SCORECARD: PhRMA Comments on:
Draft FDA Guidance "Comparability Protocols- CMC Information" (Docket No. 03D-0061, CDER 2002180.)
February 2003

Total Number of Changes Suggested: 73

Section	Guidance Line	Comment	Rationale
General comment		It is important that the definition of comparability be pre-defined in the acceptance criteria of the protocol. An example of a criterion comparing the related substance results from two processes could be that 'To demonstrate the comparability of the processes, the total related substance average from process 2 cannot exceed that of process 1 by more than 0.25%'.	
General comment		Parts V, B-G should have their own section title (section VI for example) "Specific Protocol Issues." Sections V, H & I should also be a separate section (section VII for example) "Additional Issues for Comparability Protocols on Master Files" (for example).	Overall format consistency
General comment		The usefulness of comparability protocols will be dictated by how easily they fit into overall project timelines. Two points could be addressed: 1. reduced FDA approval timeline for comparability protocol review and comment (rather than 4-6 month current PAS requirement) 2. inclusion of other FDA groups (Tox/Biopharm) in protocol review to assure completeness of FDA response	1. In some cases, it will be faster to call the FDA with a specific question, documenting the teleconference, rather than waiting for the approval of a Comparability Protocol in a PAS, and then completing the work and submitting the application (with reduced submission reporting category) to FDA. 2. Some points such as impurity qualification or dissolution evaluation include FDA groups in addition to the CMC reviewers.

Section	Guidance Line	Comment	Rationale
General Comment		Section titles constructed as questions seem odd. This construction should be avoided. Providing guidance in the form of "you should" is also odd and uncommon in Agency guidance.	Such headings are inconsistent with the format of other Agency Guidance documents. Shorter section titles would be more beneficial and easier to scan and use.
I.	24; footnote 2	Use of the same term "product" to mean anything from drug substance starting material to finished drug product allows for excessive ambiguity in later parts of the Draft. For example: ▪ In lines 40-41 and lines 98-99, GMP-type characteristics appear to apply to drug products only; ▪ It is unclear if lines 476-520 refer mainly to biological drug substances or also to the products made from them, and how the SUPAC Guidances (drug product processing) would be applied	In parts of the Draft in which the FDA recommendations might apply to more than one component, more specific verbiage to specify drug substance, intermediates or drug product should be used.
I.	33-34	FDA Draft notes that "should" (in the text) indicates an Agency recommendation, rather than a requirement. Please add a clarification indicating the wording that will be used for required elements.	Clarification of required elements "must" vs. "should" vs. "may"

Section	Guidance Line	Comment	Rationale
II.	39-45	Background or Introduction Section needs a glossary to provide the sponsor with a clear definition of regulatory and technical terms used in preparing a comparability protocol. Examples for a glossary are: *comparability protocol, comparability report, analytical reference standard, related CMC changes, unrelated CMC changes, drug substance, intermediate, drug product, isoforms, orthogonal testing, product-specific, process-specific, current protocol, obsolete protocol, qualification or validation lots, PAS, reportable categories, method validation, process validation, FDA review period, criteria for non-comparability, stability-indicating assays.*	Glossary needed
II.	42	Change "(the act)" to "(the Act)".	Typographical correction
II. A.	97-103	Indicate the difference between a comparability protocol (CP) and a validation protocol.	Once a CP is approved: a) if the change is small and the evaluation is being performed on commercial scale, a validation protocol should not be required, b) if the change is significant and the evaluation is being performed on a small scale batch under the CP, then when the change is implemented on full scale, a validation protocol will be prepared.
II. A.	98	Change "in" to "on".	Grammatical change
II. B.	107-109	In footnote 5, clarify how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached (i.e. discussions).	Clarification.

