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June 24, 2003

Dockets Management Branch (HFA-305) 4141 '03 JUN 25 A9:34
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 03D-0061, Draft Guidance For Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information.

PDA is pleased to provide these comments on the Draft Guidance For Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality.

The comparability protocol represents a useful mechanism for facilitating registration of certain manufacturing changes. It is our assessment that the utility of the Comparability Protocol is primarily limited to planned significant changes made to complex products (e.g. proteins and sterile products). It does not add significant value for those products and classes of changes already covered by a SUPAC document. Thus though useful, the proposed Comparability Protocol alone does not realize the objective of FDAMA to ease the regulatory burden on registration of post-approval changes. We believe that the clarifications, modifications, and scope redefinition proposed below could make the comparability protocol a more useful tool for the industry and the FDA.

Our comments were prepared by a committee of experts in this field. The committee believes that the draft guidance is an excellent step towards the development of meaningful guidance on comparability protocols. It has many excellent features already. The committee concluded that **the document would be more useful if**:

1. **The scope of the current draft guidance is broadened.** It is unnecessarily limited with respect to product types, in that it should include biological/biotechnological products (e.g., specified biotech products). With the consolidation of biotech products into the Center for Drug Evaluation and Research, an opportunity now exists for meaningful harmonizing of regulatory mechanisms. This document represents an excellent opportunity for such harmonizing. Further, the concepts presented in this document also generally apply to biotech products.

2. **Explicit guidance is provided in the document for companies that want to include planned changes in the initial NDA/BLA submissions.** Companies often need to optimize manufacturing processes soon after approval of the NDA/BLA approval. Changes to

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a drug product or active pharmaceutical ingredient's manufacturing process serve a variety of useful purposes, such as quality improvement, waste reduction, efficiency enhancement , etc. The ability to reasonably predict the process will significantly improve implementation by providing a predictable timeline for successful implementation. Based on the criteria for "When Might a Comparability Protocol Be Useful for a CMC Change" described in Section III.B., we suggest inclusion of a section that discusses the submission of the comparability protocol in the initial (new) submission. It could provide information regarding impact on the review cycle, location of the information in the Common Technical Document, and the mechanisms for changes to approve a Comparability Protocol after the initial submission.

3. **The ability to "bundle" the same or related changes for one or multiple products is explicitly provided.** We concur with the agency decision NOT to include provision for general protocols for multiple unrelated changes to a single product. However, the guidance should explicitly allow for making the same or related changes to multiple products, i.e., bundling, which should be applied for changes affecting multiple regulatory files. In such cases, the precedent for "bundling" multiple submissions together is well established. Examples include changing multiple solid oral products to a new packaging system (e.g., from one HDPE bottle to another HDPE bottle) or making a change to allow technology-specific multiple-product changes (e.g., new bottle for several solid orals).

4. **Information related to Drug Master Filings (DMF) is included.** The use of a Comparability Protocol when a DMF is involved should be described.

5. **Inspection timing could be coordinated through the FDA District Office at the request of the Manufacturer.** The Guidance should more clearly state whether FDA would permit a supplement in a non-prior-approval reporting category for a change to a new site that has not been inspected or does not have a satisfactory CGMP inspection, because an inspection is usually prompted by, or requested via, the PA supplement process. For instance, standard packaging site changes require CBE-30 supplements, unless the site does not have a satisfactory CGMP inspection. An approved Comparability Protocol could allow for a packaging site change to be reported in an annual report, along with a statement (Lines 570-573) that the move will be implemented only when the site has a satisfactory CGMP inspection for that type of operation. This Guidance, as written, does not provide for use of such a Comparability Protocol, which requires insuring completion of a satisfactory CGMP inspection without a PA supplement. We propose language such as (line 579): "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 CGMP inspection for the type of operation prior to commercial distribution of a change in accordance with a commitment to the approved Comparability Protocol."

6. **Data requirements for common changes.** Comparability Protocols would be more useful to manufacturers if FDA could provide data requirements for some common changes. Data requirements capturing the expected information for common changes such as alternate API supplier, API manufacturing site change, alternate testing

laboratory, product line extension (a new fill size), expiration dating reduction or stopper changes could be very useful. We have attached three examples of such potential data requirements in Attachment 2.

More specific comments are in the attachment. If you have any questions regarding our comments, or how we may assist with further development of the Guidance, please contact me.

Sincerely,

William Stoedter, RAC
Director Regulatory Affairs

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Attachment: PDA comments on the FDA Draft Guidance for Industry on Comparability Protocols- Chemistry, Manufacturing, and Controls Information

Common Data Requirements for Common Changes