## Guidance Number: 020

**Figure:**

| Comparison data | Recommended equivalence criteria |
|---|---|
| • Fewer than ten historical reference batches, or;<br>• Reference data may not be representative of current process capability, or;<br>• 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 |

## APPENDIX

**Example A:** Example for Oral Tablet, 10, 20 and 40 mg, Transferred Product.

| | **Validation report Comparison** | **Comment** |
|---|---|---|
| **Selection of Reference Batches** | Validation data was compared to one full-scale "Demonstration" 10 mg Batch (prevalidation batch before validation). | The Demo Batch Report had already included comparison to 3 stability batches from the regulatory submission and Validation batches at 3 other approved commercial sites. |
| **Data compared** | • Milled Granulation particle size analysis<br>• Powder Blend particle size analysis, density, and drug uniformity.<br>• Tablet core- content uniformity and dissolution<br>• Film-Coated Tablet- content uniformity, assay, and dissolution profile. | For 20 and 40 mg tablets with common granulation, only compression and coating data were compared to specifications. |
| **Data treatment** | Data were tabulated for side-by-side visual comparison against specifications and past results. | Results were within specification. See Examples C and D. |
| **Conclusion** | Validation batches were determined to be equivalent to batches prepared at other manufacturing sites. | |

**Example B:** Example for Oral Suspension, 40 mg/mL, New Drug Product.

| | **Validation report Comparison** | **Comment** |
|---|---|---|
| **Selection of Reference Batches** | Two regulatory submission biobatches | |
| **Data compared** | • API particle size<br>• Blend – particle size distribution, blend uniformity, and specific volume (i.e. density)<br>• Filled bottle- potency, API uniformity, and dissolution profile. | Compounding process parameters (milling and blending) were compared as well as the Quality Attributes. Extensive tables of batch information generated, such as materials, parameters and settings. |
| **Data treatment** | Data were tabulated for side-by-side comparison, Current results compared against specifications and past results. | Confirmed within previous ranges, complied with specifications. |
| **Conclusion** | Validation batches were comparable to original biobatch data filed in the regulatory submission. | Batch data essentially the same. |

**Example C**- Example of comparison of critical tablet hardness.

Check to confirm that the validation data points and reference data are within specification ranges.

| Batch | Hardness Specification Range (Target) (Newtons) | Mean (Newton) |
|---|---|---|
| Prevalidation (Demo) | 60-140 (98) | 103 |
| Validation – batch 1 | 60-140 (98) | 106 |
| Validation – batch 2 | 60-140 (98) | 104 |
| Validation – batch 3 | 60-140 (98) | 108 |

The prevalidation batch is a reference batch that was compared to previous batches in the Demo report. Mean hardnesses were similar, 103 vs 106 newtons and within the specifications.

The conclusion based on the data provided is that the validation lots are equivalent to the reference (Demo) batch.

**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

separate variance estimates of site A and Site B. (Comparison of means from two-independent; Two independent groups test, Variance Unknown

The null ($H_O$) and alternate hypothesis ($H_a$) becomes: The sites differ by at least 10 percent (an arbitrary; value, known as the equivalence limit).

$H_O$: $|\mu_1 - \mu_2| > \Delta$ = equivalence limit (10%)
$H_a$: $-\Delta \leq \mu_1 - \mu_2 \leq +\Delta$

The approach involves calculating a pooled variance ($S_p$), building a confidence interval (CI) around the difference in the site averages and comparing that to the equivalence limits. If that confidence interval is contained completely within the equivalence limits (+/- 10 percent) you conclude equivalence (disproved the difference was as big as assumed). This approach forces one to define a hypothesized X value, in this case 10%, which may be quite different depending on the circumstances.

The main formula for the confidence interval is listed below (can be found in the Bolton reference pp150-156; already cited).

