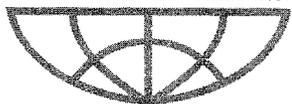


# PDA

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April 5, 2004

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

**Ref: [Docket No. : 2003D - 0493]**

**Draft Guidance for Industry on "Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment"**

PDA is pleased to provide these comments on the FDA Draft Guidance for Industry on "Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment". PDA is an international professional association of more than 10,500 individual member scientists having an interest in the fields of pharmaceutical science, manufacturing and quality. Our comments were prepared by a committee of experts in the field. These stakeholders are ready to work with FDA via PDA to further develop and refine the guidance for Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment that would ensure quality products in the market place, which is the ultimate goal of both FDA and industry.

We are pleased to offer our comments in order to further improve the document. We trust that our comments will be received as they were intended; that is, to strengthen the utility of the guidance that will be used by people with very diverse needs: ORA, Compliance, OPS, and the regulated industry.

Of particular note are the following recommendations:

- 1) The PQRI report to the 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 draft BU guidance for ANDA products also excluded these products. If they are not excluded, it is recommended that the Agency reassess the economic impact to the industry of the additional burden of now running both potency and weight variation analysis on these products.
- 2) The guidance avoids the term "Validation" and uses less descriptive titles like "verification of manufacturing criteria." The PDA feels that the reluctance to use the term "Validation" creates a disconnect with the PQRI proposal and makes the Guidance more difficult to interpret. The term "Validation" is well defined by the Industry and the FDA and the term should be utilized to denote those activities in this guidance that clearly fall under its purview.

2003D-0493

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PDA would like to praise the cooperative effort between Industry and the FDA via PQRI that has resulted in the utilization of good science and logic to bring resolution to an area of some controversy and disagreement. The resultant benefactor of this Guidance will be the consumer, who now can be assured of the efficacy of their medication.

PDA would be pleased to offer our expertise to assist in the clarification of our comments, and the continued evolution of this important guidance. We look forward to working with FDA, industry and other professional associations to develop a world-class guidance document.

**Acknowledgements:**

PDA thanks the members of the Blend Uniformity Task Force for their input in developing these comments.

<b>Name</b>	<b>Company</b>
James Bergum	Bristol-Myers Squibb Company
Jim Carron	Pharmaceutical Services Corporation
Bob Dana	Elkhorn Associates
Don Elinski	Eli Lilly and Company
Garnet Peck	Purdue University
Laura Foust	Eli Lilly and Company
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Jerome Planchar	Patheon
Richard Poska	Abbott Laboratories
George Robertson	PDA
Paul Vogel	Lachman Consultants
David Whiteman	Aventis Pharmaceuticals

PDA thanks you again for the opportunity to comment on this draft guidance. If you require further information, please feel free to contact me via the information below.

Sincerely,

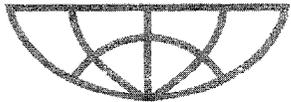


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Attachment: Comment Grid



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February 13, 2004

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R Madsen	Williamsburg Group, LLC
Jerry Planchard	Patheon
Richard Poska	Abbott
George Robertson	PDA
Paul Vogel	Lachman Consultants
David Whiteman	Aventis

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Sincerely,



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Attachment: Comment Grid

**Guidance for Industry  
Powder Blends and Finished Dosage  
Units — Stratified In-Process Dosage  
Unit Sampling and Assessment**

**PDA Comments**

<b>Comment Number</b>	<b>Line # of PDF Document Section/ Title</b>	<b>Comment/Recommendation for Revision</b>	<b>Comments regarding text</b>
1.	General Comment	The guidance avoids the term 'validation', using less-descriptive titles like "verification of manufacturing criteria". We recommend including the terms 'validation' and 'development' to clarify the purpose of various sections.	The PQRI proposal clearly defines activities that are performed during development (pre-validation) and validation. The reluctance to use the term 'validation' creates a disconnect with the PQRI proposal and makes the draft guidance more difficult to interpret.
2.	General Question	If, through development, we know that reliable blend sampling is unattainable (up to 10x) due to thief error and we have data to prove this, do we still need to pull blend samples during validation or can we skip sampling from the blend in validation and use the Stage 2 dosage unit testing to demonstrate uniformity of blend?	Continuing to utilize a flawed test would not add meaningful data to the Validation exercise.  This does not remove the obligation of the firm to use good science to continue the search for more robust sampling methodology.

