PDA
An International Association For Pharmaceutical Science And Technology
Suite 1500
3 Bethesda Metro Center
Bethesda, MD 20814 USA
Tel: (301) 986-0293
Fax: (301) 986-0296
www.pda.org

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

Ref.: [DOCID: 03D-0385, CBER200338]
Guidance for Industry – Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information; Draft Guidance – September 2003

Dear Sir/Madam:

PDA is pleased to provide these comments on the Draft Guidance for Industry on Comparability Protocols- Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality.

The comparability protocol represents a potentially useful mechanism to reduce the regulatory burden in keeping with the principles of the Food and Drug Administration Modernization Act (FDAMA) of 1997 and the Prescription Drug User Fee Act (PDUFA) of 1997 and its 2002 renewal. Though useful, the proposed Comparability Protocol guidance, as written, does not fully realize the objective of the FDAMA to ease the regulatory burden of post-approval changes. PDA believes that the clarifications, modifications, and scope redefinition proposed below could make the comparability protocol a more useful tool for the industry and the FDA.

Our comments were prepared by a committee of experts in this field. The committee believes that the guidance is an excellent beginning in the development of meaningful guidance on comparability protocols. Detailed comments are provided in the enclosed table. Comments are identified by section and line number corresponding to the PDF version of the Draft Guidance available on the FDA website. The following is a brief list of some of the major conclusions reached by the PDA review team:

1. **The current draft guidance could be greatly enhanced by a companion guidance document and/or an interactive website that provides specific examples of when comparability protocols can be applied, along with detailed test documentation requirements.** PDA suggests that FDA develop other mechanism(s) for sharing of FDA/industry experiences with the execution of successful comparability protocols. This information could include a listing of examples of changes to which comparability protocols could be applied, as well as details regarding the necessary content of such protocols. PDA has enclosed with this letter, 3 examples of changes, each with a listing of the type of content that should be considered for

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the relevant comparability protocol. PDA feels that the exchange of this type of information, as a separate listing or even as an interactive web site, would greatly facilitate the sponsor compilation and FDA review of comparability protocols.

2. **The ability to "bundle" the same or related changes for one or multiple products should be explicitly provided.** We acknowledge the Agencies reluctance to allow for the provision of general protocols for multiple, unrelated changes to a single product; however we encourage the Agency to re-consider this concept as it may apply to the use of a general protocol that specifies procedures and testing that are common to more than one change in a unit operation. The protocol could be reviewed and approved prior to implementation of the first intended change covered and then subsequent changes could also be covered under such a protocol if the procedures and testing are applicable and no other changes have been introduced in the interim.

3. **The inclusion of information related to Drug Master Filings (DMF) is of concern to us.** Previously, such information was submitted by the DMF Holder and reviewed, but not subject to approval. It is currently not clear to PDA what mechanism(s), if any, are available to signal to the DMF Holder and to each of the specific Authorized Users of the information, that a Comparability Protocol has been received, reviewed, and approved by the Agency. However, PDA believes that this could be a useful tool for both the DMF holder and the Authorized Users of the information if specific Guidance is made available to the industry; either as a part of this Guidance or that for Master Files.

4. **Inspection timing should be considered in the chronology of events between the submission of the original Comparability Protocol and the eventual supplement that provides the resultant data.** The Guidance should be more clear and should provide that the Prior Approval Supplement which contains the Comparability Protocol may be the trigger for scheduling any necessary Pre-Approval inspections. In this case, the sponsor's Comparability Protocol should be accompanied by a projected manufacturing schedule that illustrates when production of supportive batches may occur and when resultant data will be available so that the Agency reviewers, inspectors and sponsor can agree on the optimal timing for the PAI. PAI's should be scheduled by the Agency so as to ensure timely implementation of the change commensurate with the eventual reporting category for the supplement that contains the resultant data.

