

Appendix B

Matrix of Rationale for Each of the Editorial Suggestions

Justification and Rationale for the recommended word changes:

Line # in edited copy	Justifications/rationale for the change(s)
20-28	<ol style="list-style-type: none"> 1. More definition around 'powder blend' and 'dosage units' would be helpful. 2. In the introduction, it would be more helpful to highlight the ultimate benefit/goal of this guidance, rather than listing the steps to get there.
45-46	<p>The approach in the 1999 draft guidance and the subsequent recommendation proposed by PQRI are new approaches to demonstrate adequacy of mix. These are an alternative to current practice by many companies, which includes thorough development and blend uniformity validation and routine monitoring of uniformity of dosage units and in-process weight control. In order to institute the new proposal, a transition period is requested.</p>
65-68	<p>The term 'stratified sampling' in italics implies a definition (remove italics). The technical definition for stratified sampling is not limited to dosage units, thus the word order is changed to comply with the PQRI proposal and definition.</p>
69	<p>Clarity. 'Output' is not responsible for variability, location differences may be though.</p>
70-71	<p>Clarity. Note: using this test for USP CU is not the main purpose, nor is it necessarily a 'given'. A comparison must be made, so some 'qualifier' statement is good here ('in some cases' or 'when appropriate').</p>
79-81	<p>The draft guidance expanded the scope beyond the PQRI proposal. PQRI BUWG did not discuss the technical ramifications, given these higher concentrations of active. Plus, the expanded scope was not considered by the respondents in the FDA-sponsored industry survey. This change to the PQRI proposal will increase costs for NDA and ANDA products currently tested by USP Weight Variation. If FDA keeps this expansion, a statement that clearly explains the broadening of this scope is needed, otherwise MANY will be caught unaware.</p>
89	<p>'Correlate' has statistical connotation. This will be corrected throughout the document.</p>
91-93	<p>Clarity and purpose is helpful here. There have been a lot of questions about this.</p>
Footnote 6	<p>typo</p>
105	<p>Current wording gives one situation when more samples may be needed. It is not limited to strength. Can this be more general so it can be based upon science?</p>
109-111	<p>Clarity</p>
119	<ol style="list-style-type: none"> 1. Section now includes development activities, only 2. The use of the term 'development' in the section title helps clarify (to all readers) that this section is a separate procedure from that proposed in Section V.
124-132	<ol style="list-style-type: none"> 1. for clarity 2. Removed reference to comparison of in-process and final product CU (this will more likely occur during validation, to obtain a sufficient amount of data for the comparison.) 3. This evaluation does not <u>have</u> to be performed on multiple batches, the plural use of the term batch in this paragraph implies to some people that all development batches need to include this evaluation. 4. Blending deficiencies should also be corrected before validation. 5. Did the draft imply that this development evaluation may be performed using validation or production batches? This was not clear the way they were included in that sentence. If this was the intent, it may be better to add a sentence to this proposed text: "This development evaluation may be performed using validation or production batch(es) for existing products.
136-138	<p>A purpose statement will help clarify the reason for the section and for the lack of acceptance criteria.</p>
141-147	<p>Since this is the step where we identify the critical locations to sample from for validating a blend and comparing it to in-process samples, basic information provided in the validation section of the draft should also be copied here. For completeness, we recommend keeping references in both places (this is fundamental information).</p>

