PDA Comments
Draft Guidance For Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information
Draft Guidance – February 2003
Docket No. 03D-0061

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
1.	Line 90 II. Background	Please clarify how comparability protocols can be applied for changes affecting multiple regulatory files, such as a change to a container/closure system. Can the change be filed via a bundled submission route?	An underlying principle endorsed by this document is that a change must be product specific. We disagree. The greatest utility and, therefore, reduction of regulatory burden, would occur if appropriate application to multiple applications is provided. Frequently, for example, a change to a container/closure system, a raw material change, or excipient change is made to several products at one time. The ability to "bundle" comparability protocols is necessary for companies to efficiently incorporate such changes without undue constraints while confirming that product continues to meet the agreed standards.
2.	Line 98 II. Background A. What is a Comparability Protocol?	Grammatical change to: "A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes ~~in~~ **on** the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product." (change in bold) for clarification.	Typographical error: "in" should be "on".
3.	Lines 107-109 II. Background B. What is the Benefit of Using a Comparability Protocol?	Clarify footnote 5 to indicate how the reduced reporting category is ensured and how the agreement between the agency and the applicant is reached.	The general reference to the "agreed" reporting category should be further clarified in the text of the document. How will this agreement be reached? What happens if the company disagrees with the FDA position? What recourse is available to the Manufacturer if there is a desire to appeal/challenge an FDA decision?

Comment Number	Line # of PDF Document Section Title	Comment Recommendation for Revision	Comments regarding text
4.	Lines 109-111 II. Background B. What is the Benefit of Using a Comparability Protocol?	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.
5.	Line 143 II. Background D. Where Can More Information…	Add a bullet for BAC-PAC	Include reference for "BAC-PAC (Bulk Actives Post Approval Changes)" since it is applicable to this guidance.
6.	Lines 148-150 III. What to Consider… A. How Does a Comparability Protocol…	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."	The revised wording makes the meaning of the sentence clearer.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
		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)."	
9.	Lines 156-157 III. What to Consider… A. How Does a Comparability Protocol…	In some cases, a reduction of more than one reporting category may be possible (e.g., PAS to AR).	Please provide an example of when a reduction of more than one category is possible.
10.	Lines 162-238 III. What to Consider… B. What Might a Comparability Protocol…	General Concept for the Section	The guidance does not address the use of a Comparability Protocol when identical changes are made to multiple products and are submitted to FDA in a "bundled" form. Please reconsider expanding the use of the Comparability Protocol concept to allow a bundled submission for multiple product related changes, such as packaging. This will especially useful for repetitive changes.
11.	Lines 163-164 III. What to Consider… B. What Might a Comparability Protocol…	Current: "However, we recommend that each change be discrete and specific". Proposed: The use of the Comparability Protocol for technology specific changes (e.g., change in filtration process) which broadly applies to multiple products is also appropriate.	Wording should be broadened to allow technology-specific, multiple product changes (e.g., new bottle for several products).
12.	Lines 224 -226 III. What to Consider…	Change the bullet from: "A change from plant, animal, or multicellular (e.g.,	Even if the downstream purification process is extensive, it should be possible to handle such a change under a comparability protocol.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
	C. When Might a Comparability Protocol be Inappropriate?	algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal)" Change the bullet to include bolded 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.**	
13.	Line 227 III. What to Consider… C. When Might a Comparability Protocol be Inappropriate?	Change the bullet from: "A change from synthesis-derived to naturally sourced material and vice versa" Change the bullet to include bolded text: A change from synthesis-derived to naturally sourced material and vice versa, **depending on the extent of the purification process**"	Even if the downstream purification process is extensive, it should be possible to handle such a change under a comparability protocol
14.	Lines 229-231 III. What to Consider… C. When Might a Comparability Protocol be Inappropriate?	Delete lines 229 – 231 as currently stated: A move to a manufacturing site, facility, or area when a prior approval supplement is recommended because a current good manufacturing practice (CGMP) inspection is warranted (e.g., see examples in guidances listed in II.D.) Insert a new paragraph: "When a Manufacturer moves a process to a previously	If a CGMP inspection is warranted for a manufacturing site, facility, or area, it is not clear why the Comparability Protocol could not be submitted for the site change, and used to trigger the inspection. After the PAI and Comparability Protocol approval, the site change could be reported at the reduced reporting category without the need for the increased regulatory time constraints for implementation. Distribution of product would not be allowed prior to the receipt of the acceptable GMP status. As written, this represents a significant increase in the regulatory burden that is contrary to the spirit of the