   Furthermore, the Guidance should more clearly state whether FDA would permit a supplement in a non-prior-approval reporting category for a change to a new site that has not been inspected or does not have a satisfactory CGMP inspection, because an inspection is usually prompted by, or requested via, the PA supplement process.

5. **Use of Comparability Protocols for Combination Products.** When feasible, guidance regarding the mechanism(s) and data expectations for making changes to combination products should be made available to the industry. Information regarding the use of Comparability Protocols for changes to be made to combination products could be captured in such a guidance. Alternatively, the use of Comparability Protocols in this regard could also be captured in a companion Guidance or as an update to the two Guidances on Comparability Protocols.

More specific comments are in the attachment. If you have any questions regarding our comments, or how we may assist with further development of the Guidance, please contact me.

Sincerely,

William Stoedter, RAC
PDA Director of Regulatory Affairs
301-656-5900 ext. 121
Stoedter@pda.org
www.pda.org

Enclosures: Comment Grid on Comparability Protocols, Protein Drug Products and Biological Products, Chemistry, Manufacturing and Controls Information; Draft Guidance.
Examples of Data Set Requirements for Common Changes.

Comments
Guidance For Industry - Comparability Protocols- Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information
Draft Guidance – September 2003
Docket No. 03D-0385, CBER 200338

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
1.	21 I. Introduction	Tests *or* validation studies and acceptable limits to be achieved to demonstrate the lack of adverse	PDA suggests the use of the word "or" to allow more flexibility to the requirement for validation studies associated with a comparability protocol.
2.	26 I. Introduction	change "reduces the potential risk of an adverse effect" to " ensure the change will be thoroughly evaluated"	Line uses statement "reduces the potential risk of an adverse effect" In fact CP do not reduce the risk, but provide an opportunity for FDA and the sponsor to agree on how the change will be evaluated. CPs only work when the sponsor has done the appropriate background work to ensure there is no change to the critical product characteristics.
3.	Line 100 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 an appropriate comparability protocol is submitted to multiple applications. 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

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			continues to meet the agreed standards.
4.	Lines 117-119 II. Background B. What is the Benefit of Using a Comparability Protocol?	Clarify footnote 8 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?
5.	Lines 119-121 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, the 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.
6.	125 II. C. When and Why Were Comparability Protocols Created?	Eliminate or modify for clarity the entire section.	This section, as written is not clear as to why the comparability protocol was created.

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7.	Lines 170-172 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." 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.
8.	Line 174-176 III. What To Consider… A. How Does a Comparability Protocol…	Change from: "When we review a comparability protocol, we will determine if a specified change can be reported in a reporting category lower than the category for the same change implemented without an approved comparability protocol." Change to: "When we review a comparability protocol, we will determine if a specified change can be reported in a lower category than if the change was implemented without an approved comparability protocol."	Wording revised for clarity of message.

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9.	178-179 III. What To Consider… A. How Does a Comparability Protocol…	Comment: PDA agrees with the utility of a comparability protocol to allow regulatory flexibility to reduce the reporting category once the protocol is approved. Examples regarding a reduction in more than one reporting category (e.g. PAS to AR) would be useful (eg, as shown in lines 225 to 243). Additionally, PDA proposes to include a section that allows the sponsor to provide justification for the reporting category based on an assessment of the change and the probability that the change will adversely impact product quality based on the historical knowledge of the product and process.	General Comment – examples of changes would be useful
10.	183 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	A comparability protocol could be useful for a variety of CMC changes, *with* some exceptions	Word change for clarification
11.	184/185 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	Comment: PDA suggests the Agency provide clarity regarding multiple CMC changes and when would related changes not be appropriate for a comparability protocol. Additionally, clarification is needed to define a "repetitive" change? See also comment #3.	

