

March 9, 2004



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

RE: Docket No. 2003D-0493–Draft Guidance for Industry on Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment

Merck & Co., Inc is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck fully endorses the importance of developing a manufacturing process that guarantees consistent blend uniformity. As such, we welcome the opportunity to provide comment to this important draft document intended to provide manufacturers with guidance for meeting the requirements for demonstrating adequacy of mixing. The following three critical comments are intended to address important considerations for the finalization of the draft guidance.

Comment 1: Limitation of the scope of the guidance to validation and routine production, Lines 108-187

As noted above, we endorse the importance of developing a manufacturing process that guarantees consistent blend uniformity. This is a key step in our development and scale-up process, and we pay particular attention to the scale-up of the final blending step and design of the subsequent bulk powder transfer step in our manufacturing process trains. Based on our extensive development and scale-up experience, we have learned that the procedures one follows to characterize and mitigate blending and segregation issues are specific to the formulation and process equipment being used, and a “one size fits all” approach to blending and bulk transfer development is not flexible enough to allow a science-based approach. For this reason, we feel that the development path described in Section IV Parts A-C is too prescriptive. We recommend that this section be generalized by replacing lines 108-187 with the following:

“Development of a manufacturing process that guarantees delivery of a powder blend of consistent content uniformity to the tablet press, encapsulator, or filling line is a critical

piece of product development. It is therefore incumbent on manufacturers to develop robust final blending and subsequent bulk powder transfer steps to assure adequacy of mix and to demonstrate their robustness in process validation. The exact development path required for design of such a robust process depends on the formulation and the design of the manufacturing process equipment, and it should be based on application of appropriate scientific and engineering principles. An example of one development approach is described in the PQRI Blend Uniformity Working Group's final report."

Comment 2: Inflexibility of blender validation sampling requirements, Lines 194-215

While we agree that sampling of blenders with a sampling thief is often the most practical way of characterizing blend uniformity in batch blending during a validation study, the sampling requirements in Section V of the guidance are too rigid, don't generally conform with good scientific practice, and may be impractical for certain blender designs. For example, the recommendation to take at least three replicate samples from each location is inconsistent with good sampling practice of not disturbing a static powder bed by repeated sampling. Also, the recommendation of sampling convective mixers in twenty locations is arbitrary and does not consider differences in blender design (i.e. ribbon blenders vs. high-shear mixers). Therefore, we suggest that the blender sampling requirements for process validation, lines 194-215, be replaced by the language describing blender sampling in process development, lines 123-137, which requires the manufacturer to design and evaluate appropriate blender sampling plans based on applications of good scientific and statistical principles.

Comment 3: Inflexibility of stratified sampling locations for routine batches, Lines 313-315

While we agree that stratified sampling of dosage units in routine batches is the best method for characterizing blend and content uniformity, we feel that the specification of "at least 10" sampling locations may be impractical and unnecessary to assess the uniformity of the blend in some cases, for example for small batch sizes. Also, the guidance provides no flexibility in either the number or location of sampling points that would be necessary to accommodate interruptions in compressing. We have conducted statistical simulations, similar to those done by the PQRI Blend Uniformity Working Group, to assess the sensitivity of the blend uniformity acceptance criteria in the Guidance to the number of sampling locations. This analysis, summarized in the Attachment, shows that the percentage of batches that fail the Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) is insensitive to the number of sampling locations as long as (1) the total number of tablets assayed conforms with the Stage 1 and Stage 2 requirements specified in the Guidance and (2) tablets are sampled from at least five locations. For this reason, we believe that the recommendation of sampling from "at least 10 locations" is overly restrictive. We recommend changing lines 313-314 to read "You should identify at least 10 locations during capsule filling or tablet compression to represent the entire routine manufacturing batch. For very small batch sizes, it may not

be practical to collect tablets from 10 locations; in this case, the batch should be sampled in no fewer than five locations. In the event that a sampling location is missed due to a filling or compressing interruption, a batch can also be sampled in fewer than 10 locations, but no fewer than 5 locations. In all cases, a sufficient number of tablets should be collected from each location to meet the testing requirements described in Section A below. Any deviations from this approach should be evaluated and justified using sound scientific and engineering principles.”

We appreciate the opportunity to share our comments with respect to FDA’s Draft Guidance for Industry Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment. Please do not hesitate to contact me, should you have any questions.

Sincerely,



for

Donald Black, MD MBA
Vice President
Global Regulatory Policy

Attachment: Simulation of Blend Uniformity Test Results

The results reported here are based on a Monte Carlo simulation using normal distributions for location averages and within location results. For each set of conditions, 10,000 lots were simulated. The number of lots passing each set of criteria were counted and divided by 10,000 to calculate the pass percentages. The lots were processed in order to determine the pass rates we might expect in actual operation with the SCM-to-MCM switching rules in place.

We varied the overall RSD for tablets from 2-6% and examined different proportions of within- and between-location variation:

1. 80% Within/20% Between (a realistic split of variation based on past experience)
2. 20% Within/80% Between (a large amount of between location variation)

The results summarized below compare the pass percentages of stratified testing of ten and five locations. In the 5-location simulation, we assumed that two tablets were taken from each location for Stage 1 testing and six tablets were taken from each location for Stage 2 and MCM testing.

Results:

Table 1: Overall Pass Rates for 80/20 and 20/80 Location Variation Splits.

RSD	80/20		20/80	
	10 Locations	5 Locations	10 Locations	5 Locations
	100	100	100	100
	100	100	100	100
	100	100	100	100
	100	100	100	100
	100	100	99	98
	100	100	99	97
	99	99	97	94
	98	98	94	92
	94	94	89	88
	79	81	78	79
	56	59	62	69

These results show that the pass percentage is insensitive to the number of stratified sampling locations.