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II. B.	109-111	Change from: "Furthermore, because a detailed plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)." Change sentence to: "Furthermore, because a detailed plan will be submitted in the comparability protocol, FDA has the opportunity to provide input earlier in the change process and is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception)."	When using a Comparability Protocol, the applicant benefits by receiving FDA's comments regarding the change and assessing the effects of the change earlier in the process than would occur without the use of a Comparability Protocol.
II. B.	110-112	Would the FDA Review Chemist take on the role of distributing comparability protocols that cross FDA disciplines, and providing a consolidated FDA response to the NDA sponsor, or would the sponsor need to send copies for binding comment to other FDA groups?	CMC elements such as comparative dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Clarification of the administrative process needed to obtain a binding FDA agreement on the Comparability Protocol is requested.
II. B.	112-113	Indicate when validation is performed.	Validation can be performed post-approval of the CP or concurrent with CP approval.
II. D.	127-143	Additional FDA or ICH Guidances addressing dissolution testing, impurity comparisons and bioequivalence should be cited.	CMC elements such as comparative dissolution are influenced and in some cases, reviewed by, FDA groups in addition to the Chemists (for example Biopharmaceuticists or Toxicologists). Therefore, other Guidance recommendations concerning "demonstrating equivalence" should be provided

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II. D.	143	Add a bullet for BACPAC documents, and a foot note: "BACPAC (Bulk Actives Post Approval Changes)"	It applies to this guidance.
III. A.	148-150	Change from: "A comparability protocol *prospectively* specifies the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be achieved to assess the effect of CMC changes." Change to: "A comparability protocol *prospectively* specifies how the effect of CMC changes will be assessed (i.e., the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be met)."	The revised wording makes the meaning of the sentence clearer.
III. A.	152-157	Give an example of when a reduction of more than one category is possible. Indicate how the reduced reporting category is ensured. Additional detail should be provided in the guidance to explain how process complexity, robustness and capability are considered in the determination of multiple-level reporting category reductions. Specifically, a non-complex, robust, capable process should be able to readily utilize multiple level reductions, even for comparability protocols involving several related changes.	It is not clear how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached (i.e. discussions).

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III. A.	154-156	Change from: "Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30, CBE, or AR)." Change to: "Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30; from CBE-30 to CBE; or from CBE to AR)."	The current example is confusing. Going from a PAS to an AR would normally be considered a three-category reduction.

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III. B.	163	CMC changes do not have to be "related" to qualify for comparability protocol. Below are examples of unrelated manufacturing changes that could occur at different steps within a process but would still qualify for submitting a comparability protocol: ◆ Change in vendor for supplying the same starting material ◆ Modified a component(s) for milling equipment ◆ Changed hold time between two steps of a purification process ◆ Used new improved resin for a chromatography step ◆ Used a low extractable polymer for container/closure system component. A comparability report would have to demonstrate that the sum of these unrelated process changes had no adverse effect on the identity, strength, quality, purity or potency of the final drug product. Results would be compared to established specifications for the analytical reference standard used to release drug substance or drug product produced without the changes.	CMC changes do not have to be "related" to qualify for comparability protocol.

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III. B.	163-164	Change from: "However, we recommend that each change be discrete and specific". Change to: "The use of the Comparability Protocol for technology specific changes (e.g., change in filtration process) that broadly apply to multiple products is also appropriate. Process complexity, robustness and capability may help determine the appropriateness of including multiple related changes in a comparability protocol."	Wording should be broadened to allow technology-specific multiple-product changes (e.g., new bottle for several solid orals). Also, the guidance should describe situations where multiple related changes are appropriate for a comparability protocol.
III. B.	168-170	This line implies that the purpose of the acceptance criteria is to demonstrate that no adverse effect occurs as a result of the change. However, Section II D line 134 implies that the purpose of the acceptance criteria would be to demonstrate equivalence. Demonstrating equivalence and demonstrating no adverse effect are not the same.	The definition of an Adverse Effect is a key element, which should be stated in the protocol. A significant change in the production process doesn't have to mean that the product is affected adversely. Is the definition of adverse effect that there could be a change in the product's characteristics so that the patient health is at risk? Or is the change, per se, an adverse effect?
III. B & C.	183 and 211-213	The Draft appears to be stating that a change in impurities requiring a safety evaluation might or might not be amenable to a CMC Comparability Protocol. We request clarification.	The two passages seem contradictory.
III. B.	190-194	We recommend Lines 190-194 of the text be moved from the end of this section to the beginning of this section, so it appears more prominently to the reader.	Proposal will emphasize that comparability protocols should only be considered when changes associated with product-specific and/or process-specific attributes are well known, capable of being detected with established, validated or qualified, analytical procedures, and expected to meet previously approved specifications.