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12.	Lines 190-194 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	Change from: "We recommend that you include information from developmental and investigational studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, and stability data with the particular product and process, and in some cases manufacturing information with similar products or processes (e.g., for some monoclonal antibody products)." Change to: "We recommend that you include information from demonstrated process capability and stability data with the particular product and process."	Many of the recommended studies in this sentence are outside the scope of the specific change and would add an unnecessary layer of information in support of the change. Process capabilities and stability data are relevant to the particular change and are thus warranted.
13.	199 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	*whether a comparability protocol is appropriate.* Attributes can include, but are not limited to, the	Word change for clarification
14.	203 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	Delete "biochemical" from this line	Use of the word biochemical is not necessary as physiochemical properties encompass biochemical properties

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15.	216 – 219 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	Comment: This section should be revised to provide clarity of message. Revised wording: "We recommend that you consider a comparability protocol only if: (a) you expect the product resulting from the change to meet…..(b) the appropriate and sensitive….(c) the currently approved manufacturing process and equipment has been fully qualified and validated" (delete "when appropriate") The use of "non-routine characterization studies" may not be applicable in all cases and more general guidance regarding specific data requirements for specific changes may be most useful.	General Comment Addition of the word, "currently" clarifies that the change refers to the impact to approved process (pre-change). Process validation studies related to the change would typically comprise part of the comparability protocol.
16.		Comment: PDA requests that the Agency provide examples of when a comparability protocol would useful to justify changes in analytical procedures.	
17.	227/228 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	Modification of production operating parameters in fermentation and/or cell culture conditions, such as pH, dO2, and or downstream processing parameters, such as column flow rates and buffer compositions).	For clarification, this statement can be expanded to include changes in fermentation and purification.

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18.	Lines 243 III.B. When Might a Comparability Protocol Be Useful for a CMC Change?	General Comment	PDA encourages FDA to consider a mechanism for information exchange (e.g. interactive web site) such that examples of changes and data requirements included in approvable CPs can be shared. Please also see comments in the cover letter and the enclosed examples.
19.	260 to 262 III.C. When Might a Comparability Protocol Be Inappropriate?	Text should be added just following the bullets to note: "In the event a sponsor plans to implement a particular change for which said data are to be generated, but for which the sponsor feels a Comparability Protocol may be appropriate, the sponsor is encouraged to discuss this information well in advance with the Agency."	Use of a comparability protocol for CMC changes that also require additional evaluation using PK studies and possibly clinical data should be considered by the FDA.
20.	263/264 III.C. When Might a Comparability Protocol Be Inappropriate?	For certain types of changes, a comparability protocol will not be able to reduce the reporting category below PAS.	Word clarification

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21.	Lines 272-275 III.C. When Might a Comparability Protocol Be Inappropriate?	Delete lines 272-275 as currently stated: "A change in or move to a manufacturing site, facility, or area when a prior approval supplement is recommended because an inspection (e.g., a current good manufacturing practice (CGMP) inspection) is warranted (e.g., see examples in guidances listed in Section II.D.)" Insert a new paragraph: "When a Manufacturer moves a process to a manufacturing facility that has not been previously inspected, the submission of the Comparability Protocol as a Prior Approval Supplement could trigger the Agency to perform the necessary Pre-Approval Inspection. In this case, the sponsor's Comparability Protocol should be accompanied by a projected manufacturing schedule that illustrates when production of supportive batches will occur and when resultant data will be available so that the Agency reviewers, inspectors and sponsor can agree on the optimal timing for the PAI. As feasible, PAIs should be scheduled by the Agency so as to ensure timely implementation of the change commensurate with the eventual reporting category for the supplement that contains the resultant data."	If a GMP inspection is warranted/required for a manufacturing site, facility, or area, it is not clear why the Comparability Protocol could not be submitted for the site change, and the Comparability Protocol be used to trigger the inspection. Since both a Comparability Protocol and a site change, which requires a GMP inspection must be submitted as a Prior Approval Supplement the Comparability Protocol should be the trigger for scheduling of the GMP inspection. As written, this represents a significant increase in the regulatory burden, which is contrary to the spirit of PDUFA.