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Footnotes 9 & 10	9 – clarification 10 – establish typical minimum sample sizes, since this is the step where we identify the critical locations to sample from for validating a blend and comparing it to in-process samples
149-150	It is not clear what ‘sampling errors’ are to be determined. Sampling error is already covered in the next bullet, when evaluating sample quantity. Sample size is more commonly considered to be the # of samples, where this is a physical quantity.
156	Unnecessary. A sample plan includes: locations, size, and technique. These are already covered in previous bullets. Analysis is covered in the next bullet.
157-162	1. Clarity. 2. ‘Significant’ has statistical connotations. ‘High’ is consistent with PQRI terminology. 3. Analytical error is another possible cause of high within-location variance.
163-165	This bullet wraps up the entire purpose for this section about blend sampling. This sampling and testing plan should be used when pulling blend samples to validate uniformity of blend and the use of stratified dosage units (Section V, line 219).
167-168	Clarity
170-173	Define the purpose of this section (to identify in-process sampling locations), thus the lack of acceptance criteria. Note: sampling location requirements are different from validation requirements, per PQRI proposal.
176-178	‘Intervals’ describes this best. ‘Recommended’ terminology is included to be consistent with the wording used throughout the guidance.
180	To be consistent with the previous bullet, we recommend at least 7 per each location.
Footnote 14	The draft only mentions the number to be sampled. Questions arose as to how many are assayed. Since this depends upon the product performance, a minimum is suggested so that a within-location variance may be established.
182-184	Seems out of place here. See rationale for Lines 124-132.
187-191	Clarity. There was a lot of confusion with the proposed draft wording. Minimum sample size reference is added, thus this bullet provides future requirements for validation of the stratified sampling (used in Sec V).
191-192	See footnote 23, page 14. Can alternate wording be used here due to this situation?
193	Consistency
199	Another possible word choice. More specific. Obviate = prevent/ avert negate= cancel out/undo/contradict
200	Example helps, PAT is more commonly recognized
202-215	Most likely, 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.
219-220	Clarity
222-223	Moved to lines 236-237, more appropriate given the proposed format changes.
226-232	Although data are collected and analyzed separately, the overall assessment of ‘blend uniformity’ must include evaluating both dosage unit and blend data as a whole. The purpose of Section IV is to identify sampling requirements, thus it is referenced as the ideal way to identify locations prior to validation.
236-237	Moved from 222-223, since this describes the purpose for demonstrating powder mix uniformity (Sec V.A)
238-243	Moved from 285-290. This puts it into logical order.
Footnote 18	In general, weight correction also works for capsules, so ‘dosage unit’ is used.
246-249	Clarification
255-262	Instructions about how many to assay should be before, not part of, acceptance criteria provided on lines 264-266.
269-278	This incorporates the use of dosage units to assist in the investigation, using the revised FDA text for these lines.

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280-283	Per the PQRI proposal, to completely demonstrate adequate powder mix, one needs data from both blend and dosage units (due to potential post-mixing material handling segregation). The flowchart in Attachment 1 requires dosage unit testing whether blends pass stage 1 or not. After both sets of data are evaluated, then 'adequate powder mix' is demonstrated (cross-reference, Attachment 1). Given the Attachment, these lines are not needed and inappropriate.
285-290	Moved to 238-243.
Footnote 19	Clarity
296-299	<ol style="list-style-type: none"> 1. Combine this with section V, to create a 'validation' section. 2. The guidance avoids the term 'validation', using less-descriptive titles like "verification of manufacturing criteria". We recommend including industry standard terms 'validation' and 'development' to clarify the purpose of various sections. 3. This is the second-half of demonstrating adequacy of mix. 4. This section includes the classification of the uniformity.
301-303	Previously mentioned
303-306	For continuity, this is a similar purpose statement to the blend section's (lines 236-237).
306-308	Too much detail for a purpose statement. This is included later in the document.
308-310	<ol style="list-style-type: none"> 1. Generalized the statement for the purpose. 2. Classification needs to consider all batches tested.
313	Reformat this to a subsection of V.B
Footnote 20	Cross-reference
325-331	There is no connection here back to the flowchart in Attachment 1 (or possible requirements by blend to test at least 7). 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. Plus, the Attachment provides acceptance criteria. To be consistent with the blend section, the criteria are added for stratified data.
333-338, 340	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.
341	Data may not be available to be included in the application.
343	Reformat this to a subsection of V.B
345	Additional reference to shape not needed here.
350-358	For clarity & consistent terms with glossary
360-365	Clarity, all must pass 4% for validation to be 'readily pass'. Additional data are compared back to the 'readily pass' classification criteria (not SCM).
348, 367	Both are formatted within V.B.2 for clarity, since this classification is 'either/or' not separate steps.
370-371	Clarity. Plus, to be consistent with lines 362-365, which already give assay requirements.
373-379	For clarity & consistent terms with glossary
383	If appropriate, means the failing result is intrinsic to the process. If a single batch fails 'marginal pass' and the root cause is identified to be due to a deviation from the validation process (say materials were not added in correct order) or assay, we do not want to go through revalidation of all comparisons.
388-407	<ol style="list-style-type: none"> 1. Moved from development section, since sufficient data at full scale are likely not available at a sufficient amount prior to validation. 2. Added a note saying that this can be performed in development in lieu of validation. 3. Slight change to reporting reference, since it may not be available in the application, but will be available at PAI.
416	Standard test (Attachment 2) was established for routine use of n=10 locations. Slight word change emphasizes that 10 is OK.
422-423	Clarity