Section	Guidance Line	Comment	Rationale
III. C.	227	Add "For the API," at the beginning of the sentence.	Such a change for excipients should be possible in a comparability protocol. (e.g., switch from animal-based magnesium stearate to vegetable based magnesium stearate)
III. C.	224-226	Change the bullet to include underlined text: "A change from plant, animal, or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal), depending on the extent of the purification process"	If the downstream purification process is extensive it should be possible to handle such a change under a comparability protocol.
III. C.	227	Change the bullet to include underlined text: "A change from synthesis-derived to naturally sourced material and vice versa, depending on the extent of the purification process"	If the downstream purification process is extensive it should be possible to handle such a change under a comparability protocol.
III. C.	229-231	Delete lines 229 – 231 and insert the following new paragraph: "When a Manufacturer moves a process to a previously uninspected manufacturing facility, the approval of the Comparability Protocol signifies that the Manufacturer should notify the field that the facility is ready for inspection status. The inspection should be scheduled prior to the submission of the agreed data package to the review division. Upon receipt of the acceptable GMP status, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol."	Since both a Comparability Protocol and a change to a site which requires a cGMP inspection must be submitted as a Prior Approval Supplement, why would it not be appropriate for the Comparability Protocol to be used as the trigger for the cGMP inspection? Then, after the PAI and Comparability Protocol approval, the site change could be reported at the reduced reporting category.

Section	Guidance Line	Comment	Rationale
IV. A.	238-252	Where is the comparability protocol (and report) placed **within** the structure of the CTD? Would comparability protocols (CP) be placed as regional-specific templates in the specific sections under which they directly apply, (i.e. if a CP is for a drug product manufacturing process change, the template would be placed under CTD section 3.2.P.3.3 Description of the Mfg Process)? If that is the case, what would be recommended for those CPs that support multiple changes?	
IV. A.	238-240	The Draft notes that the cover letter for the application should state that a comparability protocol is in the submission, to properly direct review. It is unclear whether this is also the case for original NDA cover letters, which typically don't get into the specifics of what documentation is in the submission.	The administrative process and cover letter annotation for original NDAs needs clarification.
IV. A.	244-245	Indicate why a CP can not be submitted as a CBE or CBE-30. Why not make the submission format consistent with the nature of the change as specified in FDA guidances rather than making all protocol submissions PAS. There needs to be clarity on how long FDA will take to review a comparability protocol. When submitted as a PAS the implication is the review is up to 180 days like a PAS for all protocols. The intent of the protocol is to obtain consensus with FDA on the documentation required to support the change and the filing strategy/plan. In essence protocols are submissions without data and should track with the categories already defined in FDA guidance documents.	The bullet indicates that a CP itself is always in a PAS.

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IV. A.	246-250	Re-write to indicate that the PAS "can" include the CP.	The way it is stated may lead to an expectation that a protocol also needs to be submitted together with a proposed change which is contrary to the intent that the CP is optional (line 103).
IV. A.	251-252	This is the best way for a CP to be submitted to result in time saving when performing the change.	If the CP is submitted by itself as a PAS, the only benefit would be if the data can be generated in parallel with the approval process, and the change implemented as soon as the CP is approved.
IV. A.	254-255	Guidance states the protocol must be approved prior to implementing the change. Protocol review times are not defined or described.	If reviews are more than 30-45 days, the sponsor will lose a lot of time (i.e. getting stability studies started early) on making the change. Comparability protocol review should be less than the agency review for post-approval supplements; otherwise it defeats the purpose for a reduction in reporting category.
IV. A.	254-259	This paragraph suggests that product made under the change can be distributed after the assessment. This paragraph should also contain the following information: "The applicant must assess the effect of the changes ... and submit the changes in accord with the reporting category designated in the approved protocol prior to distributing ... "	There is no mention of a submission. The purpose of having an approved protocol is to reduce the regulatory filing requirement by (possibly) one category. If, for example, a PAS change can now be filed as a CBE-30 under a comparability protocol, then the product cannot (should not) be distributed until after the 30 days. Therefore, the concern is that the paragraph makes no mention of a filing.

