

Thomas X White
Associate Vice President
Manufacturing and Quality Control
Scientific and Regulatory Affairs



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June 14, 1999

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

Re: Docket No. 98D-0362; Site Specific Stability
Data for Drug and Biologic Applications; Public
Meeting; Request for Comments Appearing in the
Federal Register of Tuesday, March 16, 1999,
(64 FR 13029).

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, healthier and more productive lives. Investing \$24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA appreciates the opportunity that the Public Meeting and extended comment period allow for this important topic. As stated in the Notice, FDA scheduled a Public Meeting that was held on March 31, 1999 to discuss scientific issues related to a section of its draft guidance entitled "Draft Guidance for Industry--Stability Testing of Drug Substances and Drug Products," that was proposed for comment in June, 1998. At the Public Meeting FDA assembled a group of "experts" to present viewpoints on Site Specific Stability and its role, if any, in assessing the quality of marketed drugs. The Agency also used the public meeting to release for discussion and public comment a proposed revised draft on requirements for Site Specific Data in New Drug Applications.

At the close of the March 31, 1999 meeting, Dr. Roger Williams proposed a timeline for further discussion of the subject that included public comments submitted by June 14, 1999; reconvening the "expert panel" to assist FDA in evaluating comments received; considering associated issues relating to an ongoing proposed revision of the Harmonized Stability Guidance that was developed through the International

98D-0362

Pharmaceutical Research and Manufacturers of America C65

Conference on Harmonization of Technical Requirements for Drug Registrations (ICH) which will be discussed in October, 1999; and FDA making a decision on finalizing its U.S. domestic guidance for stability at the end of 1999 or early 2000. PhRMA commends FDA for pursuing such a deliberative approach for managing this important issue and we will continue to make our industry experts available to assist the FDA in their efforts to resolve the difficult question of Site Specific Stability in a sensible and scientifically sound manner.

PhRMA member firms are required to design, conduct and appropriately document stability studies deemed necessary to support New Drug Applications (NDAs). The stability characteristics of drug substances and drug products are evaluated extensively during the drug development process. The purposes of these evaluations are to identify mechanisms and rates of degradation; predict degradation levels at the proposed expiration period; evaluate and define specific packaging configurations and storage conditions; and inform the setting of appropriate product specifications for assessing quality at release as well as for post marketing control.

The results of this process continuum during development are used by the FDA in their NDA evaluation and approval. This is the scientific basis and underpinning for the assessment of stability for drug substances and drug products for which manufacturers submit supporting data and documentation in their NDAs. Through long experience and practice, PhRMA members have found this evaluative process to be site independent, assuming a robust process, using similar equipment and utilizing process validation techniques that demonstrate reproducibility of the process and equivalence of the product on scale-up. The success of such scale-up and technology transfer is judged by the consistency of measurable quality attributes during full-scale demonstration and validation runs.

In the final manufacturing facility, stability is confirmed and the firm is obligated to meet stability requirements for the first three manufactured batches after product launch. Release testing assures that every marketed batch meets its pre-determined specifications, and annual stability testing for marketed lots monitors product quality on an ongoing basis. In this drug development to scale-up to final commercial production continuum, site-specific stability has little or no utility. At the manufacturing site, the issues affecting product quality are specifically related to Good Manufacturing Practice (GMP) requirements and subject to inspection and evaluation by FDA's field investigators.

To put this issue in its simplest terms, PhRMA and its members do not understand what the problem is that the Agency is seeking to solve by reliance on so-called site-specific stability. The value of site-specific stability has not been demonstrated and, based upon the industry description of the evaluative process above, it does not provide the best method to demonstrate the assurance of a successful technology transfer. The new imposition of site specific stability requirements as proposed in the June 8, 1998 Draft Stability Guidance and in the

March 31, 1999 Proposed Revision made available at the Public Meeting is considered by the industry to be an unacceptable and unnecessary burden, with no demonstrated benefits, but with significant adverse impacts on the timely availability of new medicines.

PhRMA and its members have argued strenuously against the site specific stability approach from the first time it was proposed. On several occasions we have provided informal commentary to FDA officials in order to make clear the industry concerns with the proposed approach that, in our view, was being required in advance of its final adoption as Agency policy by certain CDER new drug divisions. In advance of the publication of the June 8, 1998 Draft Stability Guidance, PhRMA submitted to the attention of FDA a brief position paper developed by PhRMA's Technical Committee that described the potential impacts of the then "proposed" policy on drug development. This submission on September 26, 1997 is labelled as Attachment 1, is incorporated with these comments for the record.

