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March 5, 2004

Ms. Jennie C. Butler  
Administrative Proceedings Officer  
Office of the Commissioner  
FDA  
Building FHSL  
HFA-305 -- Room 1061  
Rockville, MD 20857

Re: Docket # 03D-0493  
FDA Draft Guidance on Blend Uniformity Analysis

Dear Ms. Butler:

On behalf of the Steering Committee and the Board of Directors of the Product Quality Research Institute (PQRI), I am pleased to forward comments on the FDA Draft Guidance referenced above.

The attached comments are the result of a review of the FDA Draft Guidance on Blend Uniformity Analysis made by the PQRI Blend Uniformity Working Group, the authors of the original recommendation submitted to FDA in March 2002 and subsequently revised and resubmitted in March 2002 addressing FDA's questions and concerns. The attached document reflects the views of the Working Group and PQRI. We, therefore, request that the comments be included with other public comments now posted on the FDA docket # 03D-0493, noted above.

Should you have any questions, or need clarification, please do not hesitate to contact me (203-798-5701).

Sincerely,

Gordon Hansen  
Chair  
PQRI Steering Committee

Attachments

cc: Helen Winkle  
Ajaz Hussain  
Jon Clark

PQRI Steering Committee  
PQRI Board of Directors  
PQRI Blend Uniformity Working Group

**2003D-0493**

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## BUWG COMMENTS REGARDING FDA DRAFT GUIDANCE DOCUMENT

Page #	Line #	Comment
2-4	58 – 105 Section III / Scope	<p>The following lines are suggested for inclusion in the Scope:</p> <p>After Readily Passing all validation batches (see Attachment 1), products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements.</p> <p>Comment: The PQRI report to FDA recommended the exclusion from the requirements of the guideline those products where the determination of dosage-form uniformity by weight variation is allowed. The former BU draft guidance for ANDA products also excluded these products. Not to exempt these products once they meet Readily Pass requirements will place an unnecessary burden on industry that is not required under current regulations.</p>
3	Footnote 6	PAT guidance published in September 2003, not August 2003
4	133	...designs of powder sampling devices and the...
5	153-157	Text sounds like additional sample locations should be taken in addition to the 20 stated in the bullet above this text (line 150). This was not part of the PQRI recommendation. This is may also be construed to conflict with the text in lines 254-256 (“There should be at least 20 locations with 7 samples each for a minimum total of 140 samples.”)
6	194-196	Text recommends assessing the uniformity of the blends, in-process dosage units and finished product independently. The philosophy of the PQRI recommendation was to assess blend and in-process dosage units jointly, as evidenced by them being contained on the same flow diagram for the validation approach.
6	199	Line 199 should be rewritten as follows: “...10 sampling locations in the blender or discharged bin which include areas of potential poor blending...”
7	210	The BUWG recommendation states at least 10 locations for tumble blenders and at least 20 locations for convective mixers. In the previous line (209), we use $(n) \geq 10$ ; to be consistent for convective mixers, the text in line 210 should read $n \geq 20$ .
Revised Text	216	<p>The following revision of the revision is suggested:</p> <p>If samples do not meet these criteria, we recommend that you investigate the failure according to the flow chart in Attachment 1.</p>

		<p>Assay the remaining replicate blend samples. To aid in investigating the cause of failure, dosage form samples (seven from at least 20 locations) may be analyzed. These samples should have been obtained following the procedures described in Section VI, Verification of Manufacturing Criteria. If the cause of failure is identified as a mixing problem, we recommend that you do not proceed further with implementation of the methods described in this guidance until a new mixing procedure is developed. If the cause of failure is not because of mixing, but is attributed to sampling error or other problem(s) unrelated to the homogeneity of the blend, we recommend that you proceed with the evaluation of the dosage form data as described in Section VI.</p> <p>Comment:</p> <p>Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text,  “Assay at least seven dosage units per each location, weight correct each result”  should be moved to be just under the box containing the text,  “Assay 2<sup>nd</sup> and 3<sup>rd</sup> blend samples from each location”</p>
7	220-234	Should be moved to introduction , immediately after line 197 ... “exhibit and/or validation batches”. This will allow for alternatives to blend sampling when it is demonstrated during development that blend sampling analysis does not provide useful information.
7	241	Guidance recommends that you assess the normality of the data. At our March 2002 meeting with the Steering Committee, Jerry Planchard presented slides stating that if the data is not normal, it becomes harder to comply with the PQRI acceptance criteria.
7	244	RSD for marginally pass should be expressed as $4.0 < RSD \leq 6.0\%$
Revised Text	260	Analyzing a dataset for normality without regard to location may not provide insight into the possible underlying root causes of the non-normality. Non-normality can be exhibited in both within-location residues, and in location means. The type and extent of non-normality seen in these components, when used in conjunction with a root cause tool such as Ref. 13 in the guidance, will be quite helpful in not only determining the possible causes of the non-normality, but also establishing if the process is under appropriate blend control.
8	260-261	Same comment as above (for line 241) regarding normality
9	294	...(for one batch $n \geq 140$ ) the RSD is $>4.0\%$ but $\leq 6.0$ percent. Also, this statement implies that if the RSD is $>4.0\%$ , you must

		test the remaining 80 dosage units. This is inconsistent with the PQRI recommendation that stated an acceptance criteria of $\leq 6.0\%$ . The product would be classified as being marginally passes because the RSD is $> 4\%$ . It is unclear what would happen if analysis of the additional 80 samples (should someone elect to do so) results in an $RSD \leq 4.0\%$ . Is the batch classified as readily passes, or still as marginally passes?
10	365	PQRI recommendation had criteria for the RSD of $\leq 6.0\%$ for stage 2 testing during routine production ( $n \geq 30$ ). Should clarify that the batch would still meet acceptance criteria if $5.0 < RSD \leq 6.0\%$ , but MCM testing would need to be performed.
11	385	...compare this with the MCM criteria:
11	405	...and each batch has an RSD of $\leq 5.0\%$ .
11 -12	423 – 424	These lines seem to require that the data in a submission be normally distributed. This is inconsistent with the revised line 260 that only requires the normality of the data be evaluated. Non-normal data does not necessarily imply inadequate blend uniformity. The type, source, extent and possible consequences of the non-normality must be evaluated on a case-by-case basis.
13	478	Add target strength to definition as target assay and target strength are both interchangeably
15	No Line #	Note: This comment applies to revised flow-chart. In both the Continuing Routine Testing Using Standard Criteria Method (SCM) and Marginal Criteria Method (MCM) boxes at the top of the flow charts, STM and MTM acceptance criteria should be changed to SCM and MCM.