

Recommendations & Rationale

A. General Recommendations:

It is recommended that determination of equivalence criteria includes consideration of the number of reference batches available, the statistical distribution and the confidence that data are representative of the process:

Figure:

Tabulated and/or graphical analyses are suggested to review larger sets of data points. Example D shows a tabulated comparison. Trends can be visualized graphically and related to regulatory, alert or proposed specifications.

Appropriate statistical hypothesis/tests of equivalence (e.g. interval hypothesis or equivalency test-Reference) with confidence intervals may be used. Consulting a statistical expert may be useful. See Example E.

B. Selection of reference batches:

1. New Products (i.e. new drug product at first commercial manufacturing site)

The most recent reference batches made by the same process are recommended from the following sources:

- Plant batches (Qualification, Pre-Validation or Scale-up batches), and/or
- R&D batches supporting regulatory submission (Stability, Biobatch or pivotal Phase III clinical batch(es))

In example B in the Appendix, two new submission batches were selected for the comparison to three validation batches. In this particular case, high process capability had been shown.

Typically, a larger number of reference batches are recommended for statistical purposes, if they are available. If available, data from at least 10 lots usually provide enough data to perform statistical analysis with a high degree of confidence. Potential reference batches may be excluded if deviations or failures are shown by root cause investigation to not be representative of normal processing. These exclusions should be explained with rationales that include why the batches are not representative of normal processing.

2. Existing Drug Products

a. Site Transfers (e.g. Site A to Site B)

For manufacturing site transfers, the reference batches could be selected from those prepared at the originating (sending) site (e.g. Commercial, Validation).

Consecutive reference batches are suggested for reference data from the sending site provided the same process without major changes has been used. Alternatively, original regulatory