Following the publication of the June 8, 1998 Draft Stability Guidance, PhRMA learned from its members that the Site-Specific Stability provisions as proposed in the Draft Guidance were being required for NDAs by some CDER divisions. In a December 23, 1998 letter to Dr. Roger Williams, Deputy Center Director for Pharmaceutical Sciences, PhRMA reiterated its concerns with the proposed Site-Specific Stability approach and especially noted the association's concerns with reports that the FDA was currently enforcing this controversial provision when it was contained in a draft guidance for industry that was then undergoing Agency review and not yet finalized. The December 23 letter is labeled Attachment 2 and also incorporated with these comments for the record.

After the March 31, 1999 Public Meeting, PhRMA undertook to survey its members regarding their experiences with the assessment of product quality associated with site changes in order to quantify, in some manner, the absence of stability problems associated with such transfers. Although the analysis of responses to the survey is not yet available for submission to the Docket, we anticipate submission of the results of the survey when that project is completed. We believe that the Agency will receive specific comments from individual PhRMA members addressing issues raised at the March 31, 1999 Public Meeting, including the basis given for the Agency's site-specific stability position and the revised site-specific proposal.

As noted earlier, PhRMA is very interested in providing assistance to the FDA as it endeavors to resolve the issues posed by the addition of Site-Specific Stability requirements to drug registrations. Our technical experts are available and ready to work with FDA officials in an effort to achieve a sensible, reliable and scientifically sound approach that would provide the necessary assurance that approved marketed products meet all their predetermined quality attributes. PhRMA also looks forward to and encourages FDA to schedule another expert panel session to assist FDA's efforts to resolve Site Specific Stability issues.

In regard to the industry's proven reliance upon robust process validation and technology transfer to demonstrate final product quality, PhRMA offers its assistance in appropriate educational or tutorial sessions with FDA reviewers to elucidate the essential principles associated with that approach.

Again, we appreciate the opportunity afforded industry to provide additional comments to the FDA regarding this important issue. If there are questions or a need for further information regarding these comments, please let me know.

Sincerely,


Thomas X. White

Attachments



Thomas X. White
 ASSOCIATE VICE PRESIDENT
 MANUFACTURING AND QUALITY CONTROL
 REGULATORY AND SCIENTIFIC AFFAIRS

September 26, 1997

Roger L. Williams, MD
 Deputy Director for Pharmaceutical Science,
 Office of Pharmaceutical Science
 Center for Drug Evaluation and Research
 Food and Drug Administration

Via Facsimile: (301) 594-6197

Re: Manufacturing Site Stability Data Requirements
 at Time of NDA Submission.

Dear Dr. Williams:

Roger, you and I have discussed the above referenced issue on several occasions, and I believe several other PhRMA representatives have conveyed to you the industry concern with how this issue has been directed to some industry applicants. The specific concern is with a policy that would require that at least three months of accelerated stability data on drug product that is produced at the commercial manufacturing site be submitted at the time of NDA submission; and, an additional requirement that the active pharmaceutical ingredient also must be from the commercial production site.

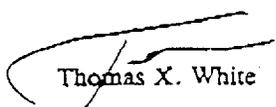
PhRMA wants to reiterate to the Agency that there would be a significant level of concern among our members if such a policy were established and made a requirement. I am attaching a brief position paper that outlines the industry's concerns and provides some of the serious impacts such a policy would have on pharmaceutical operations.

PhRMA understands that this topic is one that will be incorporated in the CDER Draft Guidance for Industry on Stability Testing of Drug Substances and Drug Products that is undergoing review within FDA. Through your efforts, several of the outstanding stability related issues that are in the proposed Draft Guidance, especially those dealing with ICH implementation, were able to be discussed and resolved by FDA/Industry working groups. Unfortunately, the site stability topic was not among those issues that had the benefit of discussion and resolution.

I hope that you review and consider the concerns raised in the attached PhRMA position paper. If you wish to have further discussion and elaboration of these concerns, we would be very willing to meet with you and your stability experts in an effort to develop a proposed CDER policy that reflects the documentation needs of the Agency, as well as the practical flexibility needs associated with pharmaceutical development and manufacturing.

Thank you for your assistance.

Regards.