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
		uninspected manufacturing facility, the approval of the Comparabilty Protocol signifies that the Manufacturer should notify the field when 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 from the Field, the Manufacturer may implement the change without delay in accordance with the approved Comparability Protocol."	Prescription Drug User Fee Act.
15.	Lines 246-250 IV. Procedures for Comparability Protocols A. How should a Comparability Protocol Be Submitted?	The current text reads: "The submission can consist of the proposed comparability protocol in: A prior approval supplement that includes the proposed comparability protocol and test and study results as specified in the proposed comparability protocol and any other pertinent information to support a change covered under the protocol. The product already manufactured with the change can be distributed only after approval of the supplement."	As written, this is not a comparability protocol but a conventional PAS. Please differentiate to indicate the benefit of including the data and results as part of the PAS. We interpret this to mean that a wide scope PAS may also include a Comparability Protocol as one of its components or something else. Also, as written this may be interpreted to indicate that a Comparability Protocol should be submitted together with the data in the initial PAS from a proposed change which is contrary to the intent that the Comparability Protocol is optional.
16.	Line 251 IV. Procedures for Comparability Protocols A. How should a Comparability Protocol Be Submitted? Reference both sections	Information Request and Clarification	Please clarify whether the Comparability Protocol should be included in the Regional Quality Section of a CTD for a new NDA submission. Also, section IV.A. would be an appropriate section for FDA to address whether the submission of a Comparability Protocol in an original application will impact the review cycle. Finally, should revisions to the comparability protocol be

Comment Number	Line # of PDF Document Section Title	Comment Recommendation for Revision	Comments regarding text
	III.B and IV.A		tracked in the annual report, similar to the CMC?
17.	Lines 254 – 255 IV. Procedures for Comparability Protocols A. How should a Comparability Protocol Be Submitted?	Change from: In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol. Change to: In all cases, a comparability protocol would be reviewed and approved by FDA prior to the distribution of product manufactured using the changed process.	The concept here is not that product cannot be manufactured, for example, in full-scale plant trials or validation studies, but that drug sponsors may implement but not distribute until approval of the Comparability Protocol.
18.	Lines 265-268 IV. Procedures for Comparability Protocols B. How Are Changes and Study Results Submitted After a Comparability Protocol Is Approved?	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 should include (1) the results of all tests and studies specified in your comparability protocol (2) discussions of deviations, investigations, and (3) other information pertinent to the change being made."	Delete items (2) and (3). GMP compliance information should not be included in the review supplement since not all investigations and deviations may be pertinent to the change being made. (Also, please define the term "deviations") For example, the presence of non-change - related, extraneous contaminants must be examined, but this is a GMP issue, not a registration issue. The guidances should allow for interim steps/meetings/teleconferences (when a manufacturer gets data resulting from execution of the Comparability Protocol) before submitting a PAS. Discussion would include justification for why the data (although not exactly as expected from protocol execution) still supports the change. When there are instances where the sponsor conclusions regarding the data are different from FDA's, the differences may be resolved much more quickly in a discussion than by submitting a new PAS and waiting for the standard PDUFA timeframes.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
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19.	Lines 276-282 IV. Procedures for Comparability Protocols B. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?	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, that should not automatically bump the implemented change 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.
20.	Lines 284 – 296 IV. Procedures for Comparability Protocols D. When Does a Comparability Protocol	General comment	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

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
	Become Obsolete?		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.
21.	Lines 302- 303 IV. Procedures for Comparability Protocols E. How is an Approved Comparability Protocol Modified?		Please clarify whether notification of editorial changes to a comparability protocol in an annual report will be voluntary.
22.	Lines 320 A new sub-section is proposed	**A new sub-section is proposed** G. Can Comparability Protocols be Used with Combination Products?	Please include a section that addresses combination products and the applicability of comparability protocols. When a change is made to a component of a combination product under a Comparability Protocol, should the Comparability Protocol also include a section on how it affects the combined product?
23.	Lines 323 V. Content of A Comparability Protocol	Change from: "We recommend that a comparability protocol be developed and used within the context of existing change control procedures."	Clarification.