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22.	273 III.C. When Might a Comparability Protocol Be Inappropriate?	Change " recommended" to "required".	The use of the term "recommended" may not be appropriate in this context, as this situation generally requires that a PAI be performed.
23.	276-277 III.C. When Might a Comparability Protocol Be Inappropriate?	Add clarifying footnote such as: "There may be some instances for which a CP for a facility change that results in a lesser reporting category for the resultant data may be acceptable to the Agency. Specific situations should be discussed with the Agency in advance of submission of the CP"	The door should be left open for application of CPs to facility changes. As written, it appears that these will not be acceptable to FDA for facility changes, however they have been (and will be) used. The proposed footnote will help to clarify that the use of a CP for a facility change can be discussed on a case-by-case basis. Additionally, examples of when this has been or could be successful would be helpful (see comments regarding a mechanism for information sharing, e.g. interactive website).
24.	287 I.V. A. How Should a Comparability Protocol Be Submitted?		The text states that the sponsor is to indicate that they are submitting a CP, without providing instruction as to where they should provide this information – Cover letter, application form, etc. Also with the advent of CTD, guidance on where the CP should be placed when submitted as part of an application would be useful (the regional information section is the obvious answer) or cross reference information to other

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25.	Line 300 I.V. A. How Should a Comparability Protocol Be Submitted? Reference both sections III.B and IV.A	Information Request and Clarification.	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. For example, must all CPs be included in the original application or can they be submitted in response to an Information Request or Complete Response letter, and if so, will this affect the overall PDUFA timelines for review and if so, how. Finally, should revisions to the comparability protocol be tracked in the annual report, similar to current CMC amendments?
26.	Line 323 – 331 IV. C. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?	Add to the end of Line 331: "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 allowed to be resubmitted as per the filing category specified in guidance for 21CFR 601.12, if applicable, or as determined in	Section IV.C. PDA feels that provisions should be made for changes to comparability protocols that do not necessarily require extensive regulatory review and require a PAS. It would be useful to have a mechanism to make changes to approved comparability protocols without submission of a PAS. 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. PDA also feels that the guidance should allow

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		consultation with the review division."	for interim steps/meetings/teleconferences (when a manufacturer gets data resulting from execution of the Comparability Protocol) prior to submitting a PAS or other appropriate submission category. 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. Furthermore, in instances 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. The aforementioned FDA/sponsor discussion should include a determination as to whether the missed acceptance criteria is of any critical consequence and/or if the original reporting category for the subject change is still appropriate.
27.	Lines 352- 353 IV. E. How is an Approved Comparability Protocol Modified?	Information Request and Clarification.	Please clarify whether notification of editorial changes to a comparability protocol in an annual report will be acceptable.

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28.	Lines 366 A new sub-section is proposed	A new sub-section is proposed **G. Can Comparability Protocols be Used with Combination Products?**	Use of Comparability Protocols for Combination Products. When feasible, guidance regarding the mechanism(s) and data expectations for making changes to combination products should be made available to the industry. Information regarding the use of Comparability Protocols for changes to be made to combination products could be captured in such a Guidance. Alternatively, the use of Comparability Protocols in this regard could also be captured in a companion Guidance or as an update to the two Guidances on Comparability Protocols. Additionally, guidance should be provided on the applicability of Comparability Protocols to fixed combination biological products in which a CP is submitted and approved for a change is made to a licensed component of a larger combination – can such a CP also cover the change as it affects the larger combination (e.g. for combination vaccines comprised of components that are separately licensed entities). Should the CP include information on how the change to the component can/will affect the combination product?