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IV. B.	265-268	Change from: "The submission would include (1) the results of all tests and studies specified in your comparability protocol (2) discussions of any deviations that occurred during the tests or studies, (3) a summary of any investigations performed, and (4) any other pertinent information." Change to: "The submission would include (1) the results of all tests and studies specified in your comparability protocol and (2) discussions of deviations, investigations, and other information pertinent to the change being made."	Not all investigations and deviations may be pertinent to the change being made. For example, the presence of extraneous contaminants must be examined, but is a cGMP compliance issue, not a registration issue.

Section	Guidance Line	Comment	Rationale
IV. C.	276-282	Current statement: "If you decide to pursue the change, you should submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as these factors relate to the safety and effectiveness of the product." Add to the end: Where unexpected data are gathered, the change should be evaluated to confirm that the expected product is not compromised and that the results were inconsequential. The results should be reported to the review division prior to formal submission of the data and, with the approval of the review division, may be submitted under the previously agreed submission requirements. Where the submission requirements of the product are not met, the submission should meet the filing requirements established in other related guidance, if applicable, or as determined in consultation with the review division.	If the studies in a Comparability Protocol lead to an unpredicted or unwanted outcome it appears that there are only 2 choices: not implementing the change and/or submitting a PAS. However, modifications to the protocol to provide for a different change should be permitted. Add a sentence to the end of the paragraph providing provision to allow for discussion if non-consequential acceptance criteria are not met. Provisions should be made that if the acceptance criteria are not met, the change should not automatically be bumped to a PAS. Also, where the Comparability Protocol criteria are not met, we recommend the use of the reporting category that would normally apply for the type of change instead of being required to submit a PAS. There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria is of so little consequence that the original reporting category is still appropriate and can be maintained.

Section	Guidance Line	Comment	Rationale
IV. D.	284-296	With regard to the determination of "obsolete", will investigators check for the "obsoleteness" of these protocols during inspections? Will FDA have any way of tracking these to determine when they become obsolete – or is it strictly up to the sponsor? FDA and sponsors can view the definition of "obsolete" (based on the considerations given here) differently. The determination that a technology is no longer adequate should lie with the firm, not with the Agency. We encourage the FDA to reconsider the practice of allowing a single individual or small component of the organization to determine that a modification is "obsolete" and, consequently, of reduced value. We encourage the Agency to evaluate only the adequacy of the change made and not the technology used to implement a change, where the change is "feasible and valuable" to the manufacturer and not necessarily at the pinnacle of technology.	General comment
IV. D.	284-296	Although the Agency intent is clear—to maintain use of appropriate protocols—the wording is ambiguous. Line 291--Replace "current FDA policy" with "current FDA Guidances". Line 295—specify how a protocol is withdrawn.	"Policy" is an overly broad term not restricted to CMC issues. Draft states that a protocol may be modified by a PAS submission (Part IV.E), but does not state how a protocol is withdrawn. PhRMA recommends the use of the Annual Report to withdraw protocols.
IV. D.	286-288	Screening for new infectious agents from a biological source is a dynamic state. Changes occur constantly as new technology and methods are acquired. Currently, there are no current compendial test methods available to quantitatively assess BSE/TSE risks. Would the CMC information required to obtain an EU Certificate be satisfactory for FDA, or would FDA require additional/different CMC information for BSE/TSE safety assessments?	

Section	Guidance Line	Comment	Rationale
IV. E.	298-312	The wording of this passage is awkward. Is the FDA trying to state that when a parameter in an approved protocol is changed we can get the change approved and the protocol approved in the same submission, thus not having to get approval for both the parameter change and the protocol change separately? The use of a decision tree or flow chart would simplify the presentation.	Clarity.
IV. E.	299-300	To avoid revising a protocol, it is recommended that, when predictable or possible, different options be submitted in the protocol.	Need for flexibility.
IV. E.	299-303	Changes to the protocol that provide increased control should be treated in the same manner as any CMC change that provides increased control. These should be filed as a CBE-30, not a PAS.	Consistency and burden reduction.
IV. E.	303	Revisions to the comparability protocol should be tracked in the annual report, similar to the CMC index. This would be a sub-CMC index for changes made to the protocol over the life of the protocol.	Need a system to track the status of comparability protocols (modifications/deletions)
IV. E.	316-317	It is stated that notification of editorial changes to a comparability protocol can be provided in the AR. It is not clear which type of changes can be made/categorized as *editorial* and thus can be provided in the AR. A clarification is requested. Examples might be included.	Clarification of procedure to be followed and submission category to be used for modifications to an approved comparability protocol.
V.	323	Change to include the underlined text: "We recommend that a comparability protocol be developed and used within the context of existing change control procedures <u>at the firm</u>."	Clarification.

