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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
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Re: Docket Number 03D-0061
Draft Guidance for Industry on Comparability Protocols - Chemistry, Manufacturing, and Controls Information

Dear Sir or Madam:

Enclosed please find comments from GlaxoSmithKline, both general and specific, for the Draft Guidance for Industry on Comparability Protocols - Chemistry, Manufacturing, and Controls Information. These comments are presented for consideration by the FDA. The specific comments are presented in order by the section of the guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this guidance. I am submitting this document both electronically (Dockets Management, Electronic Comment Submission Form) and by hardcopy. Therefore you will receive a paper copy of this letter with the comments and two additional copies through the USPS.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

03D-0061 C11

General Comments:

The document contains ambiguities that need to be defined or explained. The guidance should define comparability protocol, bioequivalence, equivalence, and equivalent product. Provide clarity on where statistical equivalence is required and where meeting the approved acceptance limits is acceptable to demonstrate equivalence.

There are no references to other bioavailability/bioequivalence guidance documents or profile or non-profile methodology using population bioequivalence methodology.

Specific Comments

Section II.A. What is a Comparability Protocol?

Inclusion of FDA's responsibilities for providing input on a comparability protocol proposal should be included in this section. The FDA should give guidance within a defined amount of time so that the sponsor can know if the protocol is acceptable or not, before commencing work.

Section III.B. When Might a Comparability Protocol Be Useful in Making a CMC Change?

The Agency should consider that multiple changes can be described in a matrix and that the changes do not have to be "related". Multiple, unrelated changes should be allowed if the analysis is appropriately designed.

Section IV.A. How Should a Comparability Protocol Be Submitted?

The Agency should define the length of time it will take them to respond to the sponsor's request for review and approval.

Section IV.C. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?

The Agency should define possibilities for a discussion with the sponsor to resolve issues with data that would prevent having to submit a prior approval submission.

Section IV.D. When Does a Comparability Protocol Become Obsolete?

Clarity is needed on what is obsolete and what is not. If a process works and is validated, but does not use new technology (software or equipment), is it obsolete? Who makes the decision about when it is or becomes obsolete? What is the determination of comparability protocol that is obsolete?

Section IV.E. How is an Approved Comparability Protocol Modified?

Clarity is needed for using a comparability protocol when it allows for a revision that is minor; can the revised comparability protocol be reported as a CBE-30 rather than a prior approval submission?

Section V.A.8. Commitment

Define obsolete.

Section V.E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?

Clarity is needed about the need for a comparability protocol when using or changing contract analytical facilities.

Section V.F. Can a Comparability Protocol Be Used for Container Closure System Changes?

Examples of acceptable comparability protocols for different dosage forms (including inhalation and nasal products) would be helpful.

Section V.I. Can a Comparability Protocol Be Included in a DMF or VMF?

This section states that comparability protocols are product specific yet a DMF is not always product specific. Clarity is needed to understand how a comparability protocol could change a DMF.