**Alice E. Till, Ph.D.**
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA



December 4, 2003

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

Re: *Draft*, Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information [Docket No. 03D-0385, CBER 200338, 68 *Federal Register*, 52776-52777, September 5, 2003]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA appreciates the opportunity to comment on the *Draft Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information.*

The comparability protocol represents a potentially useful mechanism to reduce the regulatory burden for sponsors; however, we conclude that its usefulness can be enhanced through the suggestions and revisions detailed in the attachment.

These comments represent the collective view of the membership of PhRMA. We believe the following general observations emphasize major points where the usefulness of the guidance may be enhanced.

1. **The scope of a comparability protocol as currently described in the draft guidance is too narrow.**
   The guidance suggests that a comparability protocol can describe a single or multiple related changes, but that each change should be discrete and specific. If we are to make a significant enhancement to the regulatory process, the scope of

the use of comparability protocols must be made wider. Specifically, the protocols should be made applicable to any change in the manufacturing process of either the drug substance or drug product. Allowing the use of a comparability protocol is based upon a scientific understanding of the drug substance and drug product as well as sufficient manufacturing data. The acceptability should be based upon the manufacturer's understanding of the critical process parameters, process controls, and the robustness of the process with regard to proposed changes. As these data are available, comprehensive changes to the manufacture and control of both drug substance and product should be allowed using a comparability protocol. Furthermore, if such knowledge is available, most changes made under a comparability protocol should be made using an annual report rather than the "one category lower" proposed in the guidance. This would be a more science and risk-based approach consistent with the integrated quality system being discussed as part of the "Quality for the 21st Century" initiative.

2. **The guidance should include a list of examples of changes that might be good candidates for comparability protocols.**
   Examples would ensure greater understanding of the entire concept of comparability protocols, as well as identify specific changes for consideration.

3. **If tests and studies approved in a comparability protocol do not meet predefined acceptance criteria, the guidance should allow for reporting categories other than a Prior Approval Supplement (PAS).**
   There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria are of so little consequence that the original proposed reporting category is still appropriate. Also, allowance should be made for using the reporting category that would normally apply for the change (in the absence of a comparability protocol) in the event it would be less restrictive than PAS.

Detailed comments are provided in the attachment. We trust that you will give careful consideration to our comments as you finalize the guidance. Please contact me if you need further assistance or have any questions regarding these comments.

Sincerely,

Alice E. Till

Alice E. Till, Ph.D.

CC D. Bensley (CVM); Y. Chiu (CDER); C. Joneckis (CBER); S. Moore (CDER)

Attachment

**PhRMA 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 |
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| 1. | Line 30<br>I. Introduction | Change from:<br>"This guidance also applies to new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixtures of small peptides)."<br><br>Changes to:<br>"This guidance also applies to new drug applications (NDAs), and new animal drug applications (NADAs), or supplements to these applications for protein drug products, and not sufficiently characterizable peptide products (e.g., complex mixtures of small peptides)." | This statement in the guidance implies that Abbreviated New Drug Applications (ANDAs) are an appropriate approval option for follow-on protein drugs and biological products. We strongly disagree with this on both scientific and legal grounds. Because of the complexity of protein and biological products, the safety and efficacy of follow-on products cannot be assured through the ANDA process, which requires no clinical trials other than limited bioequivalence tests. We thus believe the reference to ANDAs in this document is inappropriate and strongly suggest that it be removed. |

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| 2. | Line 100<br>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 continues to meet the agreed standards. |
| 3. | Lines 117-119<br>II. Background<br>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? |

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| 4. | Lines 119-121<br>II. Background<br>B. What is the Benefit of Using a Comparability Protocol? | Change from:<br>"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)."<br>Change sentence to:<br>"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. |
| 5. | Lines 170-172<br>III. What To Consider...<br>A. How Does a Comparability Protocol... | Change from:<br>"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."<br>Change to:<br>"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. |