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29.	Lines 368 V. Content Of A Comparability Protocol	Change from: "We recommend that you develop and use a comparability protocol within the context of existing change control procedures." Change to: "We recommend that you develop and use a comparability protocol within the context of existing change control procedures at the firm."	Clarification.
30.	Lines 372-374 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.
31.	374 to 380 V. Content Of A Comparability Protocol	Eliminate lines 374 to 380. Comment: PDA requests that Section V should be revised to provide clarity regarding use of a comparability protocol for multiple related and unrelated changes. PDA suggests that it may be possible to implement a comparability protocol for nominally unrelated changes at the same time using the same panel of analytical tests to assess product quality. This would allow manufacturers more flexibility for changes that may be associated with single or multiple unit operations.	PDA believes that because the evaluation to determine comparability for certain unit operations (eg. UF/DF, column chromatography,) is often nearly identical for a variety of different changes, it could be possible to implement different changes to the unit operations utilizing a single protocol that is reviewed and approved with the intent of implementation of the first covered change. For example, for a UF/DF step, a change in membrane surface area or the design of the membrane cartridge would require the same evaluation and have to meet the same criteria to evaluate comparability. Filing a protocol for a change to the UF/DF step could allow future changes to this step to follow the same protocol and perhaps reduce the regulatory filing burden.

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32.	Line 404 V. A. What are the Basic Elements of a Comparability Protocol? 1. Specific Tests and Studies to Be Performed	Change from: "We recommend that you include a plan, within the protocol, to compare results from routine batch release testing and, as appropriate, nonroutine testing (e.g., characterization studies) on pre- and postchange products or other material, if appropriate." Change to: "We recommend that you include a plan, within the protocol, to compare results from routine batch release testing including a comparison of purity profiles and, as appropriate, nonroutine testing (e.g., characterization studies) on pre- and postchange products or other material, if appropriate."	Critical for comparability that the purity of the material be equivalent pre- and postchange, which requires more than a comparison of batch release testing data. A comparison of chromatogram profiles will provide a more accurate assessment of the material pre- and postchange.
33.	Line 409 V. A. What are the Basic Elements of a Comparability Protocol? 1. Specific Tests and Studies to be Performed	Change from: "The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, type of product or process, and available manufacturing information." Change to: "The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, and the type of product or process."	The manufacturing information available is not within the scope of this comparability guidance, rather the data on pre- and postchanges should be sufficient to determine the equivalence of the product.

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34.	Line 421 V. 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 421: "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.
35.	Line 447-448 V. A. What are the Basic Elements of a Comparability Protocol? 3. Analytical Procedures to Be Used	General comment – FDA should propose wording to address this point.	Generally, only limited analytical procedure information may be provided in the market application for raw materials, starting materials, drug substance intermediates, excipients, and packaging materials. Information submitted in a supplement to support a change should not be more extensive than what is normally required to be included in the original market application as per FDA guidance on methods validation (e.g. regulatory specs and methods).

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36.	Line 454 to 460 V. A. What are the Basic Elements of a Comparability Protocol? 3. Analytical Procedures to Be Used	Comment: PDA is unclear as to the comment that analytical method qualification data for methods that are used for characterization testing would need to be submitted when a post-approval change is implemented. Details regarding method qualification may not always be appropriate to provide in a CMC submission. Additionally, clarity is requested regarding changes to analytical methods and the applicability of a comparability protocol for changes that are for existing methods and/or new methods.	General Comment
37.	Line 472 V. A. What are the Basic Elements of a Comparability Protocol 4. Acceptance Criteria	From line 472 remove "or tighter". At the end of the sentence on line 472 add sentence: "If a tighter acceptance criteria is proposed, an assessment should be performed to assure that the removal of impurities will not-adversely impact the product."	For biological products, better quality does not always mean "more pure
38.	Line 547 V. B. Does FDA Have Specific Concerns About Changes…? 2. Comparison of Impurity Profiles	Add as next sentence on line 547: "Comparability following a process change should, when possible be established by testing the intermediate following the change and 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.

