

Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



March 8, 2004

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

Re: Draft Guidance for Industry on Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment [Docket No. 2003D-0493, 68 *Federal Register*, 63109, November 7, 2003]

Dear Madam/Sir:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than \$30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

We appreciate the opportunity to comment on the draft guidance on a stratified sampling approach to assess uniformity of powder blends and finished dosage units, which incorporates recommendations from the Blend Uniformity Working Group of the Product Quality Research Institute (PQRI).

In addition to the attached line-specific comments, we would like to draw your attention to a discrepancy between this guidance and both the PQRI recommendation and the withdrawn draft blend uniformity guidance for ANDA products. The PQRI report to FDA recommended that the guidance requirements exclude those products where the determination of dosage-form uniformity by weight variation is allowed. This recommendation is consistent with the draft ANDA blend uniformity guidance. The scientific rationale for removing this exemption from the current draft guidance is not evident. Furthermore, disallowing this exemption represents a significant increased burden on the industry. We urge you to include the exemption in the final guidance.

2003D-0493

C7

Pharmaceutical Research and Manufacturers of America

PhRMA Comments
Docket No. 2003D-0493
March 8, 2004

We trust that you will give careful consideration to our comments as you finalize the guidance. Please contact me if you have any questions regarding these comments.

Sincerely,

A handwritten signature in black ink that reads "Alice E. Till". The signature is written in a cursive style with a large, prominent initial "A".

Alice E. Till, Ph.D.

CC J. Clark

Attachment A
PhRMA Comments on:
FDA Draft Guidance Entitled
“Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment”
(Docket No. 2003D-0493)
March 8, 2004

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
	Numerous places		We suggest replacing the word “correlation” with either the terms “relate” or “compare.”	The term “correlate” has statistical connotations	
	General comment		The guidance avoids the terms “validation” and/or “validation process,” using titles like “verification of manufacturing criteria.” We recommend including the terms “development” and “validation” to clarify the purpose of various sections.	The PQRI proposal makes it clear that certain activities should be performed during validation. The reluctance to use the term as a phase of development creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret.	
I.	18-23		The introduction should state that limitations in current blend sampling procedures might preclude the effective use of blend sampling analysis to ensure adequacy of blending and that this guidance provides an alternate approach to assessing adequacy of mixing.	This key advantage of the guidance should be stated in the beginning of the document.	
I	18-20		We suggest providing a scope for powder blends to confirm that this guidance is applicable for critical blends of powders, granules, beads, etc.	Providing this scope will provide clarity of application users.	
III	60		We suggest revising line 60 to read: “Stratified Sampling of dosage units is the process of sampling at predefined intervals	The term “stratified sampling” in italics implies a definition. The appropriate technical definition for stratified sampling is not limited to	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale
			and collection...”	dosage units; thus, the order of the words should be changed to comply with the PQRI proposal and definition.
III	82-83		We suggest revising lines 82-83 to read as follows: “Compare the stratified in-process dosage unit data with the finished dosage unit data to determine whether in-process samples may be used to assess uniformity of content.”	Clarity
III	95-96		Lines 95-96 should be revised to indicate that formulations with a very high dose and or/low potency may require <i>less</i> rigorous sampling, not more rigorous sampling.	Very high dose and/or low potency formulations tend to be less sensitive to differences in blend uniformity or less likely to result in patient subtherapeutic blood levels.
IV	108		For clarity, change the section title so that it clarifies that these exercises are Development (pre-validation) procedures. One possibility: “IV. Evaluating Powder Mix and In-Process Stratified Sampling During Process Development”	It is not clear (to all readers) that this section is a separate procedure from that proposed in Section V. A title and purpose statement will help clarify the reason for the difference in sampling scheme and lack of acceptance criteria.
IV	115		We suggest revising line 115 to read: “through assessment of data from development batches.”	This section (Sec IV) is done prior to validation (per line 112), so the reference to validation and manufacturing in line 115 is confusing.
IV – A	123		We suggest adding a “purpose statement” to this line. For example: “As part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated	This suggestion adds clarity to help others understand the importance of the section.