 Thomas X. White

Pharmaceutical Research and Manufacturers of America

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Dr. Roger Williams
September 26, 1997
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Attachment

cc: Janet Woodcock, MD
John Siegfried, MD
David Shriver, PhD
Marjorie Powell
Larry Versteegh, Procter & Gamble Pharmaceuticals

**PHARMACEUTICAL RESEARCH AND MANUFACTURERS
OF AMERICA**

**POSITION REGARDING FDA PROPOSED NEW POLICY FOR NDA DRUG
REGISTRATION STABILITY DATA REQUIREMENTS FOR DRUG
SUBSTANCE AND DRUG PRODUCT MANUFACTURING SITES**

The Technical Steering Committee is concerned that the FDA has communicated to some PhRMA member companies a requirement for additional stability data to be included in the New Drug Application at the time of initial filing. Specifically, the agency asked for at least 3 months of accelerated stability data on drug product that is produced at the commercial manufacturing site. Furthermore, the active pharmaceutical ingredient in those batches of drug product had to come from the commercial manufacturing site. Data were required on drug product from all commercial sites for drug product and all commercial sites for active pharmaceutical ingredient that were included in the NDA.

The PhRMA position is that the current practice for qualification of processes has been both successful and acceptable. Until now, the current practice appeared to be acceptable to the Agency as well. We do not understand the problem the Agency is trying to address by these additional requirements. There is no statutory basis for these requirements. There has been no public notice, no comment period, and no cost analysis associated with this action.

The requirement for additional stability data is of great and immediate concern to PhRMA. The impacts of this policy include the following:

- Development time will be lengthened, inconsistent with goals of PDUFA II.
- Earlier major capital investment at significantly increased risk will be required and will lead to idle plant capacity.
- Investment in new technology will be curtailed since companies will seek to reduce potential losses in premature major capital investment. This will have the unintended consequence of slowing the introduction of innovations in manufacturing and environmental technology.
- Earlier expenditure of substantial human resources at significantly increased risk will be required.
- Raw materials will be purchased earlier and large quantities of drug product will be produced. The product may not be able to be sold due to its age by the time approval is obtained.
- There may be negative environmental consequences arising from the need to produce and then destroy the unwanted product.

- Since this additional requirement is not contained in the ICH stability guideline that now is in force in the three regions, it would exceed the ICH stability requirements and make the NDA drug registration requirements unique in the U.S. and no longer harmonized.

We view the NDA review process as necessary to evaluate the safety and efficacy of a potential new product. Stability of product produced at a specific site is a GMP issue and therefore should not be part of the NDA review. The NDA already will contain stability data as defined clearly in the ICH guideline. The guideline was written and agreed with the active participation of the Agency over a period of years. It prescribes what is required at time of submission for drug substance in order to establish a retest date, and for drug product in order to establish expiration dating. For all the reasons that justified the ICH guideline, PhRMA believes that adherence to the spirit and letter of that document is sufficient to allow the Agency to complete its review of stability of the potential new product.

ATTACHMENT 2



Thomas X White
Associate Vice President
Manufacturing and Quality Control
Scientific and Regulatory Affairs

December 23, 1998

Roger Williams, M.D.
Deputy Center Director for Pharmaceutical Sciences (HFD-003)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Dear Dr. Williams:

I am writing again in reference to the issue of "Site Specific Stability." PhRMA continues to hear from its members regarding this topic and recent reports have expressed a strong concern that the FDA is currently enforcing the controversial provisions dealing with Site Specific Stability as proposed in the Agency's Draft Guidance for Industry on Stability Testing of Drug Substances and Drug Products of June 8, 1998.

The above mentioned draft guidance states that stability data from batches of drug substance and drug product made at their respective sites of commercial manufacture is required upon submission of an original NDA, BLA or supplements to the same in support of manufacturing changes. These data are expected to be supplied at the time of application submission. This is being requested even when an applicant supplies 12 months of data on three batches of drug substance and drug product as specified by the ICH Q1A stability guidance adopted as final by FDA, effective September 22, 1994. As you know, PhRMA has noted on several occasions and, most recently, in our Association comments submitted to the Docket for the draft guidance that the proposed FDA approach is inconsistent with the intent and spirit of both Section 124 of FDAMA and the adopted ICH stability guidance.

PhRMA has interpreted Section 124 of FDAMA to mean that an NDA or BLA can be approved based on data obtained using drug substance and/or drug product made in pilot or small scale manufacturing facilities which may be other than the ultimate commercial sites of manufacture. We think this interpretation is consistent with the intent of Congress as represented in the House and Senate Committee reports.

