9.8.18 Nonparametric

A nonparametric tolerance interval is available if data do *not* follow the normal distribution, but the large sample size is generally required.

9.8.19 Random lots

The FDA suggests that one sample is selected randomly from each lot for both the reference and the test. The fact is that the developer may not have the luxury of securing a sufficient number of originator lots to randomize the selection; the same may hold true for the test lots. Several publications have criticized that the differences between lots and heterogeneity among lots are major challenges to the validity of the FDA's proposed approaches for both equivalence testing for CQAs in Tier 1 and the concept of quality range CQAs from Tier 2. This is not entirely correct since released lots are supposed to have homogeneity, a concept that may be alien to many researchers who have criticized this approach. The FDA expects the lots of reference product used for establishing the acceptance criteria be selected on a random basis. Given the limited number of reference lots available to the developer, how does one assure this randomness? Also, how is the selection of the number of samples tested related to the confidence level used in a Tier 1 test?

In practice, it may be a challenge when there are a limited number of lots available. Thus, the FDA suggests the sponsor providing a plan for how the reference variability σ_R will be estimated with a justification. The developer may start with a larger number of lots of reference product and randomly select the desired number that will have to be justified on the basis of the power (probability of confidence interval within the limits).

9.8.20 Number of lots

The number of selected lots tested side by side will depend on three factors:

- *The power of testing accepted*; Figure 9.13 provides a correlation curve between power, confidence level, and the number of lots. Generally, like the bioequivalence testing, an 80% (0.80) power will be accepted.
- *Confidence level*; generally it is taken to be 5% giving a CL of 0.90, but the FDA has allowed testing at 0.814 and 0.852.
- *Standard deviation*; large standard deviations can be reduced either by increasing the number of lots or adjusting the analytical methods that are less variable.

With sample size ranging from 3 to 12 and with confidence level (CL) set to 0.814, 0.852, and 0.9, the probability (confidence interval within limits) (Power) will be ranging from 0.10596 to 0.97097 when testing