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**PDA Comments**

<b>Comment Number</b>	<b>Line # of PDF Document Section/ Title</b>	<b>Comment/Recommendation for Revision</b>	<b>Comments regarding text</b>
3.	General Comment	There is a key piece missing in the guidance and that is a review of the Method development summary report and the method validation package.	These two tools are the key to discovering a root cause of an analytical error. This is especially important when an unidentified analytical error continues to occur. This evaluation should occur concurrent with a lab investigation. This review should be performed before any retesting has occurred. The documents if well defined will provide guidance on where the method has critical steps that may not be defined. In addition a well-written controlled document will have described why critical changes were made to the methodology. In the cases of compendial methodology it is always good to look at the method validation of the firms own product. This will demonstrate where the application of the compendial method on the firms product may not be as rugged or robust.

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4.	58	<p>The following lines are suggested for inclusion in the Scope:</p> <p>“After Readily Passing all validation batches, products that are allowed to meet USP requirements using content uniformity by weight variation are exempted from future routine blend testing requirements.”</p>	<p>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.</p>
5.	60	<p>Change line 60 to read: “Stratified Sampling of dosage units is the process of sampling at predefined intervals and collecting...”</p>	<p>The term ‘stratified sampling’ in italics implies a definition. The appropriate technical definition for stratified sampling is not limited to dosage units, thus change the order of the words to comply with the PQRI proposal and definition.</p>
6.	95-97	<p>Remove sentence, “ Formulations with extremely low dose and/or high potency may call for more rigorous sampling...units.</p>	<p>Sentence is ambiguous in that it calls for more rigorous sampling, but gives no guidance or reference to how to accomplish these ends.</p>

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7.	99	Remove sentence When using the methods...maybe observed.	Observation of trends is obvious. The sentence adds nothing to the dialogue.
8.	100	Remove the words "these types of".	For Clarity
9.	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.
10.	115	Change 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.

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11.	123	<p>Add a 'purpose statement' to this line. For example:</p> <p>"As part of development, we recommend that you assess critical events in the blend process and determine appropriate sampling techniques for demonstrating a validated blend process. As part of this evaluation, we recommend the following procedures."</p>	Clarity, to help others understand the importance of the section.
12.	137 & 140	Change the word 'Significant' to 'High' in both lines.	To prevent confusion with statistical significance and to comply with PQRI terminology.

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PDA Comments**

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13.	146	<p>Add 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>	Clarity, to help others understand the importance of the section.
14.	149	Remove the words, "and location".	The term location in reference to compression and filling is confusing. Interval is the standard industry descriptor.

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15.	160-161	Change 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...”	To clarify purpose and prevent some confusion over the statistical use of the term ‘correlate’.
16.	163 - 164	Change “data described above” to “uniformity”	Compare powder mix uniformity to the dosage unit uniformity (clarity)
17.	169-170	Examples of state of the art should be given or one could generally use the P.A.T., Process analytical Technology as a descriptor example.	Clarity
18.	172	Change section title to “Establish the relationship between stratified in-process samples and the finished product”	Clarity, also removes the term ‘correlate’ which has statistical connotations.

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19.	Lines 172-185	<p>Reformat for clarity:</p> <p>Move this section under the topic of Section VI, with the additional option that if this verification has previously been completed in development, that it is not necessary to repeat the evaluation</p>	<p>Most 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.</p>
20.	Line 174	<p>Add a purpose statement to this line: "In order to use in-process samples to fulfill the compendial uniformity of dosage units requirement for finished products, we recommend the following steps:"</p>	<p>It is currently unclear why this section is important.</p>

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21.	Line 186	Add a bullet pt.: · “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 stratified testing for blend uniformity.”	To provide guidance if a relationship cannot be established at that time.
22.	188	Validation is misspelled	Spelling error
23.	195	Remove the word “independently”	Although data are collected and analyzed separately, the overall assessment must include evaluating both dosage unit and blend data as whole. The addition of this word in this sentence does not add value and may confuse.

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24.	198	Insert the words "if practical" after the word blender. Alternatively, the words "in the blender" could be dropped.	Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained.
25.	Footnote 14, page 6.	Replace tablet with "dosage unit".	Guidance covers both tablets and capsules.
26.	205-210	<p>Line 205 (#2) should contain:</p> <p>2. Collect at least 3 replicate samples from each location.</p> <p>Line 208-209 should be changed from a 'bullet' to a '#3', adding the deleted sentence from #2 to the end:</p> <p>3. Assay one sample per location ( ..... blender). Samples should meet the following criteria:</p>	Instructions about how many to assay should be before, not part of, acceptance criteria provided on lines 211-213.

