General Discussion:
This document provides information on demonstrating batch homogeneity of final APIs (small and large molecules) and critical intermediates

This procedure provides document for performing a homogeneity evaluation in support of API process validation. The following components of the evaluation are described:

- Materials to be tested
- Selection of test methods for examining homogeneity
- Sampling plan – when to collect samples, from what locations, and the of samples
- Selecting acceptance criteria for evaluating homogeneity test results.

General Comments
Homogeneity is the acceptable distribution of chemical and physical properties within a batch, based on predefined criteria. The intent of examining homogeneity during the validation is to demonstrate that the quality of a sample collected from any location within a batch is representative of the quality of the entire batch.

For large molecules the evaluation of homogeneity must consider the consistency of the profile of heterogeneity of product-related molecular variants. This profile should be consistent throughout a batch and similar between batches.

Unless previously performed in another study, examination of API homogeneity must be performed during process validation. If homogeneity was shown in a previous study, the following should be considered to determine if this study is still applicable:

___ Was the API prepared by the same process?
___ What processing changes have been made, and what potential impact (if any) do these changes have on API homogeneity?
___ Was the API prepared in the same (or equivalent) equipment?
___ Was the API prepared at approximately the same batch size (e.g. within +25% linear scale of the validated batch size)?

Requirements, acceptance criteria, and conclusions for the homogeneity study may be included in the process validation documents, or may be presented in separate documentation that is referenced in the validation documents.

Materials to be tested
___ Homogeneity shall be demonstrated for finished APIs unless otherwise justified and documented.
___ The need to show homogeneity of isolated critical intermediates should be considered on a case-by-case basis depending on how the intermediate is used in subsequent processing. In general, studying the homogeneity of an intermediate is of less importance than that of a final

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Method variability: replicate determinations on sample 8 of Batch 101	Results for Impurity A
Determination 1	0.40
Determination 2	0.36
Determination 3	0.39
Determination 4	0.42
Determination 5	0.44
Determination 6	0.39
Mean	0.4000
Standard deviation of Method for Impurity A	0.0276
Method variance for Impurity A ($= S^2_{method}$)	0.0007600

Use of the F-test begins with the assumption of a null hypothesis, H_0: "The variability of the sample set is not different than the variability of the method, with 95% confidence." The 95% confidence level is a standard degree of certainty that is widely accepted for evaluations such as this. The null hypothesis is true when the calculated F value, a ratio of variances, is less than a value of Critical F obtained from a statistical table (or see reference 4 for an on-line resource for finding Critical F values). using values for a one-tailed test with P = 0.05 (i.e., probability of 5% that null hypothesis is not true, which is the same as 95% confidence that the null hypothesis is true).

The F function used for obtaining Critical F values should be based on a one-tailed test, which is appropriate for this application because we are concerned only about values where sample set variance is greater than method variance, and not the inverse situation. Thus, in circumstances where method variance is greater than the variance from the sample set being examined, no calculation of F is needed because the sample data shows little variability, confirming homogeneity. The Critical F value obtained from the table is also dependent on the number of "degrees of freedom" from the numerator and denominator used to calculate F from the data being analyzed. The degrees of freedom of each variance determination = number of determinations minus 1. Thus, if ten data points were used to determine the variance of the numerator and six data points were used to determine the variance of the denominator, the degrees of freedom from the numerator and denominator are nine and five, respectively, and

therefore critical F is 4.772, as obtained from a statistical table of critical F values for a one-tailed test with P = 0.05.

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