PhRMA has also questioned FDA's proposed requirement for "site specific stability" data as presented in the June, 1998 draft guidance as likewise inconsistent with the intent of the 1994 ICH Q1A guidance on stability. That guidance specifically states that pivotal stability batches may be made in pilot scale facilities if the sponsor of an application provides a commitment to place the first commercial batches into a post-approval stability program. The intent of the ICH guidance is clearly that the pivotal stability batches could be made in facilities other than the ultimate commercial facilities since there is a qualifying statement that, "The batches manufactured to a minimum of pilot plant scale should be by the same synthetic route and use a method of manufacture

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and procedure that simulates the final process to be used on a manufacturing scale." (see September 22, 1994 FR pages 48755 for drug substance and 48756 for drug product.)

PhRMA has discussed the industry's position on site specific stability on several occasions and in several venues with FDA. In December 1997, FDA and AAPS sponsored a workshop on streamlining IND and NDA CMC submission requirements. At that workshop two breakout sessions were held to discuss the value of site specific stability in transfer of manufacturing processes from pilot plants to commercial facilities. The report of those breakout groups made it clear that site specific stability was considered to have little or no value in assessing the technical transfer of manufacturing processes but rather that validation of the full scale process at the commercial site should be the true test of technical transfer.

In a meeting between representatives of the innovator and generic pharmaceutical industry and Office of Pharmaceutical Sciences personnel (including yourself) on July 22, 1998, FDA and industry exchanged their respective positions on the subject of site specific stability. It was apparent to the industry representatives present that FDA is uncomfortable approving NDAs without reviewing some type of manufacturing data obtained from material made at the commercial site. The FDA position that three months accelerated data from the commercial site will aid in assessing the integrity of technical transfer and that this will safeguard the American public from receiving product that presents a danger to health is erroneous. The likelihood that a technical transfer problem would be detected based on accelerated site specific stability data is highly unlikely. In the event that an out of specification situation might arise from the analysis of stability data of new products, it is still unlikely that patients would be at risk since there are often more than adequate safety margins between approved specifications and the specifications qualified in clinical and nonclinical studies.

Our members are not completely sure that FDA is fully aware of the implications of the proposed site specific stability requirement for the pharmaceutical industry, particularly the innovator companies. In order to have three months stability from a commercial site of drug product manufacture using drug substance made at its commercial site of manufacture at the time of application, a company must have these respective facilities available and qualified at a minimum of 9-12 months prior to NDA submission for substance and 6 months for product. These timelines will encompass manufacture, release, stability, aging, stability testing, data review and report writing. Once these materials are made they must be held in inventory during the review and approval process. Of more concern however, is that a sponsor must make the significant capital investment in construction and maintenance of facilities needed to manufacture drug substance and product at a time when it is not totally certain that a product will

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successfully get through pivotal clinical trials. At a time when both industry and the Agency are working to decrease development timelines and costs, the imposition of this unnecessary requirement further exaggerates those factors. It also places unnecessary financial burdens on sponsors, particularly smaller companies with no justifiable benefit to the public.

It should be noted further that site specific stability is not a requirement in other major countries and is a source of major disagreement in the planned update and revision of the Q1A guidance and ongoing deliberations regarding the Quality section of the common technical document within ICH.

PhRMA is particularly concerned that the guidance was issued as a draft containing such a controversial provision. Despite knowing industry's position on the issue, the Agency proceeded to publish the stability guidance containing this clause. In other cases where controversial issues existed, there was an attempt by the Agency to seek input and resolve the controversies prior to publication of a draft guidance. The FDA approach also represents a requirement over and above those identified in the ICH Q1A guidance. FDA has stated many times that it would abide by ICH guidances and that these guidances represented the ceiling rather than floor of submission requirements.

As noted above, our members are most concerned with reports that FDA is currently enforcing this controversial provision when it is contained in a draft guidance that is undergoing Agency review following a public comment period, and is not yet finalized.

Following our last discussion of this topic, Ken Furnkrans notified PhRMA that the FDA is planning to establish an expert working group in the the near future to discuss this topic and that we will have an opportunity to participate in that activity. We appreciate that opportunity and look forward to those discussions. However, because this topic to continues to be of such importance to our members I wanted to note PhRMA's concern for the record.

Sincerely,



Thomas X. White

PRMA

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