



Schering-Plough

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

Re: Docket No. 03D-0493 Draft Guidance for Industry: Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment

Dear Sir/Madam

Schering-Plough has reviewed the above referenced Draft Guidance, and we offer the following comments for your consideration.

We have two general comments applicable to the entire document. The terms “correlate,” “correlation,” and “correlating” are used throughout the document. These terms have specific statistical meanings, therefore we recommend that more general terminology with a flexible method of evaluation be used; e.g., “relating,” “compare,” or “associate.” The terms “locations” and “intervals” are used interchangeably throughout the guidance, we suggest that one term be used for consistency.

The remaining comments reference specific sections of the Draft Guidance.

Section III. SCOPE

This guidance will be difficult to apply to bi-layer, tri-layer, and compression coated tablets because an accurate measurement of each layer’s weight cannot be determined to comply with the weight correction requirement. We believe the scope of this guidance should be limited to single-layer tablets.

Section IV. CORRELATION OF IN-PROCESS STRATIFIED SAMPLING WITH POWDER MIX AND FINISHED PRODUCT

A. Assessment of Powder Mix Uniformity.

To promote efficiency and consistency in the development process, selection of the sample size should only require analysis and explanation if quantities larger than the historical 1-3X are used. In addition, it should be acceptable to follow a standard

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sampling method and size such that additional development will only be required on an exception basis for new products.

We recommend that line 135 of the guidance be revised to read “Design blend-sampling plans and evaluate *the results* using appropriate statistical analyses.”

It is unclear what the intent of “Quantitatively measure any variability...” is. Would comparison of RSDs be sufficient?

B. Correlation of Powder Mix Uniformity with Stratified In-Process Dosage Unit Data

Line 149 of the guidance requests sampling “defined intervals and locations.” Please clarify the difference between an interval and a location.

The minimum of 140 samples may be excessive during early stages of development when the batch size is typically very small.

Please clarify what is meant by “significant events in blending process” from line 161. Is this for the compressing/filling operation?

C. Correlation of Stratified In-Process Samples with the Finished Product

Process validation is not required to be completed prior to submission of the regulatory application, therefore data available for inclusion in the submission should only be pilot scale.

Section V. EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY

The recommendation to sample 20 locations to adequately validate convective blenders is excessive. Not less than 10 locations should be adequate to capture worst case locations in convective blenders. Likewise for the ribbon blender, not less than 10 should be adequate.

Please clarify what is meant by “additional” in lines 225-226.

Section VI. VERIFICATION OF MANUFACTURING CRITERIA

A. In-Process Dosage Unit Sampling and Analysis

We propose that the wording for lines 262-263 be revised to read “..significantly affect your ability to ensure batch homogeneity, they should be *controlled* (or *accounted for*).”

B. Criteria to Meet the *Readily Pass* Classification

C. Criteria to Meet the *Marginally Pass* Classification

Are these to be based on “weight corrected results” or “as is”?

Section VII. ROUTINE MANUFACTURING BATCH TESTING METHODS

A. Standard Criteria Method (SCM)

For Stage 1 testing, we suggest that at least 7 dosage units should be collected in case the MCM plan is required. Otherwise, there may not be sufficient sample collected upfront and it may be difficult to resample the exact same locations.

Section VIII. REPORTING THE USE OF STRATIFIED SAMPLING

A. Applications Not Yet Approved

We note that this section contains recommendations for submissions, however we remind the Agency that validation studies are not required to be completed prior to application submissions, therefore most of these data would not normally be available.

Schering-Plough thanks you for the opportunity to present our comments on this draft guidance.

Sincerely,



Gretchen Trout
Director, Regulatory Affairs and Policy
Worldwide Regulatory Affairs