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| 6. | Line 174-176<br>III. What To Consider...<br>A. How Does a Comparability Protocol... | Change from:<br>"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."<br>Change to:<br>"Using the information submitted by the manufacturer, we will be able to determine if the change submitted under an approved Comparability Protocol will reduce the reporting/review requirements for the change submitted without an approved comparability protocol. Also, where multiple changes are included, the agency will be able to provide information on each of the specific changes." | Clarification is needed in this sentence if determination of filing category for change will be identified. Comparability Protocols will be most useful if FDA declares the filing category for each proposed change covered. |
| 7. | Lines 178-179<br>III. What To Consider...<br>A. How Does a Comparability Protocol... | Clarification. | Please provide an example of when a reduction of more than one category is possible. |
| 8. | Lines 183-243<br>III. What To Consider...<br>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 be especially useful for repetitive changes. |

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| 9. | Lines 190-194<br>III. What To Consider...<br>B. What Might a Comparability Protocol... | Change from:<br>"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)."<br>Change to:<br>"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. |
| 10. | Lines 243<br>III. What To Consider...<br>B. What Might a Comparability Protocol... | Add at the end of the section:<br>"Examples of various changes that could be supported by a comparability protocol are provided in Attachments 1 through 3." | Examples would provide clarification of the instances in which a comparability protocol could be used as well as the data required for showing comparability. |

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| 11. | Lines 272-275<br>III. What To Consider...<br>C. When Might a Comparability Protocol be Inappropriate? | Delete lines 272-275 as currently stated:<br>"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.)"<br>Insert a new paragraph:<br>"When a Manufacturer moves a process to a manufacturing facility that has not been previously inspected, the approval of the Comparability Protocol signifies that the Manufacturer should notify the field that the facilities are ready for inspection. 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." | If a GMP 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 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 the GMP 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. As written, this represents a significant increase in the regulatory burden, which is contrary to the spirit of PDUFA. |
| 12. | Lines 292-294<br>IV. Procedures For Comparability Protocols<br>A. How should a Comparability Protocol Be Submitted? | Clarification | Please indicate why a Comparability Protocol cannot be submitted as a CBE or CBE30. The bullet indicates that a Comparability Protocol itself is always a PAS.<br>We can envision a scenario where changes were required/negotiated after initial review of a comparability protocol via a prior approval supplement. It seems that the resubmission of the revised comparability protocol should be allowed as a CBE or CBE-30. |

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| 13. | Line 300<br>IV. Procedures For Comparability Protocols<br>A. How Should a Comparability Protocol Be Submitted?<br>Reference both sections III.B and IV.A | 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.<br>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.<br>Should revisions to the comparability protocol be tracked in the annual report, similar to current CMC amendments?<br>Finally, it should be made clear whether protocols can be submitted as amendments to marketing applications (NDAs/BLAs) and, if so, what impact this may have upon review timelines under PDUFA. |
| 14. | Lines 314<br>IV. Procedures For Comparability Protocols<br>B. How Are Changes and Study Results Submitted After a Comparability Protocol Is Approved? | Information Request and Clarification. | The guidance should allow for interim steps/meetings/telcconferences (when a manufacturer gets data resulting from execution of the Comparability Protocol) prior to 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. |

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| 15. | Lines 328-331<br><br>IV. Procedures For Comparability Protocols<br><br>B. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol? | Current statement:<br>"If you decide to pursue the change, we recommend that you 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 they may relate to the safety and effectiveness of the product."<br><br>Add to the end:<br>"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.<br><br>We suggest adding a sentence to the end of the paragraph allowing for discussion if unexpected study results are obtained. Provisions should be made that if the acceptance criteria are not met, it should not automatically bump the implemented change to a PAS.<br><br>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 are of so little consequence that the original reporting category is still appropriate and can be maintained. |
| 16. | Lines 352- 353<br><br>IV. Procedures For Comparability Protocols<br><br>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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| 17. | Lines 366<br>A new sub-section is proposed | A new sub-section is proposed<br>**F. 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? |
| 18. | Lines 368<br>V. Content Of A Comparability Protocol | Change from:<br>"We recommend that you develop and use a comparability protocol within the context of existing change control procedures."<br>Change to:<br>"We recommend that you develop and use a comparability protocol within the context of existing change control procedures at the firm." | Clarification. |
| 19. | Lines 372-374<br>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. |
| 20. | Lines 372-380<br>V. Content Of A Comparability Protocol | Information Request and Clarification. | For the sake of clarity, we recommend that the guidance explain that it is not necessary to complete in-process testing for each change in a set of interrelated changes, but just on the "set" of changes taken together. |

