Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
This document addresses the equivalency comparison of manufacturing process data from drug product (DP) validation batches to previous batches (called "reference" batches), when applicable.

A new or modified drug products should be demonstrated to be equivalent to previously produced product. Comparisons must be done as part of process validation studies for new product and significantly modified processes that require validation.

For new products, equivalency of validation data (e.g. finished product, critical in-process tests or critical parameters) to biobatch(es) or pivotal clinical batches is shown. For all equivalency studies, it is expected that the results of the validation batch testing be within registered specifications.

In cases where the specifications may not be reflective of recent process capability, it is recommended that additional criteria such as meeting the upper statistical limit of historical data, be considered for validation equivalency criteria.

Document is provided on
A) Selection of reference batches for the comparison,
B) Types of data that are compared for the most common dosage forms,
C) General acceptance criteria, and
D) Conclusion.

Document on types of statistical methods one can use to compare data is shown (**Appendix**) and examples are given. Reference batches are those batches that form a clinical or marketed-product basis (e.g. bioequivalence, bioavailability or production).

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:

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.
- Oral Powders/Suspensions for Reconstitution-API uniformity, reconstitution times
- Emulsions-assay, impurities, content uniformity, pH, viscosity, rheology (pourability), preservative content, mean particle size of dispersed phase
- Ointments/Creams/Pastes/Lotions/Gels/Solutions,-

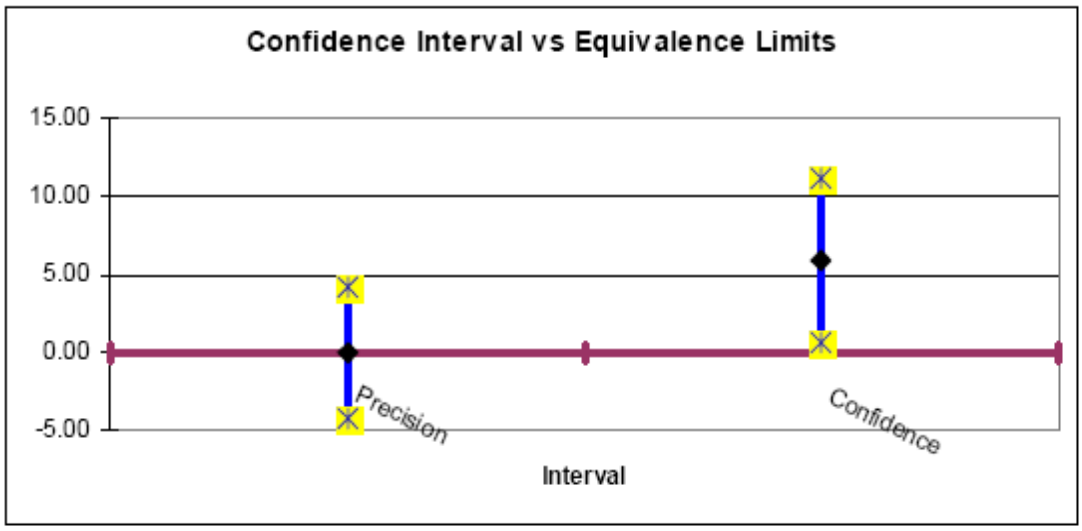
APPENDIX

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 • Powder Blend particle size analysis, density, and drug uniformity. • Tablet core- content uniformity and dissolution • 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.	

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.