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
			blend process. As part of this evaluation, we recommend the following procedures.”		
IV. A.	125-126		<p>We suggest adding a footnote to the end of this sentence.</p> <p>*Sampling can be done from other equipment that is being used to mix the blend, such as a fluid bed.</p>	Clarification is needed to insure that the guidance can also be used with non-traditional processing equipment	
	IV. A.		We suggest changing “Sample Size” to “Sample Quantity”	Clarity as sample size relates to a volume measurement.	
IV - A	137 & 140		We suggest changing the word “Significant” to “High” in both lines.	Because the term “significant” may imply “statistical significance,” the change would avoid confusion and comply with PQRI terminology.	
IV. A.	138-139		We suggest adding to this section that within-location variance may also indicate analytical errors.	This is another factor that may produce within location variance.	
IV-B	146		<p>We suggest adding a “purpose statement” to this line. For example:</p> <p>“Prior to validation, we recommend that you assess the in-process dosage unit data to identify locations throughout the compression/filling operation that have a higher risk of producing failing finished product uniformity of content results and to identify trends due to segregation or poor powder mix. We recommend the following steps:”</p>	Adding a purpose statement would help others understand the importance of the section.	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
IV - B	160-161		We suggest changing lines 160-161 to read: "Prepare a summary of the data (and analysis), identifying the significant events in the manufacturing process that may impact blending and from this, identify the stratified sampling that may be used to verify powder mix uniformity. We...."	This change would help clarify purpose and prevent some confusion over the statistical use of the term "correlate."	
IV - B	163 - 164		We suggest changing "data described above" to "uniformity."	This change would provide clarity when comparing powder mix uniformity to the dosage unit uniformity	
IV - C	172		We suggest changing this section title to: "Establish the relationship between stratified in-process samples and the finished product"	Because "correlate" has statistical connotations, changing the title would help clarify its intent.	
IV - C	172-185		We suggest that FDA move this section under the topic of Section VI, with the additional option that if this verification has previously been completed in development, it is not necessary to repeat the evaluation.	Many companies will use the extended testing during validation to compare in-process to finished product, in order to obtain better estimates. During development, it may not be practical to obtain a sufficient amount of data to demonstrate equivalency or "correlation" between final and in-process product.	
IV.C.	174		We suggest changing the sentence to: "We recommend the following steps to support the use of the stratified in-process sample data as an alternative to the USP Content Uniformity Test:"	Because content uniformity testing of the stratified in-process samples is more rigorous than that for the USP Content Uniformity test the results from the stratified samples would be harder to pass since it would be more likely to include outliers.	
IV - C	186		We suggest adding another bullet point: "If the in-process samples cannot be used to assure uniformity of dosage units, then the compendial test on the final product will need to be continued in addition to in-process	This bullet provides guidance and flexibility if a relationship cannot be established at that time.	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
			stratified testing for blend uniformity.”		
V.	188		“Validation” is misspelled.		
	193-196		We suggest changing this paragraph to: “In order to establish uniformity of blend during validation and/or exhibit batches, we recommend an assessment of both powder blend uniformity and in-process dosage unit uniformity. We recommend that sampling locations and acceptance criteria should be identified prior to the manufacture of these batches. (insert footnote 15 here)”	The PQRI BUWG recommendation states both blend and dosage unit evaluations are needed to establish uniformity. This also clarifies footnote 15.	
	197		Please consider moving the last 2 paragraphs (Line 224 through 233) before sampling specifics starting with line 198.	Moving these paragraphs provides background acknowledging that blend sampling may not be appropriate in all cases.	
	198		We suggest rewording this section to read as follows: “1. Identify at least 10 locations to collect powder blend samples. If taken from the blender, they should include areas that may be problematic in terms of uniform blend.”	The suggested change provides background acknowledging that blend sampling may not be appropriate if demonstrated in product development.	
V	Amendment line number 216 (new text)		We recommend the following change to this paragraph: “If samples do not meet these criteria, we recommend that you investigate the failure according to the flowchart in Attachment 1 by assaying the remaining replicate blend samples and at least 7 dosage units from each in-process sampling location. Identify the	At the December 2003 PQRI workshop, it was identified that the flowchart 1 is slightly incorrect. This change would address the situation if blend samples do not pass stage 1, dosage units are assayed to help identify blending sample error, prior to deciding if sample error is present.	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
			root cause of the failure. If the root cause is a mixing problem, we recommend that you proceed no further with implementation of the methods described in this guidance until you develop a new mixing procedure. If the cause of the failure is attributed to sampling, assay, or another problem unrelated to homogeneity of the batch, we recommend you use the methods described in Attachment 1 and Section VI (Verification of Manufacturing Criteria) to determine adequacy of mix. We also recommend that if you cannot identify the cause of the failing criteria that you not proceed any further with implementation of the methods described in this guidance.”		
V.	233		Please clarify that this should reference footnote 9.	Footnote 8 refers to FDA/ORR Compliance Guideline, not the PDA Technical Report No. 25.	
VI	236-314		We suggest reformatting these sections for clarity. Combine this section VI with section V to create a “validation” section.	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.	
VI. Revised Attachment 1. and Table of Contents	237		We suggest revising the title of section VI to: ANALYSIS AND CLASSIFICATION OF IN-PROCESS DOSAGE UNITS FOR BLEND UNIFORMITY ASSESSMENT. (Note this title is also used in the Revised Attachment and the Table of Contents)	The proposed title more accurately reflects what is contained in this section. This section refers to the <u>assessment</u> of blend and dosage units against criteria and <u>classification</u> as “readily pass” “marginally pass” or “inappropriate”.	
VI	240		We suggest changing “normality” to	A normal distribution is acceptable, but not	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale
			“distribution of the data.”	required. A unimodal shape or bell shape with short tails (high peak of data in the center) while not a “normal” distribution, is a preferred shape when describing batch uniformity. .
VI	282		We suggest changing this line to read: “If your test results meet this criterion for all batches, they are classified as ...”	This draft guidance does not explicitly state that all validation batches must readily pass in order to use SCM.
VI.	243-245		The guidance should clarify the rationale for the classification values [readily pass (RSD ≤4.0%), marginally pass (RSD ≤6.0%) or inappropriate (RSD > 6.0%)].	Assigning values to the target values would help clarify this section.
VI.	244		Express “marginally pass” as RSD greater than 4.0% and less than or equal to 6.0%.	This change provides clarity.
VI	250		We recommend changing the wording of this section to: “Prior to the manufacture of the batch, carefully identify locations...” (Consider adding a cross-reference to Section IV-B as the recommended approach.)	The current wording does not explicitly state that sampling locations should be determined “prior” to the validation exercise, as the PQRI proposal does.
VI - A	257-258		Please consider adding at the end of the bullet: “Assay all 7 per location if required in Section V.”	There is no connection back to the performance of the blend (Sec V). If one has to assay 7 per location to satisfy blend homogeneity, the same samples may be used to demonstrate in-process performance.
VI - A	Between 258 and 259		We recommend adding: “Analyze the dosage units according to the flowchart in Attachment 1.”	There is no connection back to the flowchart in Attachment 1. The PQRI document provides acceptance criteria for the stage 1 data (3 per location) and also provides stage 2 sample sizes

