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June 25, 2003

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

RE: [Docket No. 03D-0061] ***Draft Guidance for Industry on Comparability Protocols-Chemistry, Manufacturing and Controls (CMC) Information***

Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R & D) pipeline has produced many of the most important pharmaceutical products on the market, today.

FDA, hereafter referred to as *The Agency*, is encouraging industry to use comparability protocols to speed up post-approval changes in lieu of gaining prior approval for these changes. In this new *Draft Guidance for Industry: Comparability Protocols - Chemistry, Manufacturing, and Controls (CMC) Information*, hereafter referred as *The Draft Guidance*, *The Agency* provides recommendations on preparing and using comparability protocols that can be submitted in NDAs and subsequent supplements. Comparability protocols can be submitted for changes to the manufacturing process, analytical procedures, manufacturing equipment, manufacturing facilities, container closure systems and process analytical technology (PAT). Because of Merck's vast experience in this area, we are well qualified and very interested in *The Draft Guidance* and provide the following comments.

GENERAL COMMENT

Merck & Co., Inc. strongly supports the development of *The Draft Guideline* and applauds *The Agency* for its efforts. We believe that efficient use of comparability protocols should provide regulatory relief by expediting the review and approval of post-approval changes. This will ultimately bring quality medicines to patients in a timely manner.

SPECIFIC COMMENTS

Line 97-99 ***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.***

Comment 1: This statement appears to be incomplete. For added clarity, we recommend that the sentence be modified as follows:

> "A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes with potential to have an adverse impact on the identity, strength, quality, purity, and potency of a specific drug product as these relate to the safety and effectiveness of the product."

Line 152-154 ***With a comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be implemented without an approved comparability protocol.***

Comment 2: The statement appears to be incomplete. We recommend modifying the sentence as follows:

> "With a comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, if it were to be reported without an approved comparability protocol."

Line 20-24, Footnote 2 The general term "product" as used in *The Draft Guidance* means drug substance, drug product, intermediate, or in-process material, as appropriate.
and
Line 217-221 ***Specific examples of changes that may be difficult to justify under a comparability protocol can include: A change in the drug substance or drug product specifications.***
and
Line 420-422 ***In general, the drug substance and drug product specification would be identical to that in the approved application.***

Comment 3: The definition of "product" in footnote 2 of *The Draft Guidance* makes reference to in-process material. Line 217-221 indicates that it may be difficult to justify a change in drug product specifications under a comparability protocol. Line 420-422 also indicates that, in general, drug product specifications should remain unchanged. We recommend that *The Draft Guidance* allow for increased flexibility by removing in-process material from the definition of "product." In certain instances a change to an in-process control can be justified, provided that approved finished product specifications are met. When a process change is proposed, a comparability protocol may still be appropriate if there is a change in the in-process controls, as long as finished drug substance and/or drug product specifications continue to be met. For example, a change to the manufacturing process for a tablet should be submitted under a comparability protocol even if the in-process hardness range changes - provided that all release specifications (including dissolution) are met.

Line 255-259 ***Furthermore, an applicant who is using an approved comparability protocol to implement post-approval CMC changes must assess the effect of the changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product prior to distributing product made with the change.***

Comment 4: The sentence should be deleted as it appears to be unnecessary and does not provide additional information on how a comparability protocol can be submitted. Furthermore, it is redundant with Line 97-99.

Line 276-278 ***In certain instances, the tests and studies specified in an approved comparability protocol can lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance criteria).***

Comment 5: Lines 276-278 indicate that the applicant can elect not to implement the change in an approved comparability protocol. Further guidance is needed on how the applicant can notify *The Agency* of its intent not to proceed with the proposed change in an approved comparability protocol supplement. Should notification to *The Agency* be made through a written correspondence, Intent to Withdraw letter, Annual Report, etc.?

Line 319 ***V. Content of a Comparability Protocol***

Comment 6: Section V describes the basic elements of a comparability protocol. However, *The Draft Guidance* does not indicate that the applicant should submit a timeline for implementation of the change. *The Agency* should confirm that once approved, the change described in a comparability protocol could be implemented at the applicant's discretion (with no limit on timing).

Line 345-349 ***A list should be included of the specific tests (e.g., release, in-process) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation) you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change.***

Comment 7: We recommend deleting the phrase at the end of the sentence "directly affected by the change," since this is redundant with "effect of the change" in that same sentence.

Line 359-361 ***Retained samples of prechange material can be used for comparison, provided there is no significant change in material on storage (e.g., level of degradants increasing over time).***

Comment 8: We recommend changing the word "degradants" to "degradation products."

Line 367-368 ***A comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and post-change product.***

Comment 9: The statement indicates that a comparability protocol should include a plan for stability studies to demonstrate the equivalence of pre- and post-change material. We recommend that *The Draft Guidance* allow for increased flexibility by prefacing the statement with the phrase "if appropriate," since some proposed changes may not warrant the performance of stability studies.

Line 385-387 ***Analytical procedures would be chosen capable of detecting new impurities or other changes in a product that can result from the change.***

Comment 10: For added clarity, we recommend that the sentence be modified as follows: "If applicable, analytical procedures should be capable of detecting new impurities or other changes in a product that can result from the change."

Line 392-393 ***In this situation, submission of results for pre- and postchange products using both the old and new analytical procedures may be warranted.***

Comment 11: This statement seems to indicate that an assessment should be made using both the old and new methods. We recommend that *The Draft Guidance* allow for increased flexibility by deleting the references to the use of old and new methods. We recommend modifying the sentence as follows: "In this situation, submission of results for pre- and post-change products using the analytical procedures suitable for the intended purpose (i.e., monitoring new process impurities) may be warranted."

Line 406-410 ***However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA.***

Comment 12: For added clarity, we recommend that the sentence be modified as follows: "However, if analytical procedures (new or revised) are specified in and provided as part of a comparability protocol, then the results from validation or qualification of the procedures should be provided when a post-approval CMC change implemented using the approved comparability protocol is reported to FDA."

Line 506-511 ***We recommend that the effect of the change on downstream processes be examined. Downstream processes such as purification steps can be affected by higher product yields or shifts in impurity profiles when upstream processes are modified. For example, adventitious agent removal or inactivation may have to be reassessed for processes involving materials or reagents derived from a biological source. A comparability protocol would discuss how to ensure that the entire manufacturing process is adequately controlled.***

Comment 13: The discussion on downstream processing appears to contradict a basic premise of BACPAC I which is that impact of changes can be adequately assessed at the first suitably controlled intermediate following the change. We request that *The Agency* addresses this apparent inconsistency.

Line 517-519 ***We recommend a statement is included that controls, including those that have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new production process, if appropriate.***

Comment 14: The sentence appears to be incomplete and we recommend that it be modified as follows: "We recommend a statement be included that controls, including those that have been validated to monitor the inactivation and removal of impurities or contaminants, will be revalidated for the new production process, if appropriate."

Line 552-553 ***Comparability protocols may be most useful if applicants are planning to change to equipment with a different operating principal.***

Comment 15: To correct a minor grammatical error, we recommend that the word "principal" be changed to "principle."

We welcome the opportunity to provide feedback on the *Draft Guidance for Industry: Comparability Protocols - Chemistry, Manufacturing, and Controls (CMC) Information.*

Sincerely,

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