$S_p$ is the pooled standard deviation. T is the critical value corresponding to 90% confidence (two 1-sided alpha=0.05 tests) and $n_1 + n_2 - 2$ df.

$$S^2_p = \frac{(n_1 - 1)S^2_1 + (n_2 - 1)S^2_2}{n_2 + n_2 - 2}$$

$$S^2_p = \frac{(9)(6.2^2) + (9)(7.4^2)}{18} = 46.589$$

$$S_p = 6.826$$

$$CI = (\overline{X_1} - \overline{X_2}) \pm T * S_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

Tcrit = 1.73 (from t Distribution Table: df = 18. $\alpha$=0.10) and Sp = 6.826 $n_1$=$n_2$=10

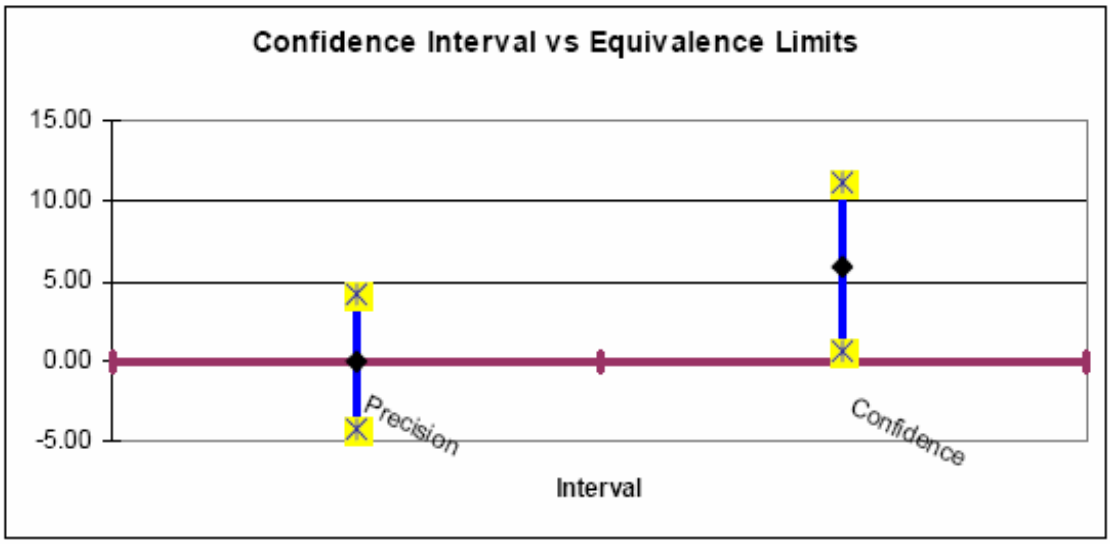
Assuming a 10% Equivalence Limit (arbitrary): 0.10 * Site A mean (sending site) = 0.10 * 41.5 = +/- 4.15; df = 10 + 10 - 2 = 18

$$CI = (41.5 - 47.4) \pm 1.73 * 6.826 \sqrt{\frac{1}{10} + \frac{1}{10}}$$

CI = 5.9 +/- 5.3 = 0.6 to 11.2

Since the confidence interval does not cover 0, the difference between the sites is significant at the 90% confidence level.

The confidence interval is partially outside equivalence limit (see plot). Equivalence has not been demonstrated.




Also note *Calculated t* can be compared to the *Critical t*

$$t.calc = (\overline{X_1} - \overline{X_2}) / S_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \qquad t = (41.5 - 47.4) / 6.826 \sqrt{\frac{1}{10} + \frac{1}{10}}$$

$$t.calc = (5.9) / 3.053 = 1.93$$

Since the t calc (1.93) exceeds the t critical (1.73) the results also show significance at the 90% confidence level.

While the variances are close (6.2 vs. 7.4), the mean assay were determined by the t-test to be significantly different. The overall conclusion is therefore that the lots produced at site B are not equivalent to those produced at site A.