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:

Comparison data	Recommended equivalence criteria
• Fewer than ten historical reference batches, or; • Reference data may not be representative of current process capability, or; • The quantitative reference data do not exhibit a symmetrical distribution.	Results meet registered specifications
Ten or more reference batches with a non-Gaussian distribution of quantitative data, but there is confidence that the data are representative of current process capability	Results meet specifications and are within historical ranges (minimum and maximum values)
Ten or more reference batches with a normal (Gaussian) distribution of data, and there is confidence that the data are representative of current process capability.	Results meet specifications and are within the statistical limit (mean +/- three standard deviations) when compared to reference data

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:

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.

- The historical reference batches should be predetermined and included or referenced in the validation protocol. Reference batches are usually the most recent (e.g. last 30 production batches). A link to original clinical batches is typically unnecessary if it is existing product that has already been validated. One does not need to repeat information in other documents such as regulatory submissions, Technology Transfer, Change Control or other Comparability or Equivalency studies. These studies can simply be referenced in the protocol.

- There are critical quality attributes (e.g. impurities) which often have relatively small values. These may result in a variance of less than 1. In these cases, an F-test (ratio of variances) may be significant in a statistical sense, but not in a practical sense. Therefore, in these cases, the data should be reviewed for practical significance.

C. Type of Data for Comparison, from common dosage forms:

1. Results from routine analytical release testing should be examined when performing the equivalence comparison. Results from testing of the validation batches will be compared to historical results obtained using the same analytical methods. A change in an assay method thus requires careful consideration, unless it has already been shown to give equivalent results to the earlier method.

2. Select tests that provide quantitative results. Tests that provide qualitative results ("Meets Test", "Positive") are generally of less value to equivalence evaluations.

3. Critical Quality Attributes comparison-
Examples of potential critical quality attributes (CQAs) are shown below. Drug product attributes that are identified as critical need to be evaluated for equivalency.

- Tablets -assay, degradation impurities, dissolution, content uniformity, friability, hardness, moisture, film-coated tablets -inspection attributes.

- Capsules-assay, impurities, dissolution, weight variation, content uniformity, moisture, microbial limits. Softgels may include leakage, appearance for precipitation/cloudiness.

- Powder Blends-particle size distributions, density, API uniformity, moisture content, flowability.

- Suspensions/solutions – assay, pH, viscosity, specific gravity, sedimentation volume /redispersibility/mean particle size, preservative content, microbial content.

Example D – Example of comparison of Blend Uniformity.

Check to confirm that the validation data points and reference data are within specification ranges. For example, the individual blend uniformity data points indicate results are well within the specification range. The 3 reference batches are the 2 regulatory submission/stability batches and the 1 demonstration batch.

Batch	Mean (% assay)	Range (%)
Specification Acceptance criteria	--	*90.0- 110.0*
Regulatory submission Stability batch 1	101.2	99.4- 102.8
Regulatory submission Stability batch 2	99.6	97.8- 101.8
Demonstration batch	100.3	95.2-104.3
Validation – batch 1	102.3	99.2- 108.7
Validation – batch 2	100.3	99.5- 101.4
Validation – batch 3	101.2	99.0- 102.7

The conclusion based on the data provided is that the validation lots are equivalent to the reference batches.

Example E – Interval Hypothesis test (Equivalency test)

An existing product is transferred from site A to site B and the average in-process assay result is compared using 10 production batches at site A and 10 batches at site B. The in-process assay is a critical test according to past history as it assists in monitoring the stability of the active ingredient. .

Site	N	Average assay (mg/capsule)	Std.Dev.(S)	Variance (S^2)	*d.f.*[1]
A	10	41.5	6.2	38.44	9
B	10	47.4	7.4	54.76	9
Total	20				18

Notes: [1]*degrees of freedom (N -1) .*

Assuming the goal is to prove equivalence the appropriate test is called an interval hypothesis test (or equivalence test). Assuming equal variance, this test would have a "pooled" variance term instead of