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale
				and acceptance criteria, if needed.
VI - A	Amendment line number 260 (new text)		We suggest revising this section to: “Conduct an analysis of the dosage unit stratified sampling data to assess the active ingredient distribution throughout the batch (e.g., visual assessment of a histogram or a probability plot). Indications of trends, bimodal distributions, or other forms of a distribution other than bell-shaped should be evaluated.”	A normal distribution is acceptable, but not required A unimodal shape or bell-shape with short tails (high peak of data in the center) is not a “normal” distribution, but it is a preferred shape when describing batch uniformity. .
VI - A	265		Change “normality” to “distribution (e.g., unimodal, bell-shaped, normal).”	A normal distribution is acceptable, but not required.
VI - A	268		Please consider removing the phrase “In addition to this analysis of batch normality” and replace with “Additionally, we recommend ...”	Reference to normality does not add to the meaning of this section.
VI - B	273		We suggest revising this section to read: “For each separate batch, compare the weight-corrected test results to the following criteria.”	The recommended changes would help the draft guidance reflect the intent of the PQRI proposal
VI - C	289-291		We suggest revising this section to read: “If your dosage unit test results fail to meet the criteria for the readily pass classification, compare the weight corrected test results to the following criteria.”	This change is necessary to comply with the Amended line 283, which describes how many to test. In addition, it helps clarify that the data are weight corrected for those not familiar with the PQRI proposal.
VI - C	293		We suggest revising this to read: “ ... results (for <i>each</i> batch n > 60) the ...”	
V.I.D.	308-315		Please consider moving Sub-section V.I.D to Section VII.	It is more appropriate to place this section under “ROUTINE MANUFACTURING” rather than