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39.	Lines 568-570 V. B. Does FDA Have Specific Concerns About Changes…? 4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials	Change from: "We recommend that you include in the protocol a statement 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 that you include in the protocol a statement that, where appropriate, controls, including those that have been validated to inactivate and remove impurities or contaminants, will be reassessed and revalidated for the new production process	Validation may or may not be appropriate in all cases. Each case will require individual evaluation.

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40.	572 V. C. Does FDA Have Specific Concerns About Changes in Analytical Procedures That Should Be Addressed in a Comparability Protocol?	PDA proposes the following paragraph re-wording for Section V, Part C entitled, "Does FDA Have Specific Concerns About Changes in Analytical Procedures That Should Be Addressed in a Comparability Protocol?" A comparability protocol for changing an analytical procedure should describe the nature of the change (revision of an existing procedure, or new procedure based on a different principle). We recommend that your design of the comparability protocol include an assessment of the suitability of the analytical procedure. Additionally, the protocol should provide the plan for validation of the changed analytical procedure. The plan should include prespecified acceptance criteria for relevant validation parameters such as precision, range, accuracy, specificity, detection limit, and quantitation limit[17]. The validation plan should include an assessment of matrix effects by process buffers/media, product-related contaminants, or other components present in the dosage form. The comparability protocol should identify any statistical analyses that you will perform and whether you intend to perform product testing to compare the two procedures. The need and plan for providing product testing to determine how the results of the two procedures may differ and why should be included	Clarification is provided by included suggested paragraph edits to distinguish between comparability protocols and methods validation.

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		When you use the new revised analytical procedure for release or process control, you should not delete the old test or relax acceptance criteria that were approved in your original application, unless and until FDA informs you that the approved acceptance criteria are no longer required.	
41.	Line 632 V. E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?	General comment on an area change.	FDA should discuss their expectations for use of a Comparability Protocol for the relocation of the same 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.
42.	Line 635 V. E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?	Add to the end of line 635: "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 GMP 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 Agency to schedule inspections related to the implementation of the comparability protocol. See comments in the cover letter and #21 for additional recommendations for scheduling of PAIs. The Guidance should also provide information regarding how(mechanism) the compliance status (VAI, NAI, OAI) of a facility/site is communicated to the sponsor, such that the sponsor can make decisions regarding implementation and product distribution.

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			The Guidance should more clearly state whether FDA would permit a supplement in a reporting category other than prior-approval for a change to a new site, which has not been inspected or does not have a satisfactory GMP inspection, since prior approval inspections are typically prompted by, or requested via, the PA supplement process. For example, an approved Comparability Protocol could allow for a packaging site change to be reported in an annual report, along with a statement (Lines 628-629) that the move will be implemented only when the site has a satisfactory GMP inspection. This Guidance, as written, does not necessarily provide for use of such a Comparability Protocol, which places the responsibility of insuring the completion of a satisfactory GMP inspection without a PA supplement.

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43.	633-635 V. E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?	Need clarification on the examples.	The examples given in the guidance include sites that under BLAs have traditionally been PAS or AR depending on the situation. New sites for Drug intermediates have usually been a PAS. Moving to a new testing contractor have usually been a CBE-30. Relocation of testing laboratories within space directly controlled by the sponsor, or approved contract testing lab have usually been an AR Including reference to these examples here without the qualifiers that are included in the changes to be reported guidance (1997) (move to new contract site or taking testing in house) could cause confusion.
44.	649-652 V. E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?		The facility changes listed are exactly the type of facility change that should be allowed under a CP. Should be clarified to indicate that in some cases the downgrading of the supplement that includes the resultant data may not be appropriate. As written, may be interpreted that CPs are not allowed for facility changes.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
45.	658 V. F. Can a Comparability Protocol Be Used for Container Closure System Changes?	PDA requests that examples regarding changes in container/closure be included in this guidance document to fully understand the applicability of a comparability document for changes of this nature.	General Comment
46.	Lines 658-663 V. F. Can a Comparability Protocol Be Used for Container Closure System Changes?	Add to the ends of lines II.B., (L 123) and V.F. (L 663) and: "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 Section."	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 annual reportable but rather a list of supporting data. Please clarify the use of the word "repetitive" in line 662. 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?

