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

RE: [Docket No. 2003D-0385] Draft "Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information"

Merck & Co., Inc. is a leading worldwide, human health products 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 important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

We have a focus on the development and production of vaccines that have helped to protect millions of children and adults from severe diseases. The regulation of these, and other biological products currently in development at Merck & Co., Inc., have benefited or will benefit from the use of comparability protocols. As such, we appreciate the opportunity to provide our comments to this important draft document. This guidance will provide the framework to help the innovator determine the best approach to evaluate and report process changes and facilitate the implementation of these changes. We appreciate the continued focus of the Agency on innovative approaches to biologics regulation; from early development to post-approval changes. We fully support development of this guidance document. The comments that we are providing are intended to enhance the information found in the draft document and expand its usefulness.

General Comments

Scope of Products Covered by the Guidance: As noted above, comparability applies to the innovator of the product making changes to its manufacturing process[1] and filing to the BLA. Any reference to abbreviated new drug applications should be eliminated from the guidance document[2]. Complexities and uniqueness of the biological processes and

[1] In this guidance, "manufacturing process" should be defined to refer to the process itself, analytical tools used to monitor the process or product, containers used to hold final products or intermediates, critical raw materials used as input to the process and/or manufacturing facilities and utilities.
[2] Line reference 30 – 32.

products inextricably link the product with the process and provide a rationale for keeping the comparability guidances for biologics and small molecules separate, as they are today. We support the continued separation of the guidance documents describing comparability protocols for drugs and biologics.

Use of Comparability Protocols for Multiple Products: Comparability protocols are clearly described as protocols that may cover multiple, related changes. We strongly suggest that the cross-product use of protocols be allowed. We can envision changes that would affect multiple products (such as a switch to a new container, stopper, raw material or analytical test method). In these cases, the evaluation of any potential effect of the change on the product may be using a common approach to testing or stability monitoring. The implementation of cross-product manufacturing changes would be facilitated through the use of comparability protocols in that the change would be implemented at the same time across the product lines, at a time determined by the manufacturer following satisfactory completion of the protocol specifics and FDA approval. Comparability protocols should be allowed for changes that affect multiple products within a given facility (e.g. changes to shared utility systems such as WFI, HVAC, compressed gasses, clean steam). Facilitating simultaneous implementation of process changes across product lines is of great benefit to the manufacturer and the supply chain. For example, if the comparability protocol specifies the replacement of a historical test method with a new test method, the simultaneous switch of methods will prevent the testing laboratory from performing two assays for a single analyte.

Reporting Category for Comparability Protocols: The guidance states that comparability protocols are approved through a PAS and all modifications to the protocol should be submitted as a PAS. We request consideration of a decreased reporting category for minor modifications to the comparability protocol.

Examples of Comparability Protocols: The guidance document clearly lists CMC changes that would not be applicable to a comparability protocol[3]. There is also a listing of comparability protocol topics that have been submitted by manufacturers[4]. The guidance would benefit from a listing of potentially allowable process changes that the Agency has determined could be covered by comparability protocols due to their experience across sponsors. This would help to inspire the use of comparability protocols by providing for more examples to stimulate thought. One common use of a comparability protocol may be to describe changes in critical raw materials, such as switching to a new source of critical raw material (e.g. non-animal derived). We request that this be provided as an example of the use of comparability protocols.

We also request the Agency consider the following as a potential example of a situation that may be covered by a comparability protocol. There may be certain instances where, upon approval of the product, the specification limits are determined by a limited number of data points. It may be a viable approach to employ a comparability protocol,

[3] Section III C, Line 245
[4] Section III B, Line 222

specifying additional characterization testing, to evaluate lots that fall outside of these initial specification ranges. This innovative approach to product evaluation may be useful in the initial stages of licensure.

Proactive Nature of Comparability Protocols and Process Changes: The guidance is unclear in its description of the extent of the proactive nature of the protocol itself. The main purpose of a comparability protocol is to reduce the regulatory review period of the change. Toward that end, the studies described within the protocol may be initiated at any time. Frequently, studies will be initiated prior to the submission of the protocol to the FDA, although it is recognized that this is done at risk since FDA approval of the plan is still pending. We suggest the following edit "A comparability protocol ~~prospectively~~ specifies the planned CMC change, the tests and studies hat will be performed, analytical procedures that will be used, and acceptance criteria that will be met to assess the effect of CMC changes"[5].