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27.	Line 216 (revised)	<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. 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, evaluate the dosage form data as described in Section VI</p>	<p>Attachment 1 needs to be slightly revised to conform to this change in wording. The box containing the text,</p> <p>“Assay at least seven dosage units per each location, weight correct each result”</p> <p>should be moved to be just under the box containing the text,</p> <p>“Assay 2nd and 3rd blend samples from each location”</p>

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28.	224-233	<p>Move section under V. 1.</p> <p>After the word risk in line 224 add “or physically impractical ( example, large V-Blender.</p>	<p>This section seems to describe the general practice of sampling. It would flow better if placed as suggested, where the guidance discusses locations of sampling.</p> <p>Some blender installations due to size of the blender or room considerations do not lend themselves to safe or practical sampling in the blender. In such cases sampling from drums after discharge may be justified as long as location sequence is maintained.</p>
29.	236-314	<p>Reformat for clarity:</p> <p>Combine this section VI with section V, to create a ‘validation’ section. Rename this subsection to refer to something referring to ‘in-process dosage unit uniformity (or homogeneity)’</p>	<p>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.</p>

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30.	240,265	Change "normality" to "distribution of the data"	Actually, 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. A normal distribution is acceptable, but not required.
31.	241	Add the word 'the'. "Determine the RSD..." and remove the last 3 words from the sentence "that were developed."	clarity
32.	243 & 282	On Line 282, change "If your test results meet this criteria for all batches, they are classified as ..."	Draft does not explicitly state that all validation batches must readily pass in order to use SCM

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33.	250	<p>Change wording to:</p> <p>“Prior to the manufacture of the batch, carefully identify locations...”</p> <p>(Consider adding a cross-reference to Section IV-B as the recommended approach.)</p>	Current wording does not explicitly state that sampling locations should be determined “prior” to the validation exercise, as PQRI proposal does.
34.	257-258	<p>At the end of the bullet, add:</p> <p>Assay all 7 per location if required in Section V.</p>	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.
35.	Between 258 and 259	<p>Add :</p> <ul style="list-style-type: none"> <li>• Analyze the dosage units according to the flowchart in Attachment 1.</li> </ul>	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 and acceptance criteria, if needed.

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36.	Amendment line number 260 (new text)	Change 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.”	Actually, 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. A normal distribution is acceptable, but not required.
37.	265	Change “normality” to “distribution (e.g., unimodal, bell-shaped, normal)”	See comment number 36 above.
38.	268	Remove the phrase “In addition to this analysis of batch normality” and replace with “Additionally, we recommend...”  Change “normality” to “distribution (e.g., unimodal, bell-shaped, normal)”	See comment number 36 above.

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39.	273	Change to "For each separate batch, compare the weight-corrected test results to the following criteria:"	Clarification for those not familiar with PQRI proposal
40.	277	Add a space between 'to' and '110.0'.	typo
41.	289-291	Change to "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:"	To comply with the Amended line 283, which describes how many to test. Plus, clarify the data are weight corrected for those not familiar with PQRI proposal.
42.	293	Change to "...results (for each batch $n \geq 60$ ) the..."	Must be for each batch. - Clarification
43.	314	There is no mention about including the beginning and end of the batch in the 10 locations for stratified sampling. Is this intentional?	The PQRI proposal specifically states that the beginning and end of the batch should be included in the 10 locations for routine testing (pp 8-9 of 15).
44.	319	Delete the word "the" that precedes "routine".	Clarity

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45.	337	<p>In addition to the amendment text, add another bullet:</p> <ul style="list-style-type: none"> <li>• Previous routine test was per SCM and passed SCM criteria.</li> </ul>	<p>3 scenarios to use SCM exist in PQRI document:</p> <ol style="list-style-type: none"> <li>1. Validation was readily pass and we are just starting production</li> <li>2. Routine test method is SCM and we continue this as long as we keep passing</li> <li>3. Routine method is MCM, but switching rule is met</li> </ol>
46.	354-355	<p>Change the first sentence to the same wording used in the first sentence of 368-369.</p>	<p>The first sentence should be the same; so the difference in wording is confusing. Line 368 is written more clearly.</p>

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47.	Line 366	Add the following bullet following Line 366: All samples within 75%-125% of label (not corrected for dosage form weight)	Without this statement, it is possible that a core (uncoated) tablet could exceed 75% - 125% of label and still pass the routine criteria. If CU testing for compendial requirements is being done on the coated product, and if this did not again occur, this batch would technically meet all requirements.
48.	375-376	Change "either...is met" to "any...are met"	
49.	382	In addition to the amendment text, add another bullet: <ul style="list-style-type: none"> <li>• Previous routine test used MCM and passed MCM criteria</li> </ul>	3 scenarios to use MCM exist in PQRI document: <ol style="list-style-type: none"> <li>1. validation was marginally pass and we are just starting production</li> <li>2. routine test method is MCM and we continue this until we can switch</li> <li>3. last batch started as SCM, but had to go to MCM to pass</li> </ol>