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
47.	Lines 675-677 V. H. Can a Master File Be cross-referenced in an Applicant's Comparability Protocol?	Change from: "We recommend that you include, in the protocol, a commitment to provide a letter authorizing us to review the master file when a postapproval CMC change implemented using the approved comparability protocol is reported to us." 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. General Comments regarding utility of the use of CPs in DMFs	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 application 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 market application 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. Related Comment (see also cover letter and Comment #50): As MF are not "approved" documents, how is the Comparability Protocol to be approved when submitted to a MF? How is notification of

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
			"acceptance" of the Comparability Protocol received from FDA? It is currently not clear to PDA what mechanism(s), if any, are available to signal to the DMF Holder and to each of the specific Authorized Users of the information, that a Comparability Protocol has been received, reviewed, and approved by the Agency. However, PDA believes that this could be a useflu tool for both the DMF holder and the Authorized Users of the information if specific Guidance is made available to the industry; either as a part of this Guidance or that for Master Files.
48.	V. H. Can a Master File 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.

Comment Number	Line # of PDF Document Section/ Title	Comment/Recommendation for Revision	Comments regarding text
49.	Line 687 V. I. Can a Comparability Protocol Be Included in a Master File?	The text notes that Comparability Protocols are "product specific". Change from: "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.
50.	Lines 687-692 V. H. Can a Comparability Protocol Be Included in a Master File?	Recommended text: "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 market application holder can reference the comparability protocol in the DMF and be required to do no additional work? It is currently not clear to PDA what mechanism(s), if any, are available to signal to the DMF Holder and to each of the specific Authorized Users of the information, that a Comparability Protocol has been received, reviewed, and approved by the Agency. However, PDA believes that this could be a useflu tool for both the DMF holder and the Authorized Users of the information if specific Guidance is made available to the industry; either as a part of this Guidance or that for Master Files.

Examples: Data Set Requirements for Common Changes

FDA is encouraged to consider a mechanism for information exchange (e.g. interactive website) such that examples of changes and data requirements included in approvable Comparability Protocols can be shared. This information could include a listing of examples of changes to which comparability protocols could be applied, as well as details regarding the necessary content of such protocols and would greatly facilitate the sponsor compilation and FDA review of comparability protocols.

The following represent examples of detailed test documentation for three common manufacturing changes for which a comparability protocol may be submitted.

Comparability Protocol

Sample Data Requirements - #1

New rubber stopper compound as an alternate to the current approved stopper. Such a change would be applicable across an entire product line. The data package should include:

- Specifications and Certificate of Analysis for the new stopper; include copies of the applicable test methods;
- One commercial-scale batch of drug product at the approved facility, filled and finished with the current approved commodities; one commercial-scale batch for each list number (or fill size);
- Certificate of Analysis for each commercial-scale batch;
- Stability protocol/testing matrix; include upright and inverted vials, at accelerated and real time conditions (i.e., 40°C/75% RH and 25°C/60% RH, respectively) at standard intervals;
- Scientific report containing a minimum of three months of accelerated stability data;
- Material evaluation of the stopper, including USP Biological Reactivity, USP Systemic and Intracutaneous Toxicity, Cytotoxicity and USP Physiochemical tests;
- Sterility assurance package including depyrogenation study of the proposed stopper;
- Blank batch record for each drug product list number (or fill size);
- Executed batch record for each drug product list number (or fill size); and
- Specifications and methods referenced in the above studies.