Comparability Protocols for Facility Changes Requiring and Inspection: With respect to the use of a comparability protocol for a manufacturing facility change, it is unclear why the agency does not support the use of a protocol when a pre-approval inspection is involved. The submission of a comparability protocol describing a new manufacturing facility could be the trigger for scheduling the inspection. The predefined approach for comparability may allow for a reduced reporting category, allowing use of the new facility for manufacturing earlier than more traditional filing mechanisms, upon completion of a satisfactory inspection and verification of GMP compliance by the FDA.

Specific Comments (noted in *italics*)

Lines 20 – 21: Current text: A comparability protocol is a comprehensive plan that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity or potency of the product, as they may relate to the safety or effectiveness of the product.

Proposed text: A comparability protocol is a comprehensive plan that describes the specific tests *or* validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for *specific* manufacturing changes on the identity, strength, quality, purity or potency of the product, as they may relate to the safety or effectiveness of the product. In the context of this guidance, manufacturing changes may indicate changes to the manufacturing process, modifications to the facility or utilities, changes in the container (or container components/closures) used to hold products or intermediates, changes in critical raw materials, or changes in analytical methods, specifications or Process Analytical Testing criteria. The guidance describes the use of comparability protocols that may be specific for one or multiple, related manufacturing changes that are planned for a single product or that may affect multiple products.

[5] Line 170

Rationale: It may not be appropriate in every case to supply validation studies therefore tests and validation studies is changed to tests *or* validation studies. Use of the term specified has other connotations and should be replaced by specific tests described in the protocol. It is appropriate to define manufacturing changes as the scope is wider than just changes in process. Also, as we suggest above, the use of comparability protocols should be expanded to encompass cross-product changes. Similar rewording should be applied to Lines 105 – 113: What is a comparability protocol?

Line 135: The use of comparability protocols for expanded types of CMC changes has allowed some applicants to implement CMC changes sooner. Clarity is requested for the term "expanded types of CMC changes". Similar clarity is requested when the term "repetitive changes" is used (Lines 185 and 662).

Line 183: When might a comparability protocol be useful for a CMC change? We request FDA consider the use of comparability protocols to cover multiple-phase upgrades to facilities (such as renovation of equipment cleaning/sterilization areas and culture media preparation areas). These types of changes lend themselves to a comparability protocol approach because the affected utilities can be subjected to rigorous re-qualification using predetermined specifications.

Line 260: (paraphrased) Comparability protocols are not recommended for CMC changes that require PK/PD data to evaluate the effect of the change. We request that stringency be eliminated from the guidance document; there may be instances when PK/PD testing is a part of the evaluation of a CMC change and, upon returning acceptable results, would support the implementation of the change.

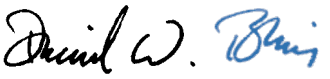
Line 287: We recommend that you indicate that you are submitting a comparability protocol. Please provide guidance as to the method and timing of appropriate communication concerning the submission of a comparability protocol.

Line 317: (paraphrased) 3) the sponsor is requested to submit a summary of all investigations performed. We request that the following be added: 3) a summary of those investigations related to activities within the scope of the comparability protocol. The comparability protocol is used to evaluate the effects of specific manufacturing changes and only deviations and investigations related to the scope of those changes should need to be summarized in the protocol report.

Line 328: (paraphrased) If the results of the comparability study do not meet all predefined criteria of the approved protocol, a PAS should be submitted to justify why the change is being pursued. We do not agree that all out of criteria results would necessitate a PAS. We suggest that the sponsor present the final report, explaining any out of criteria results and submit to the agency using a reporting category proposed by the sponsor.

We appreciate the opportunity to share our comments with respect to FDA's Draft Guidance for Industry: Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information. Please do not hesitate to contact me, should you have any questions.

Sincerely,



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