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
				under "VERIFICATION OF MANUFACTURING CRITERIA."	
VII.	320-322		We recommend adding a statement that routine testing of powder mixes can be replaced by testing in-process stratified samples.	This change would make explicit that one of the key advantages of this guidance is to allow the manufacturer to do in-process testing of dosage units instead of testing the powder mix for routine production.	
VII - A	337		In addition to the amendment text, please consider adding another bullet: "Previous routine test was per SCM and passed SCM criteria."	Three scenarios to use SCM exist in the PQRI document: 1. validation was readily pass and we are just starting production 2. routine test method is SCM and we continue this as long as we keep passing 3. routine method is MCM, but switching rule is met.	
VII. A.2.	348		We suggest adding a footnote as follows: (3) weight correct ¹⁷ ¹⁷ Allow for the option of not weight correcting the stratified unit dose data during routine batch manufacture.	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both the routine criteria and the content uniformity test	
VII. A.2.	361-363		We suggest adding "weight corrected" to this sentence: "To perform the stage 2 test, we recommend that you assay the remaining two dosage units (from stage 1) for each sampling location and compute the mean and RSD of weight corrected ¹⁷ data combined from both stage 1 and stage 2."	Using non-weight corrected data to pass routine manufacturing criteria is more stringent, but it allows for only one set of calculations to pass both the routine criteria and the content uniformity test	
VII - B	382		In addition to the amendment text, please	Three scenarios to use MCM exist in the PQRI	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
			consider adding another bullet: “Previous routine test used MCM and passed MCM criteria”	document: 1. validation was marginally pass and we are just starting production 2. routine test method is MCM and we continue this until we can switch 3. last batch started as SCM, but had to go to MCM to pass.	
VII - B	383		Please consider adding sample size to this section: “...from Stage 2 SCM ($n > 30$) analysis...”	Adding sample size would help clarify the sample size FDA expects.	
VII. B.	385		Please confirm that MVM designated in the section is a typo and should be “MCM” criteria.	The MCM terminology needs to be consistent within the guidance document.	
VII - B	390		We suggest adding one word: “We recommend that all results obtained from analysis...”	This addition helps clarify FDA’s intent.	
VII - B	Amendment line number 395 (new text)		We suggest revising the last sentence: “That is, to establish justified assignable cause(s), take necessary corrective actions, and if appropriate, repeat the powder mix assessment, stratified sample correlation, and initial criteria establishment procedures.”	If a single lot fails SCM and MCM, and the root cause is identified to be due to a deviation from the validated process (say materials were not added in correct order), we do not want to have to go through revalidation of all correlations, just reject lot and put measures in place to prevent reoccurrence. But, if the process is “broken” and must be fixed, then this all needs to be done.	
VII. C. Table of Contents	401		Please consider using “Criteria” instead of “Test” as in “Switching to the Standard Criteria Method (SCM) from Marginal Criteria Method (MCM).”	The MCM and SCM terminology need to be consistent within the guidance document.	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale
			(Note this is also in the Table of Contents)	
VII - C	404		We suggest revising "... criteria and result in RSD ..." to "criteria and for each batch the RSD ..."	. This has currently been misread that all batches are combined together to get RSD. The change would clarify that each batch RSD must meet this.
VIII	416		We suggest revising this sentence to read: "We recommend that you provide the following information, if available, in the ..."	Most valuable data would be generated from validation batches which most likely are not made at the time of filing.
	416,429,436		Please consider consolidating all information provided into a single REGIONAL CTD section.	Information is spread over different sections of each application, making it difficult to compile, link and review. As this information is only required in the US, it should be included in the Regional section of the CTD.
VIII.A.	422-423		We recommend adding unit dose to this sentence: "Summary of data analysis from the powder mix assessment and from stratified <i>unit dose</i> testing."	This change clarifies that analysis of the stratified unit dose data along with the blend data is needed.
VIII.A	423-424		We recommend changing "demonstrating a normal distribution" to "evaluating the distribution."	A normal distribution is acceptable, but not required.
VIII.A.	426-427		We suggest revising the sentence to: "Summary of the blend and in-process dosage unit analysis demonstrating that it met the minimum criteria for validation and establishing initial criteria."	Modifying this sentence to include the stratified dosage unit data as there may be sampling errors confounding the blend data.
VIII. A.	439-440		We suggest revising the sentence to:	The original PQRI document showed that