Comparability Protocol

Sample Data Requirements - #2

A new drug substance manufacturer as an alternate or replacement to the current approved manufacturer. Such a change would be applicable across an entire product line. The data package for an alternate vendor of a bulk drug substance should include:

- Copy of the FDA's Establishment Inspection report for new manufacturer; this information may or may not be available from the new vendor. Typically contained in the manufacturer 's Type II DMF or is considered proprietary in nature;
- Overview of the manufacture of the drug substance (current versus new manufacturer process) with differences explained;
- Impurity profile comparison at either the drug substance or drug product stage; data should be a side by side comparison of all attributes to demonstrate comparability and equivalence of the drug substance manufactured at the two facilities; comparison should be of historical drug substance (minimum of three consecutive lots) versus new drug substance (minimum of three consecutive lots); comparable quality consists of comparable structural analysis, glycoform analysis, and bioassay, as appropriate, as well as impurity profile and other physiochemical properties;
- Updated components and composition statement, if applicable, if creating a new drug code for new vendor drug substance;
- Updated raw materials and controls section: provide new manufacturer 's name and address, Type II DMF Letter of Authorization, supplier's COA, specifications and data for drug substance manufactured by the new manufacturer, including spectra and chromatograms;
- Updated facilities address section: provide new manufacturer 's address, including brief description of the facility, GMP certification letters, debarment certification letter (if applicable) and Central File Number;
- Blank master batch records for the largest intended commercial batch size for all impacted list #s- one example for each configuration versus each list #;
- Executed batch records: one executed batch record for all impacted list numbers;
- Certificates of Analysis for finished drug product;
- Analytical methods for the API;
- Stability protocol/testing matrix; include upright and inverted vials, at accelerated and real time conditions (i.e., 40°C/75%RH and 25°C/60%RH, respectively) at standard intervals;

Comparability Protocol

Sample Data Requirements - #2

(Continued)

- Stability data/report: if change is limited to an alternate manufacturing site where impurity profile comparison demonstrates equivalent drug substance or drug product, and similar equipment and manufacturing processes are used, stability data on the drug substance may not be necessary; provide the standard stability commitment to conduct long term stability studies in accordance with the approved marketed product stability protocol on the first commercial production batch of drug product made with the new drug substance; include results from some accelerated stability data; and
- Statistical analysis comparison: build this in as a requirement for New Drug Division submissions - analysis of impurities, etc of historical drug substance (minimum of three consecutive lots) versus new drug substance (minimum of three consecutive lots).

Comparability Protocol

Sample Data Requirements - #3

Alternate manufacturing site (alternate company site, USA or Puerto Rico, or from contract manufacturer to company site) for the Drug Product. The sample data requirements reflect a drug product manufactured at more than one product strength. The data package should include:

- Copy of the FDA's Establishment Inspection report for new manufacturing site and/or GMP and debarment certification letters;
- The manufacturing and controls section, including components and compositions, process, container/closure system, test methods and specifications, are the same as in the current approved NDA. Additionally, the equipment used in the manufacture of the drug product is of the same design and operating principle. Only the manufacturing site for the finished product is new;
- Microbiology/sterility assurance package;
- Blank master batch records;
- Executed batch records: three (pilot) batch records for the lowest product strength and three (pilot) batch records for the highest product strength;
- Certificates of Analysis for each lot of finished drug product;
- Stability data of the finished dosage form: a bracketing approach can be utilized for the stability studies. Three (pilot) batches of the lowest product strength and three (pilot) batches of the highest product strength should be manufactured and placed on stability (25°C/60%RH) at standard intervals; provide a comparison of stability data of the drug product from the current approved facility and the new manufacturing site; provide three months of stability data;
- Commercial stability study commitment: three commercial batches for each product strength utilizing the approved marketed product stability protocol;
- Expiration date; and
- Labeling: revise to correctly reflect "Manufactured for XXX, City, State, ZIP Code, USA" or "Manufactured by XXX, City, State, ZIP Code, USA."