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August 18, 2000

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

Re: Docket No. 98D-0362; Draft Guidance for Industry on
Stability Testing of Drug Substances and Drug Products;
Notice of Availability; Federal Register of June 8, 1998
(63 FR 31224)

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, happier and more productive lives. Investing more than \$26 billion in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA submitted comments to the Docket on the referenced draft guidance on December 8, 1998 and with this submission wishes to provide additional comment regarding section V. Approved Stability Protocol (Lines 846-895) of the Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products. Since this is a very important section, PhRMA has continued to evaluate the detailed language contained in the proposed draft guidance as well as our substantive comments relative to section V. PhRMA continues to feel strongly that the section should be revised and urges the Agency to consider the following comments prior to finalizing the guidance.

In general, section V is too detailed, listing requirements that may be appropriate for certain uses of the stability protocol, but not to others. PhRMA believes that the approved stability protocol should provide the essential elements that are applicable to the majority of the uses for which it is designed. It should avoid specifying items that are optional, subject to change, or only occasionally useful. In addition, this section of the guidance need not specify requirements that are specified in other parts of the guidance or in other guidances, such as analytical validation or storage statements. Specific comments on section V of the draft guidance follow, and a draft revised section on the stability protocol is attached.

Pharmaceutical Research and Manufacturers of America

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Specific Comments

Line 848 - Change “detailed” plan to “essential elements”. Excessive details will limit the utility of the protocol, not enhance it.

Lines 852-3 - Eliminate the sentence on consultation with FDA. It is generally known that such consultation is available for special instances, and FDA has a guidance on special protocol review. However, for standard stability programs that are run according to ICH, such consultation is not necessary.

Line 852 - For clarity, add a discussion of the submission and approval of the protocol to become the **approved stability protocol**.

Line 859 - Add the option to reference methodology in other parts of the submission to avoid duplication.

Line 860-64 - Delete the sentence on analysis and approaches for the evaluation of results. Unless FDA is going to allow sponsors to extend expiration dates based on extrapolation, this is generally not applicable to post-approval expiration date extensions or manufacturing changes. Also, delete the section on validation. This is adequately covered by GMPs and other guidances.

Line 868-9 - Delete “at CRT, refrigerator temperature, or freezer temperature.” The storage statement is addressed elsewhere.

Line 870 - Delete “properly designed” and add “or reference” after “include”.

Line 871 - Delete. The technical grade of drug substance and excipients are defined by the specifications and are subject to change using appropriate filing mechanisms depending on the nature of the change. It should not be necessary to update the stability protocol if the specifications for the drug substance or excipient changes.

Line 872 - Delete “Type, size and” Type and size of batch is generally specified in the stability commitment, or, in the case of a post-approval change, by an appropriate guidance.

Line 873 - Delete “size, and source” of the container closure. For a new submission these are specified elsewhere, and for post-approval changes, these may be the very thing that the stability test is evaluating.

Line 873-4 - Add a new line for "Name or identifier of the drug substance or product and dosage strength to which the protocol applies."

Line 880 - Delete. Sampling plan should be covered by GMPs and the sponsor's SOPs.

Line 881 - Delete. Statistical analysis for purposes of extrapolating expiration dates beyond the available long term data is useful for new submissions, but would rarely be useful for ongoing programs. Extension of expiration dates is generally based on actual long-term data, and most submissions for manufacturing changes would not have enough data points to make statistical analysis meaningful.

Line 882 - Delete. If the data presentation were to be part of the protocol, it would require a supplement to revise the format of the data presentation.

Line 883 - Delete. The proposed retest period is in another part of the submission, and the actual expiration dating period will change as more data become available.

Line 884 - Delete. The stability commitment is presented in another part of the submission and need not be duplicated in the protocol.

Line 887 - Change "has probably not yet" to "may not have".

Line 895 - Add a section that indicates that SUPAC and other guidance from FDA should be considered for protocols for post-approval changes. See the attachment for proposed wording.

A draft revised discussion of the approved stability protocol is attached for FDA consideration. PhRMA is requesting that this proposed revision be incorporated into the draft guidance.

PhRMA appreciates the opportunity to submit further commentary on the draft guidance. Please let us know if there are questions relating to the comments, or if the Agency needs additional information.

Sincerely,



Thomas X. White

Attachment

V. APPROVED STABILITY PROTOCOL

A. Stability Protocol

A stability protocol in an application provides the essential elements of a plan that is used to generate stability data to support the retest period for a drug substance or the expiration dating period for a drug product. It also may be used in developing similar data to support an extension of that retest or expiration dating period via annual reports under 21 CFR 314.70(d)(5), or to support manufacturing or packaging changes in accordance with SUPAC and other relevant guidance documents. To be considered an *approved stability protocol*, the protocol must be submitted in an original NDA, ANDA, or prior approval supplement, then be reviewed and approved by the Agency.

To ensure that the identity, strength, quality, and purity of a drug product are maintained throughout its expiration dating period, stability studies should include the drug product packaged in the proposed containers and closures for marketing as well as for physician and/or promotional samples. The stability protocol may also include an assessment of the drug product in bulk containers to support short-term storage prior to packaging in the market container.

The stability protocol should include or reference methodology for each parameter assessed during the stability evaluation of the drug substance and the drug product.

The stability protocol for both the drug substance and the drug product should be designed in a manner to allow storage under specifically defined conditions. For the drug product, the protocol should support a labeling storage statement. See Sections II.B.5 and 6.

A stability protocol should include or reference the following information:

- Number of batches
- Name or identifier of the drug substance or product and dosage strength to which the protocol applies
- Intended use of the protocol (e.g., validation batches, annual batches)
- Type of containers and closures

- Test parameters

Page 2 (Attachment, PhRMA Comments to Docket, August 18, 2000)

- Test methods
- Acceptance criteria
- Test time points
- Test storage conditions
- Container storage orientations (if applicable)

Information located in other sections of the submission may be referenced in the protocol. The use of alternative designs, such as bracketing and matrixing, may be appropriate (see Sections VII.G. and H.).

At the time of a drug application approval, the applicant may not have manufactured the subject drug product repeatedly on a production scale or accrued full long-term data. The expiration dating period granted in the original application is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA, or on acceptable accelerated data for an ANDA. It is often derived from pilot-scale batches of a drug product or from less than full long-term stability data. An expiration dating period assigned in this manner is considered tentative until confirmed with full long-term stability data from at least three production batches reported through annual reports. The stability protocol approved in the application is then crucial for the confirmation purpose.

Other Protocols:

Stability protocols for changes in formulation, process, or packaging changes will be based on the Approved Stability Protocol and take into consideration SUPAC and other relevant guidance documents for post-approval changes for the determination of the required number of lots and filing requirements.