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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Dr. Stephen Moore

June 25, 2003

Docket No: 03D-0061

Re: Draft Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information

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Dear Dr. Moore:

The above referenced FDA draft guidance entitled Comparability Protocols – Chemistry, Manufacturing, and Controls, issued February 2003 has been reviewed by scientists at Johnson & Johnson Pharmaceutical Research, LLC. The following comments are provided for your consideration.

General Comments

This draft guidance attempts to be responsive to industry's need for more predictable, resource-efficient, and scientifically sound regulatory pathways for post approval changes made to pharmaceutical drug substances and products. Our scientists appreciate the potential benefits of defined protocols but have the following major concerns:

In order to enhance the usefulness and effectiveness of comparability protocols to industry, a higher level of protocol review is requested at FDA. We recommend that a Comparability Review Committee (similar to the SUPAC Review Committee) be established to oversee protocol practice in order to ensure consistency across divisions on various issues, to shorten approval times and to provide further guidance such as Question and Answer documents for the benefit of industry.

The requirement for early submission of highly defined protocols seems to suggest that all process changes, container-closure component changes, analytical detection requirements, etc. are anticipated at NDA filing or early in the review process. In fact many changes are not anticipated and detailed information impossible to provide. If provided, the level of specificity may define the protocol so narrowly as to diminish future usefulness. If specifics are provided, protocol amendments would likely be required later as additional information and experience is gained. This would diminish the usefulness/benefits of using protocols. Further clarification and guidance is requested from FDA to achieve a workable balance between the need for specifics and the realistic limits of industry information and experience.

Several more general comments are offered for your consideration, followed by a listing of major and minor comments by section and line number.

- As noted in Section III B, reporting changes under an approved protocol would normally result in the reduction of a reporting category. This outcome is clearly beneficial and examples of the types of changes where this reduction may apply would be extremely valuable.

- The draft guidance states in Section III A, that protocols may be used effectively for changes to the container-closure system and other changes of a repetitive nature. When multiple related and repetitive changes are involved, particularly with container/closure system changes, may the requirements of the protocol focus on the "worst-case" changes such as a new closure on the smallest container, etc? Would it be permissible to "Bundle" protocols to facilitate multiple related changes across products lines? Specific reference to (and more detailed explanation of) the potential requirements for Sunset Testing, Skip Testing and other testing theories under the protocol system would be extremely valuable. Specific guidance regarding the potential requirements for changes to BCS I category products would also be greatly appreciated.

- Our scientists have expressed a general concern regarding the benefit of submitting comparability protocols versus a potential increase in the number of submissions required to gain approval of a post approval change as described in the SUPAC guidance. The benefit of a reduced reporting category in some cases may be outweighed by the need to submit the comparability protocol in advance, keep it updated or alternatively withdraw it. It would be useful to include further discussion of the benefits to industry balanced with the "costs" of submitting and maintaining protocols throughout the product lifecycle, addressing the following issues:

  - The mechanism for withdrawal of a Comparability Protocol
  - Under Section IV.A., if a comparability protocol for an unforeseen change is not submitted in the NDA, an additional Prior Approval Supplement would be required. Please provide clarification regarding the advantages of submitting protocols via the Prior Approval Supplement route. While it is clear that submitting protocols at the time of filing may decrease the future regulatory filing burden, submitting protocols via Prior Approval Supplements (with or without supporting data) offers few filing advantages and is essentially similar to current filing practices.
  - The mechanism for discussing comparability protocols with the reviewer prior to a non-approval letter or other adverse ruling so that approvals are not negatively impacted
  - If protocols are used aggressively, there may be a "perception" that product development is weak, thereby jeopardizing dossier approval
  - Changes reportable under an Annual Report or Changes Being Effected Supplement will take longer to implement when reported under a protocol

Other Comments by Section:

Part II A

- Line #97: *"A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product."*
  This definition references the drug product and not the drug substance. Reference to the drug substance should be included.

Part II.B.

- Line #109: *"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).*
  The term "less likely" is vague. The sentence should be revised to read "*...it is anticipated that the FDA would not need to request additional information to support changes made under the protocol.*"

- Line #112: *"The use of a comparability protocol could allow an applicant to implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol."*
  The word "could" should be replaced by "will". The sentence should be revised to read "*The use of an approved comparability protocol will allow an applicant* to *implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol.*"

Part II.C

- Line #117: **For many years, applicants (upon FDA approval) have used protocols to implement certain types of CMC changes (expiration dating period extension, container-closure component interchangeability, etc.) Would these protocols need to be updated or withdrawn to comply with the requirements set forth in this draft guidance or be grandfathered?**

Part III.C

- Line #211: "A CMC change that requires efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities)"
  The word "clinical" should be added. The sentence should be revised to read "A CMC change that requires clinical efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities)." The implication from this section is that a protocol should not be used for BA/BE studies. More specific information on the types of CMC changes that are inappropriate for protocol use would be very helpful.

- Line #217: *"Specific examples of changes that may be difficult to justify under a comparability protocol can include (list of examples):"*
  Please provide specific information on the rationale for excluding these examples from protocol use.

Part IV.D

- Line #283: *"When Does a Comparability Protocol Become Obsolete?"*
  Clarification is requested regarding how a protocol is determined to be obsolete. Does FDA anticipate making this determination or assigning an expiration date? A provision should be added to permit the "review of an existing protocol without submitting it as a prior approval supplement.

Part V.A

- Section 2, Line #374: *"In some cases, no stability studies may be warranted or a commitment to report results from stability studies in an AR can be sufficient. If no stability studies are planned, we recommend that this be stated clearly."*
  Please provide an example of when stability studies would not be needed.

- Section 418: *"You should include the acceptance criteria (numerical limits, ranges or other criteria) for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and post-change material."*
  Further clarification is requested for this paragraph (i.e. whether specification and process changes can be included in the same protocol).

Part V.C

Line #527: *"The comparability protocol would be designed to demonstrate that the proposed changes in the analytical procedures improve or do not significantly change characteristics used in methods validation that are relevant to the type of analytical procedure (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, range)."*
The phrase "...*do not significantly change*"...should be changed to "...does not adversely change". The sentence should read as follows "The comparability protocol would be designed to demonstrate that the proposed changes in the analytical procedures improve or do not adversely change characteristics used in methods validation that are relevant to the type of analytical procedure (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, range)."

- Line #545: *"When used for release or process control, use of the new revised analytical procedure should not result in deletion of a test or relaxation of acceptance criteria that are described in the approved application."* **The following text should be added, "Except where the new method provides better or equivalent QA and assures the safety, efficacy and quality of the product." Therefore, it is recommended that the sentence should be revised to read "When used for release or process control, use of the new revised analytical procedure should not result in deletion of a test or relaxation of acceptance criteria that are described in the approved application, except where the new method provides better or equivalent QA and assures the safety, efficacy and quality of the product."**

We greatly appreciate the opportunity to comment on this draft guidance and look forward to working closely with the FDA on future documents. If you have questions or need assistance, please contact me directly at 609/730-3425.

Sincerely,

Sue Halley
Manager
Global Chem-Pharm Regulatory Sciences
Johnson & Johnson Pharmaceutical Research and Development