



March 8, 2004

Via fax and UPS

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

Re: Docket No. 2003D-0204

Draft Guidance for Industry on Powder Blends and Finished Dosage Units--Stratified In-Process Dosage Unit Sampling and Assessment [Federal Register Volume 68, No. 216, page 63110, November 7, 2003]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Powder Blends and Finished Dosage Units--Stratified In-Process Dosage Unit Sampling and Assessment".

This draft guidance is intended to respond to industry concerns regarding FDA policies on demonstrating the adequacy of in-process powder mixing and uniform content in finished products under 21 CFR 211.110(a)(3).

We offer the following comments/clarification for your consideration.

Lines 18-20: "This guidance is intended to assist manufacturers of human drug products in meeting the requirements of 21 CFR 211.110 for demonstrating the adequacy of mixing to ensure uniformity of in-process powder blends and finished dosage units."

Recommendation: For clarity, we suggest that a definition of finished dosage units should be included in the glossary. We also request clarification on whether these guidelines apply in situations where the final dosage form is a powder (e.g., a reconstitutable suspension).

Lines 60-62: "Stratified sampling is the process of sampling dosage units at predefined intervals and collecting representative samples from specifically targeted locations in the compression/filling operation that have the greatest potential to yield extreme highs and lows in test results."

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Recommendation: The definition of "*stratified sampling*" does not match exactly with the one provided in the glossary section (Line 472). In addition, it is not clear why this definition is included in the Scope section. For clarity, we suggest that a single definition be provided for "*stratified sampling*".

Lines 95-97: "*Formulations with extremely low dose and/or high potency may call for more rigorous sampling than that described in this guidance to assess the uniformity of powder blends or the uniformity of content of the finished dosage units.*"

Recommendation: Lines 95-97 indicate that, "*Formulations with extremely low dose and or/high potency may call for more rigorous sampling...*" Conversely, for clarity, we suggest adding text to also indicate that formulations with very high dose and or/low potency may require less rigorous sampling.

Lines 123-141: "*We recommend the assessment of powder mix uniformity using the following procedure:*

- *Conduct blend analysis on hatches by extensively sampling the mix in the blender and/or intermediate bulk containers (IBCs).*
- *Identify appropriate blending time and speed ranges, dead spots in blenders, and locations of segregation in IBCs. Determine sampling errors.*
- *Define the effects of sample size (e.g., 1-10X dosage unit range) while developing a technique capable of measuring the true uniformity of the blend. Sample quantities larger than 3X can be used with adequate scientific justification. Appropriate blend sampling techniques and procedures should be developed for each product with consideration to various designs of blend powder sampling and the physical and chemical properties of the blend components.*
- *Design blend-sampling plans and evaluate them using appropriate statistical analyses.*
- *Quantitatively measure any variability that is present among the samples. Attribute the sample variability to either lack of uniformity of the blend or sampling error. Significant within-location variance in the blend data can be an indication of one factor or a combination of factors such as inadequacy of blend mix, sampling error or agglomeration. Significant between-location variance in the blend data can indicate that the blending operation is inadequate."*

Recommendation: For clarity, we suggest adding text to provide guidance on types of sampling device(s) that can be used. We also suggest adding text to provide guidance on ensuring that once the samples are taken and the testing point is reached, no additional sampling or subdivision will be done by the lab and that the entire sample is analyzed.

In addition, we suggest that the assumption of having no dead spots for bin blenders and fluid bed should be declared as acceptable. For clarity, we suggest adding text to indicate the manner in which the Agency expects industry to determine sampling errors.

Further, for clarity, we suggest including text to describe what is meant by "blend-sampling plan". We also suggest adding text that indicates that within-location variance may also indicate analytical errors.

Lines 148-152: *"Conduct periodic sampling and testing of the in-process dosage units by sampling them at defined intervals and locations throughout the compression or filling process. Use a minimum of 20 appropriately spaced in-process dosage unit sampling points. There should be at least 7 samples taken from each of these locations for a total minimum of at least 140 samples."*

Recommendation: A total sample size of 140 tablets is reasonable - although, taking 7 samples from each of the 20 locations seems like a lot of sampling. We suggest reducing the number of locations to 14 or 15, but keeping the total sample size the same.

Lines 196-197 and Footnote 15: *"We recommend you use the following steps to identify sampling locations acceptance criteria prior to the manufacture of the exhibit and/or validation batches." Footnote 15: "This is described in Section IV of this guidance."*

Recommendation: In Footnote 15, the meaning of "this" is unclear. We suggest adding text to clarify Footnote 15.

Line 232-234: *"As an alternative, you can substitute procedures described in the PDA Technical Report No. 25, (see reference in footnote 8) to ensure that the blend is uniform and that the method meets or exceeds the criteria described above."*

Recommendation: Footnote 8 refers to the FDA/ORA Compliance Guideline, which is unrelated to the text in Lines 232-234. More appropriately, Footnote 9 states the following *"If blend sampling error is detected, more sophisticated, statistical analyses should be applied to assess the situation, such as the use of methods described in J Berman, DE Elinski, CR Gonzales, JD Hofer, PJ Jimenez, JA Planchard, RJ Tlachac, PF Vogel, "Blend Uniformity Analysis: Validation and In-Process Testing." Technical Report No. 25, PDA J Pharm. Sci. Technol. 51(Suppl 3i-iii), S1-99, 1997."*

We suggest revising the text in Lines 232-234 to read as follows: *"...(see reference in footnote 9)..."*

Lines 416-434: *"We recommend that you provide the following information in the Manufacturing Process and Process Controls section of the application (CTD 3.2.P.3.3):*

- *Statement that the methods in this guidance are being used to demonstrate the adequacy of powder mix or a description of alternative methods that demonstrate the adequacy of the powder mix.*
- *Summary of data analysis from the powder mix assessment and from stratified sample testing*
- *Summary of the in-process dosage unit stratified sampling data analysis demonstrating a normal distribution of active ingredient in the batch*

- *Summary of the powder mix sampling data analysis demonstrating that it met the minimum criteria for validation and establishing initial criteria*

We recommend that you provide the following information in the Drug Product Specification section of the application (CTD 3.2.P.4.1):

- *Statement in the product specification stating that the methods in this guidance are being used to demonstrate finished product uniformity of content or a description of alternative methods used to demonstrate finished product uniformity of content*

Recommendation: It is not clear in the guidance that, in addition to providing a description of an alternative method, the alternative method should be documented. For clarity, we suggest adding text to indicate that alternative approaches to those described in this guidance should be documented.

Lines 436-443: *"We also recommend that you provide the following information in the Pharmaceutical Development Information section of the application (CTD 3.2.P.2.2):*

- *Summary of data analysis for correlation of in-process dosage unit stratified sampling with finished product uniformity of content*
- *Summary of data analysis for correlation of powder mix uniformity with in-process dosage unit stratified sampling"*

Recommendation: CTD 3.2.P.2.3 (Manufacturing Process Development) appears to be a more appropriate section to describe the summary information mentioned in Lines 436-443, rather than in CTD 3.2.P.2.2. CTD 3.2.P.2.2 seems to better correlate with summary information mentioned in Lines 416-427. For clarity, we suggest revising the CTD reference in Line 437 to read "(CTD 3.2.P.2.3)".

On behalf of Aventis, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Powder Blends and Finished Dosage Units--Stratified In-Process Dosage Unit Sampling and Assessment* and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.

Vice President, Head US Regulatory Affairs