Section	Guidance Line	Comment	Rationale
V.	325-328	Allow for writing CPs as technology specific, across several products; or to address a change that affects the manufacturing of several or numerous products, particularly when the change is necessitated by new FDA or ICH guidances. Allow for cross-reference of protocols between products. Indicate the mechanism for this to happen.	Writing a CP technology specific, across several products, will result in time saving not only for industry but also for the FDA reviewers. It would be advantageous to obtain FDA agreement on how to file changes that could impact many products. For example, the improvement or development of a new method for evaluation of residual solvents used in the production of APIs. Often the same methods and same types of test data will be generated for multiple APIs each of which may be used in multiple products. As the comparability protocol is currently conceived such a change would require a separate protocol to be filed as a PAS for each drug product.
V.	330-334	Proposed change and data required to support it in a protocol should be in the context of current registration commitments. Example cited is not a good one.	The example cited implies that submitting a protocol for a simple raw materials change in a fermentation process would result (in FDA's mind) in the need to assess a range of fermentation and product isolation parameters that are not likely to be registered or for that matter well enough understood to discern equivalence or difference before/after the change.
V.A.2., 3. & 4.	Entire section	Use of a decision tree or flow chart would simplify the presentation, in particular for validation requirements of release and/or development characterization testing.	Several concepts are presented in "dense" text. The appropriate extent of validation information to be provided in the CMC supplement (in particular for characterization testing referenced in a comparability protocol) is unclear and may be excessive.
V. A. 2.	368	Inclusion of stability protocol information into the comparability protocol.	Cross-reference to an approved stability protocol should be adequate.

Comment: It is not clear to me what we are recommending here

Section	Guidance Line	Comment	Rationale
V. A. 2.	373	Add the following after the sentence ending in line 373: "Generally, data submitted as part of post implementation commitments may be provided to the FDA as a component of the Annual Report for the product."	Not all data will be collected at the time that information is provided in the follow-up submission, e.g., real-time stability data.
V. A. 3.	397-398	Change from: "Validation of new modified analytical procedures or revalidation of existing analytical procedures should be performed, as appropriate. Change to: "Modified analytical procedures should be validated, as appropriate, for their intended use Validation data should be retained at the manufacturing site for all methods."	Generally, only limited analytical procedure information is provided in the NDA for raw materials, starting materials, drug substance intermediates, excipients, and packaging materials. This section should not require more extensive information to support a change than what is required for a new drug. Analytical procedures are validated as appropriate for their use. This information should be held and be available at the manufacturing site.
V. A. 3.	398-401	Change to include the underlined text: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided (e.g., in AR or CBE) when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA."	Clarification

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V. A. 5.	440-444	Revise this paragraph to read as follows: "The comparability protocol should identify the following information, which will be submitted to FDA at the time a post approval CMC change is implemented under the FDA-approved comparability protocol: 1. the type (e.g., release, long-term or accelerated stability data) of data 2. the amount of data (e.g., 3-months accelerated stability data). 3. the data that will be generated prior to distribution of the changed product, where appropriate (e.g., when the proposed category is a CBE-30, CBE-0, or AR)."	The sentence is too long, leading to confusion.
V. A. 6.	455	The first sentence states that " ...use of an approved comparability protocol **may** justify a reduction in reporting category." Although the FDA intent that a protocol does not automatically result in a reduced reporting category is understood, this reduced regulatory burden is a primary motivator to the effort of submitting a comparability protocol for approval.	Most sponsors would probably not go to the trouble of preparing a comparability protocol if they would not get a reduction in reporting category.
V. A. 6.	460	FDA should clarify what the mechanism would be for reaching "agreement" with the applicant	