Comment Number	Line # of PDF Document Section Title	Comment/Recommendation for Revision	Comments regarding text
		Change to: "We recommend that a comparability protocol be developed and used within the context of existing change control procedures at the firm."	
24.	Lines 325-328 V. Content of A Comparability Protocol	General Comment	Allow for writing Comparability Protocols as technology specific, across several products, which will result in time saving not only for industry but also for the FDA reviewers.
25.	Line 373 V. Content of A Comparability Protocol A. What are the Basic Elements of A Comparability Protocol? 1. Specific Tests and Studies to be Performed	Add to 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.
26.	Line 397-398 V. Content of A Comparability Protocol A. What are the Basic Elements of A Comparability Protocol? 3. Analytical Procedures to	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	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.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
	be Used	be retained at the manufacturing site for all methods."	
27.	Line 398 – 401 V. Content of A Comparability Protocol A. What are the Basic Elements of A Comparability Protocol? 3. Analytical Procedures to be Used	Change from: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA." Change to: "The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided **(i.e., in AR or CBE)** when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA."	Clarification
28.	Line 426-436 V. Content of A Comparability Protocol A. What are the Basic Elements of A Comparability Protocol? 3. Analytical Procedures to be Used	The text reading: "If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the recommended reporting category for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), the change would be reported as recommended for the specification change. If the recommended reporting category for the specification change is the same or lower than the	The intent of this text is not understood. Please clarify lines (revision of a drug product or drug substance specification), which is very confusing.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
		designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when a post approval CMC change implemented using the approved comparability protocol is reported to FDA.	
29.	Lines 484-486 V. Content of A Comparability Protocol B. Does FDA Have Specific Concerns About Changes…? 3. Comparison of Physical Characteristics	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 **(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.**	As per BAC PAC I, an examination of physical characteristics is required only when equivalence is demonstrated after the final solution step.
30.	Lines 491-492 V. Content of A Comparability Protocol B. Does FDA Have Specific Concerns About Changes…?	Change from: "The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts." Change to:	As per BAC-PAC I, demonstration of equivalence includes assessing residual levels of existing and any new solvents.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
	3. Comparison of Impurity Profiles	"The studies would assess product-related impurities and process-related impurities, including, if applicable, in-process reagents, catalysts, **and solvents**."	
31.	Line 494 V. Content of A Comparability Protocol B. Does FDA Have Specific Concerns About Changes…? 3. Comparison of Impurity Profiles	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.
32.	Lines 518-520 V. Content of A Comparability Protocol B. Does FDA Have Specific Concerns About Changes…? 3. Effect on Process Controls and Controls of Intermediates and/or In-process Materials	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.
33.	Line 576	General comment on the section	FDA should discuss their expectations for use of a Comparability Protocol for the relocation of the same

Comment Number	Line # of PDF Document Section/ Title	Comment Recommendation for Revision	Comments regarding text
	V. Content of A Comparability Protocol E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?		equipment to another already compliant, inspected, or approved area. This could be offered as a positive example of when a Comparability Protocol can decrease reporting burden.
34.	Line 559-579 V. Content of A Comparability Protocol E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?	Add to the end of line 579: "If the submission of the prior approval Comparability Protocol supplement would require a site inspection, the applicant is responsible for insuring that the site has a satisfactory CGMP inspection for the type of operation prior to commercial distribution 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 provide for use of such a Comparability Protocol, which imposes the responsibility of insuring completion of a satisfactory CGMP inspection without a

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
			PA supplement.
35.	Lines 581-586 V. Content of A Comparability Protocol F. Can a Comparability Protocol Be Used for Container Closure System Changes?	Add to the ends of lines II.B., (L 114) and V.F. (L 586): Comparability Protocols are not 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 Section	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. 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?
36.	Lines 599-602 V. Content of A Comparability Protocol H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?	Change from: The protocol would include a commitment to provide a letter authorizing the FDA to review the master file when a post-approval CMC change implemented using the approved comparability protocol is reported to the FDA. Change to: The DMF holder should confirm that changes are properly reported to the FDA. Additional updates may be	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. 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

Comment Number	Line # of PDF Document Section/ Title	Comment Recommendation for Revision	Comments regarding text
		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.	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 MFs are not "approved" documents, how is the Comparability Protocol to be approved when submitted to a MF? How is notification of "acceptance" of the Comparability Protocol received from the FDA?
37.	V. Content of A Comparability Protocol H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability Protocol?	General Comment	A review period for veterinary Comparability Protocols should be defined. Veterinary drugs are currently outside the scope of PDUFA and CVM offers no review period.
38.	Line 612 V. Content of A Comparability Protocol H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability	The text notes that Comparability Protocols are "product specific". Change to: Comparability Protocols are specific for changes that may apply to a single product or multiple products where the same change is made.	The Comparability Protocol may become a significant component in multi-product manufacturing facilities. In such cases a simple cross- reference between files should be adequate and the Comparability Protocol would not be product specific.

Comment Number	Line # of PDF Document Section/ Title	Comment Recommendation for Revision	Comments regarding text
	Protocol?		
39.	Lines 610-617 V. Content of A Comparability Protocol H. Can a Comparability Protocol be Included in a DMF or VMF	Recommended Language: 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 gain by 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 not be required to do additional work.