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437-445	There are 3 scenarios that permit SCM. This adds clarity. Many have been confused by the current wording
461-464	The first sentence should be the same as 477-478; so the difference in wording is confusing. Line 477 is written more clearly.
469-470	Clarity
477	"and uniformity of content" is throughout this document. There are at least 3 possibilities, however (1) data are not comparable (for a coated tablet) and both test must be performed (2) data are comparable and the routine blend test is used to demonstrate both (3) data are comparable and the same assay results are evaluated using both USP CU criteria and routine blend test criteria. Please consider this in your revision.
483-485	For consistency with the opening sentence for section VI. A. Deleted info is previously provided and was not re-stated at the SCM discussion.
487-495	There are 3 scenarios that require MCM at the start of the test, plus the movement from SCM to MCM within the flowchart. This adds clarity. Many have been confused by the current wording.
497-501	To be consistent with the level of detail provided for SCM (lines 453-455), plus the reference to stage 2 SCM (line 500) is only appropriate for 1 of the 4 previous scenarios.
509-510	Focus on the primary purpose of the test. Per USP, it is allowable to use a replacement test if you have demonstrated an equivalency to an in-process test.
511-513	Clarity and consistency with section title.
514	If a single lot fails 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) or assay, 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.
516-517	Another opportunity to discuss PAT type technology.
519	Incorrect terminology
524	Clarification. This has been misread that all batches are combined together to get RSD. Each batch RSD must meet this.
536 & footnote 23	We believe these data are important to summarize, but we are afraid that to meet customer-driven, quick submission timelines that possibly only small-scale batch data will be available at submission. Sufficient full-scale data are collected prior to PAI, so summaries can be available at the manufacturing site for FDA review (and submitted in Annual Updates). Requiring this in the submission may lead companies to making these judgments based upon small-scale batches, which may not include all potential blend uniformity issues as full-scale. Please give consideration to how this section (and all references to it) may be revised to consider this.
541	Standard
550	Same issue as above
556-563	Same problem occurs with lines 559-563, regarding batch size data available at initial submission.
592-597	To match the technical PQRI definition and to clarify that this sampling strategy is a type of random sampling.
599	Both are used interchangeably in the document.
606	In general, weight correction also works for capsules, so 'dosage unit' is used. (example referencing a tablet is OK)

Line # in edited copy	Justifications/rationale for the change(s)
Attachment 1	<ol style="list-style-type: none"> 1. change title to agree with section title 2. move box with “assay at least 7 dosage units.” up to after the “assay 2nd and 3rd blend...” box, since the dosage unit data is generally used as part of the investigation to help correlate blender problems or identify sample bias. 3. add a new box after mixing problem is NOT identified, to clarify that dosage units are used to verify (at least 7 have been assayed). 4. example at bottom, changed terms to match more-common used ‘potency’ in document
Attachment 2	<ol style="list-style-type: none"> 1. There has been confusion over the 4 boxes. 2. Please incorporate the common industry term ‘validation’. It is highly recommended that you consider using this proposed text or something close to it for the 3 scenarios listed within each criterion. 3. Text in first diamond is changed to match new text replacing the 4 boxes. 4. When switching from SCM stage 2 to MCM, we need to clarify that all SCM data is included (prevent incorrect interpretation), thus the additional statement.