Comment: Is there a suggested revision here? If not, this should be deleted

Section	Guidance Line	Comment	Rationale
V. A. 7.	463-469	Delete this paragraph.	As it is difficult to determine prospectively (without the actual data in-hand) what steps would be taken if equivalence is not demonstrated, this paragraph should be omitted. Moreover, if equivalence isn't demonstrated, why refer to the protocol? Most sponsors would merely submit a "standard" PAS and request approval based on the included data (with justification).
V. B. 2	494	Revise to add the underlined text: "...or that they are <u>appropriately reduced</u>, removed, or inactivated by..."	In some cases, a low level might be good enough.
V. B. 1.	484-486	Change from: "A comparability protocol would normally include a plan to compare the physical characteristics (e.g. polymorph forms, particle size distribution) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product." Change to: "A comparability protocol would normally include a plan to compare the physical characteristics (e.g. polymorph forms, particle size distribution) when <u>(1) comparability is established after the final solution step of the drug substance synthesis and (2) these characteristics are relevant to the safety and/or efficacy of the drug product.</u>	As per BACPAC I, an examination of physical characteristics is required only when equivalence is demonstrated after the final solution step.

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V. B. 2.	491-492	Change from: "The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts." Change to: "The studies would assess product-related impurities and process-related impurities, including, if applicable, in-process reagents, catalysts, and solvents."	As per BACPAC I, demonstration of equivalence includes assessing residual levels of existing and any new solvents.
V. B. 2.	494	Add as next sentence on this line: "Comparability of the impurity profile can be established by testing an appropriate isolated intermediate following the change or the drug substance."	It is necessary to confirm that the demonstration of comparability at a certain step will not require complete processing from the modified step through unmodified steps to drug substance.
V. B. 2.	497-498	Does reference to a "relevant FDA guidance" exclude ICH Q7A?	

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V. B. 4.	518-520	Change from: "We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new production process, if appropriate." Change to: "We recommend a statement be included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be reassessed for the new production process, and revalidated, if appropriate."	Validation may or may not be appropriate in all cases. Each case will require individual evaluation.
V. C.	522-548	Since the regulatory filing requirements for the analytical changes would still apply, and the science surrounding analytical validation requirements is well documented, it is doubtful that the use of comparability protocols for analytical changes would provide significant sponsor benefit.	Time required might exceed timing of submission without approved comparability protocol, with little increased risk.
V. C.	546-548	Change the text to permit the following: 'When used for release or process control, use of the new revised analytical procedure should not result in relaxation of acceptance criteria that are described in the approved application. Deletion of a test described in the approved application should be possible when the comparability protocol has been applied and results demonstrate that the test can be replaced by a traditional analytical method or a PAT method with greater efficacy, e.g. tighter acceptance criteria than applicable to the deleted test'.	Proposal recognizes that analytical procedures including PAT can be developed with specifications that provide improvements over those contained in the approved application.
V. D.	550-557	SUPAC guidance should be cross-referenced.	

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V. E.	559-579	Add to the end of line 579: "If a Site Inspection is required and would typically be initiated by the submission of a prior approval supplement, the applicant is responsible for insuring that the site has a satisfactory cGMP inspection for the type of operation prior to implementation of a change in accordance with a commitment to the approved Comparability Protocol."	We suggest that the Manufacturer should be able to work with the local FDA office to schedule inspections related to the implementation of the comparability protocol. The Guidance should more clearly state whether FDA will permit a supplement in a non-prior-approval reporting category for a change to a new site which has not been inspected or does not have a satisfactory cGMP inspection; since prior approval inspections are usually prompted by, or requested via, the PA supplement process. For instance, standard packaging site changes require CBE-30 supplements, unless the site does not have a satisfactory cGMP inspection. An approved Comparability Protocol could allow for a packaging site change to be reported in an annual report, along with a statement (Lines 570-573) that the move will be implemented only when the site has a satisfactory cGMP inspection for the type of operation. This Guidance, as written, does not necessarily provide for use of such a Comparability Protocol, which places the responsibility of insuring completion of a satisfactory cGMP inspection without a PA supplement.
V. E.	570-579	If a change in manufacturing site is proposed for an aseptically processed product, would FDA sanction the site change if the specific facility or area had successfully met a cGMP inspection within two years of when the comparability report is submitted? If not, would successful media fills (3 lots) be satisfactory evidence if the last inspection period exceeded two years at the time the comparability report is submitted?	Clarification needed.