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| 21. | Line 404<br>V. Content Of A Comparability Protocol<br>A. What are the Basic Elements of a Comparability Protocol?<br>1. Specific Tests and Studies to Be Performed | Change from:<br>"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."<br>Change to:<br>"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 post-change products or other material, if appropriate." | It is 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 post-change. |
| 22. | Line 409<br>V. Content Of A Comparability Protocol<br>A. What are the Basic Elements of a Comparability Protocol?<br>1. Specific Tests and Studies to be Performed | Change from:<br>"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."<br>Change to:<br>"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 post-changes should be sufficient to determine the equivalence of the product. |

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| 23. | Line 421<br>V. Content Of A Comparability Protocol<br>A. What are the Basic Elements of a Comparability Protocol?<br>1. Specific Tests and Studies to be Performed | Add the following after the sentence ending in line 421:<br>"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. |
| 24. | Line 447-448<br>V. Content Of A Comparability Protocol<br>A. What are the Basic Elements of a Comparability Protocol?<br>3. Analytical Procedures to Be Used | Change from:<br>"As appropriate, you should validate new or modified analytical procedures (with establishment of corresponding acceptance criteria) or revalidate existing analytical procedures.<br>Change to:<br>"As appropriate, you should validate new or modified analytical procedures (with establishment of corresponding acceptance criteria) or revalidate existing analytical procedures. Validation data should be retained at the manufacturing site for all methods." | Generally, only limited analytical procedure information is provided in the NDA/BLA 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. |
| 25. | Line 472<br>V. Content Of A Comparability Protocol<br>A. What are the Basic Elements of a Comparability Protocol | From line 472 remove "or tighter".<br>At the end of the sentence on line 472 add sentence:<br>"If a tighter acceptance criteria is proposed, an assessment should be performed to assure that the downward shift in the impurity profile (i.e. more pure material) does not adversely impact the product." | For biotechnology-derived products, better quality does not always mean "more pure". In certain products the impurities could act as stabilizers, or act to enhance or inhibit the activity of the active ingredient. For example, a more highly pure product (which can also be the case with less pure product) may cause an immune response or |

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| | 4. Acceptance Criteria | | product aggregation. |

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| 26. | Line 547<br>V. Content Of A Comparability Protocol<br>B. Does FDA Have Specific Concerns About Changes...?<br>2. Comparison of Impurity Profiles | Add as next sentence on line 547:<br>"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. |
| 27. | Lines 568-570<br>V. Content Of A Comparability Protocol<br>B. Does FDA Have Specific Concerns About Changes...?<br>4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials | Change from:<br>"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."<br>Change to:<br>"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 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. |

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| 28. | Line 632<br><br>V. Content Of A Comparability Protocol<br><br>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. |
| 29. | Line 635<br><br>V. Content Of A Comparability Protocol<br><br>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:<br>"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 local FDA office to schedule inspections related to the implementation of the comparability protocol.<br><br>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. Completion of a satisfactory GMP inspection is only allowed with a PA supplement. |

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| 30. | Lines 658-663<br>V. Content Of A Comparability Protocol<br>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:<br>"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.<br>Please clarify the use of the word "repetitive" in line 662. Does this mean:<br>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? |

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| 31. | Lines 675-677<br><br>V. Content Of A Comparability Protocol<br><br>H. Can a Master File Be Cross-Referenced in an Applicant's Comparability Protocol? | Change from:<br>"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."<br><br>Change to:<br>"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.<br><br>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.<br><br>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? |

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| 32. | V. Content Of A Comparability Protocol<br><br>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. |
| 33. | Line 687<br><br>V. Content Of A Comparability Protocol<br><br>I. Can a Comparability Protocol Be Included in a Master File? | The text notes that Comparability Protocols are "product specific".<br><br>Change from:<br>"Comparability protocols are product specific."<br><br>Change to:<br>"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. |
| 34. | Lines 687-692<br><br>V. Content Of A Comparability Protocol<br><br>H. Can a Comparability Protocol Be Included in a Master File? | Recommended Verbiage:<br>"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? |