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50.	383	Add sample size: "...from Stage 2 SCM (n $\geq$ 30) analysis ..."	For additional clarification
51.	Line 384	Change "Marginal Verification Method (MVM)" to "Marginal Criteria Method (MCM)"	Correction
52.	390	Add 1 word: "We recommend that all results obtained from analysis..."	Clarification
53.	Amendment line number 395 (new text)	Minor changes to 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
54.	Line 396	Or adopt at, in or on-line measurement systems to ensure adequate powder mix assessment.	PAT initiative mentioned in line 71

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55.	404	Change "...criteria and result in RSD..." to "criteria and for each batch the RSD..."	Clarification. This has currently been misread that all batches are combined together to get RSD. Each batch RSD must meet this.
56.	Line 416	(CTD17 3.2.P.3.3). Replace with P.3.4	Drug Product Draft Guidance January 2003 lists controls for critical steps under P.3.4
57.	Delete 418-420	Replace with: Methods that will be used to demonstrate the adequacy of powder mix.	It is not customary to place detailed descriptions of sampling plans in the drug product application. These are compliance issues and can be examined by the investigator at the PAI.
58.	Delete 421-426	Replace with: Data that confirms suitability of the powder mix and dosage product uniformity	Once again the detailed requirements for data presentation in an application are inappropriate
59.	423-424	Change "demonstrating a normal distribution" to "evaluating the distribution"	A normal distribution is acceptable, but not required.
60.	Line 429	(CTD 3.2.P.4.1) Replace with P.5.1	P.5.1 applies to specifications for drug products

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61.	Delete Lines 431-433	Replace with: Test procedures and acceptance criteria for finished product uniformity of content	Here too the detailed requirements for data presentation in an application are inappropriate
62.	Line 436	(CTD 3.2.P.2.2) Replace with P.2.3	P.2.3 applies to manufacturing process development.
63.	Delete Lines 438-442	Replace with: Data that relate powder mix uniformity, in-process dosage uniformity and finished product uniformity	It is recognized that powder mixing is a critical step but statistical correlation is not required to show adequate control and goes beyond the requirements presented earlier in this Guidance
64.	456	Change 95.0% to 95.0% of target	The document should state that the blend is expressed as a percent of target. Otherwise the 10% absolute doesn't make sense.

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65.	471-475	comment 60: lines 471-475 Change 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.	To match the technical PQRI definition and to clarify that this sampling strategy is a type of random sampling.
66.	Attachments	Change attachment 2 in two places: Replace 'Adequacy of mix is demonstrated' to 'Adequate Powder Mix'.	This change makes Attachment 1 and 2 agree with one another.
67.	Attachment 1	Other attributable cause (analytical error)	

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68.	Revised Attachment 1 flowchart, line 498	Move box "Assay at least 7 dosage units per each location, weight correct each result" (from line 507) up to after box that says "Assay 2nd and 3rd 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.
69.	Revised Attachment 1 flowchart, line 508	Replace box that says "Assay at least 7 dosage units per each location, weight correct each result" with box that says "Use dosage units to verify adequacy of powder mix"	Although the results were assayed earlier to help in the blend investigation, now we have identified blend sample error so they must be used to demonstrate uniformity of mix.  Note: Comment can be disregarded if comment 74 is accepted.
70.	Revised Attachment 2 flowchart	Change STM to SCM and Change MTM to MCM in top 2 boxes	Typos  Note: Comment can be disregarded if comment 74 is accepted.

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71.	Revised Attachment 2 flowchart	In top left box, change first criteria to “last batch was tested using SCM and met SCM acceptance criteria”	Clarification (because someone will read into this that if it was tested per MCM, but “met SCM acceptance criteria”, then SCM is OK now...)  Note: Comment can be disregarded if comment 74 is accepted.
72.	Revised Attachment 2 flowchart	In top right box: remove the first sentence, “Last batch met STM acceptance criteria”	This is not clear as written. 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, they would <u>not</u> use MCM.
73.	Revised Attachment 2 flowchart	Add document section numbers to a few boxes	To clarify and to connect back to the text
74.	Revised Attachment 2 flowchart	Change box: “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”	Clarity. Some have misread that we would not have to use all previously generated data.

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75.	Specifically 80, 82 & 160 and globally wherever the term occurs	Change "Correlate" to "Compare"	"Correlate" has a specific statistical meaning.
76.	Specifically 108, 115, 143, 146, 167, 172, 238, 438 & 441 and globally wherever the term occurs.	Change "Correlation" to "Comparison"	"Correlation" has a specific statistical meaning.
77.	477	Replace with term, "Target Strength"	Clarification

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78.	N/A		<p>An exact definition is needed in the document of the term “ Powder Blend.”</p> <p>Specifically:</p> <p>Clarification is needed concerning whether a wet granulation is included in this definition.</p> <p>Clarification is needed concerning whether the following encapsulated bead products are included in this definition:</p> <ul style="list-style-type: none"> <li>• Single bead type</li> <li>• Multiple bead type</li> </ul>