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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

July 24, 2003

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

Re: Draft Guidance for Industry on Comparability Protocols - Chemistry, Manufacturing, and Controls Information [Docket No. 03D-0061, 68 *Federal Register*, 8772-8773, February 25, 2003]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The comparability protocol represents a potentially useful mechanism to reduce the regulatory burden for sponsors; however, we conclude that its usefulness can be enhanced through the suggestions and revisions detailed in the attachment.

In addition, the following general observations highlight major areas where the usefulness of the guidance may be enhanced.

1. **The scope of a comparability protocol as currently described in the draft guidance is too narrow.**
   The guidance suggests that a comparability protocol can describe a single or multiple related changes, but that each change be discrete and specific. If we are to make a significant enhancement to the regulatory process, the scope of the use of comparability protocols must be made wider. Specifically, the protocols should be made applicable to any change in an entire process, such as synthesis or purification of a drug substance or a

03D-0061 C13

process change anywhere in the manufacture of a drug product. The key to allowing use of a comparability protocol in such circumstances is the availability of sufficient manufacturing science data to demonstrate adequate understanding of the substance and product in the light of the proposed changes. Do we understand the critical process parameters and controls necessary to make the substance or product? Do we understand how robust the substance or product is in the face of changes? If these data are available, then more comprehensive changes to the manufacture and control of drug substance and drug product should be allowed using a comparability protocol. Furthermore, if such knowledge is available, all changes made under a comparability protocol should be made using an annual report rather than the "one category lower" proposed in the guidance. (We acknowledge that the guidance indicates a reduction of more than one category is possible "in some circumstances".) This would be a more science and risk-based approach, consistent with the integrated quality system being discussed as part of the Quality for the 21st Century initiative.

2. **Additional details should be provided about comparability protocols included in an original submission.**
   While we agree that comparability protocols may be quite useful in an initial submission, several questions surrounding their use in that manner need to be addressed in the guidance. For example, will their use lengthen the review time? When and how should the reviewer be alerted to the existence of a comparability protocol in an initial submission?

3. **The guidance should include a list of examples of changes that might be good candidates for comparability protocols.**
   Examples would ensure greater understanding of the entire concept of comparability protocols, as well as identify specific changes for consideration.

4. **Step down reporting can be enhanced.**
   The draft guidance states that a comparability protocol typically allows the reporting of changes one category lower than normally would be the case. As noted above, we maintain that the guidance should more appropriately emphasize consideration of product/process complexity, robustness and capability in determination of single versus multiple reporting category reductions. Thus, the overall process should be a major consideration in addition to the changes described in the comparability protocol to help the Agency determine whether a proposed reporting category is appropriate.

5. **The submission, review, and approval of comparability protocols in DMFs require greater clarity.**
   As DMFs have not been subject to approvals, will the Agency begin treating DMFs (or parts of DMFs) differently? How will a DMF holder and

all authorized users know when a comparability protocol has been reviewed and approved by the Agency?

6. **If tests and studies approved in a comparability protocol do not meet predefined acceptance criteria, the guidance should allow for reporting categories other than PAS.**
   There should be some allowance for discussion with the FDA reviewer to determine if the missed acceptance criteria are of so little consequence that the original proposed reporting category is still appropriate. Also, allowance should be made for using the reporting category that would normally apply for the change (in the absence of a comparability protocol) in the event it would be less restrictive than PAS.

We appreciate the opportunity to comment on the draft guidance on comparability protocols – chemistry, manufacturing, and controls information. We trust that you will give careful consideration to our attached comments as you finalize the guidance.

Please contact me if you have any questions.

Sincerely,

Alice E. Till

Alice E. Till, Ph.D.

Cc A. Hussain

Attachment