Section	Guidance Line	Comment	Rationale
V. F.	581-586	Add to the ends of lines II.B., (L 114) and V.F. (L 586): "Comparability Protocols are not needed to provide a list of supporting data that the applicant will provide to support changes that current guidance classifies as annual reportable. This information must accompany the change when it is reported in the Annual Report." Please clarify the use of the word "repetitive" in line 585. Does this mean ▪ a single change applied to numerous applications or ▪ a series of changes that have predefined acceptance criteria but which may extend beyond any single change?	Prior to the 11/99 PAC Guidance, applicants included a form of Comparability Protocol or interchangeability protocol which described changes that appeared to reduce the reporting category from CBE to AR (based on 21 CFR 314.70 requirements). In alignment with the allowable changes in the 11/99 PAC Guidance, there is no need to describe minor, annual reportable changes in a Comparability Protocol, except to provide a list of supporting data that the applicant will provide. FDA should state that they do not expect to see Comparability Protocols for Container/Closure changes that are described as annual reportable in the 11/99 PAC Guidance to simply provide a list of supporting data. ▪
V. H.	595-606	Spell out DMF/VMF holder and NDA/ANDA/NADA/ANADA holder responsibilities in communicating with one another when a comparability protocol references a DMF/VMF that is not held by the NDA/ANDA/NADA/ANADA holder.	This section needs clarification.

Section	Guidance Line	Comment	Rationale
V. H.	599-606	Change from: The protocol would include a commitment to provide a letter authorizing the FDA to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported FDA. Change to: The DMF holder should confirm that changes are properly reported to the FDA. Additional updates may be provided at any time or during the annual update. This information should include updated reference citations in the DMF. The DMF holder may unilaterally expand the information supporting the NDA holder by inclusion of additional reference information in the update.	The Guideline for Drug Master Files (September 1989) does not indicate that a new authorization letter is required whenever a change is made to a specific DMF. However, this section appears to require a NEW Letter of Authorization if there is an NDA change which may reference a different master file or, perhaps a different portion of a master file. However, this section, as written, implies that the NDA holder has intimate knowledge about the content of the master file and must understand that the initial authorization did not grant access to existing sections of a master file. Many master file holders are very reluctant to provide details about their master files that would allow for or facilitate clean, clear references. Please clarify why the FDA needs a copy of the DMF authorization letter from the DMF holder when the regulatory file is reviewed for a change contained in a DMF (e.g. container resin change). We believe that a new DMF authorization letter is unnecessary since the FDA must have received the DMF letter at the time of original review of the regulatory file. As DMFs are not "approved" documents, how is the Comparability Protocol to be approved when submitted to a DMF? How is notification of "acceptance" of the Comparability Protocol received from FDA?

Section	Guidance Line	Comment	Rationale
V. I.	608-617	This section implies that a DMF/VMF can be changed using a comparability protocol. We would like to see this clarified. Changing a DMF/VMF under a comparability protocol is another of those changes potentially impacting multiple products manufactured by multiple drug product manufacturers. Would the DMF/VMF (e.g. API) and corresponding NDA/ANDA/NADA/ANADA (e.g. Drug Product) protocols need to cross reference one another? Sometimes the drug product manufacturers are unwilling to divulge the use of an API produced under certain DMF/VMFs.	Clarify the section
V. I.	610-617	Recommended Verbiage: The provisions for submitting a comparability protocol in a master file will be the subject of future revisions to CDER's Guideline for Drug Master Files and CVM's Guidance for Industry for the Preparation and Submission of Veterinary Master Files. Until those revisions have been made, comparability protocols for master files are not included within the context of this Guidance.	We are uncertain of the benefit that a DMF holder will have providing a Comparability Protocol, since they have no regulatory "Prior Approval" issues with which to contend. Do you intend this to say that the NDA holder can reference the comparability protocol in the DMF and be required to do no additional work?