis where variation is high.

9.8.29 Combining lots

Biosimilar developer conducts several biosimilarity studies at different stages and accordingly conducts analytical and functional similarity testing. Can these lots be combined to provide a composite description instead of one study?

As reported by the FDA in its Briefing Report, data from different studies can be combined to produce the acceptance criteria and for testing as long as there is a bridging evidence between the sets of lots that were tested separately. The argument provided by the FDA is based on philosophical syllogism and goes as follows. If A=B, and B=C, then C must be equal to A. The EP2006 commercial was similar to EP2006 clinical, which was similar to both U.S. and EU Neupogen. Therefore, EP2006 must be highly similar to U.S. and EU Neupogen. However, the FDA may be changing its mind on this. It is not sure if this is the current expectation of the FDA. However, the FDA may change its mind as more data become available, so, to improve the power of testing, the developer may offer data with combined study lots.

9.8.30 Release criteria

One question that resonates in the mind of biosimilar developers relates to the importance of release testing. It is likely that a developer would use a different set of testing to establish analytical similarity than that used for release purpose, though inevitably some tests will overlap. However, the release criteria may not be used to establish analytical similarity since these ranges may be based on generally analytical standards; for example, it would be admissible to have a 10% variability in the content of drug for release purpose, but for similarity purpose, the developer must demonstrate the similarity with the variability in the reference product, lot to lot. That number may be significantly lower than 10%, so while all lots of a biosimilar product may pass release criteria, they may fail in analytical similarity testing.