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
			“Summary of data analysis for in-process dosage unit stratified sampling and finished product uniformity of content to support the use of the stratified in-process sample data as an alternative to the USP Content Uniformity Test.”	stratified samples are more discriminating than finished product samples, therefore it isn’t clear what value is added by "validating" the stratified samples by correlating with finished product samples.	
	471-475		We recommend changing this definition to: “Stratified Sampling is the process of collecting a representative sample by selecting units deliberately from various identified locations within a lot or batch, or from various phases or periods of a process. Stratified sampling of dosage units specifically targets locations throughout the compression/filling operation that have a higher risk of producing failing results in the finished product uniformity of content, then random dosage units are selected within these identified locations.”	This change would help bring the draft guidance and the PQRI definition in harmony. It also serves to clarify that this sampling strategy is a type of random sampling	
	477		Please consider adding “target strength” to the definitions.	Target assay and target strength are used interchangeably, but no definition is provided for target strength.	
Revised Attachment 2	Top two boxes		We suggest changing STM and MTM to SCM and MCM.	The MCM and SCM terminology need to be consistent within the guidance document.	
General Comments on multilayer tablets			We suggest adding direction to industry as to how the guidance is to be applied to multilayer tablets when actives are in the different layers. The guidance should indicate how to evaluate	If there are two different assays for the two different actives, one could be in a situation of having to apply SCM for one active and MCM for the other. The acceptance criteria are based on weight	

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale
			stratified samples of bilayer tablets.	corrected data; the guidance should also provide for use of non-weight corrected data.
Attachment I	Revised Attachment 1 flowchart, line 498		Please consider moving the box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) immediately after box that says "Assay 2 nd and 3 rd blend samples from each location".	The dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias.
Attachment I	Revised Attachment 1 flowchart, line 508		We recommend replacing the box that says "Assay at least 7 dosage units per each location, weight correct each result" with a box that says "Use dosage units to verify adequacy of powder mix."	This addresses the situation when we have identified blend sample error so they must be used to demonstrate uniformity of mix.
Attachment II	Revised Attachment 2 flowchart		In the top left box, we recommend changing the first criteria to "last batch was tested using SCM and met SCM acceptance criteria"	This clarification is suggested to insure that someone will not read into this that if it was tested per MCM, but "met SCM acceptance criteria", then SCM is OK now
Attachment II	Revised Attachment 2 flowchart		In the top right box: we recommend removing the first sentence, "Last batch met STM acceptance criteria."	The first sentence does not add clarity. Simply, if the last batch was tested using MCM (or started as SCM but had to go to MCM), then the next batch must be tested using MCM. If the last batch was tested per and met SCM, MCM would not be used.
Attachment II	Revised Attachment 2 flowchart		Please consider changing the box stating: "You may add results from analysis of remaining samples" to "In addition to the stage 2 results, you may add results from analysis of remaining samples."	The proposed change would clarify that the intent is to use all previously generated data.
Attachment II	Revised Attachment 2		We recommend adding document section numbers to a few boxes.	This change would help to clarify and to connect back to the document text.

Section	Guidance Line	Current Guidance Cross-Reference	Comment	Rationale	
	flowchart				
Attachment II	Revised Attachment 2 flowchart		<p>We recommend listing the 3 situations that allow one to test SCM and the 3 that allow MCM in a bullet list above the flowchart. Begin the flowchart with the first diamond.</p> <p>Use SCM routine criteria if:</p> <ol style="list-style-type: none"> 1. validation was readily pass and you are just starting production, or 2. routine test for the previous batch was SCM and it passed SCM criteria, or 3. routine test for the previous batch was MCM, but switching rule is met <p>Use MCM criteria if:</p> <ol style="list-style-type: none"> 1. validation was marginally pass and you are just starting production, or 2. routine test for the previous batch was MCM, or 3. routine test for the previous batch started as SCM, but had to go to MCM to pass 	The suggested change would help clarify the flow because we feel that the 4 boxes at the top of the flowchart are confusing.	