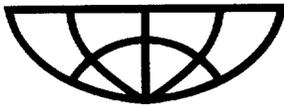


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June 14, 1999

Dockets Management Branch (HFA-305)

Food and Drug Administration

5630 Fishers Lane

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Rockville, MD 20852

Re: [Docket No. 98D-0362] Site Specific Stability Data for Drug and
Biologic Applications; Public Meeting; Request for Comment

Dear Madam or Sir:

PDA is pleased to have the opportunity to provide comments on FDA's revised proposal on Site Specific Stability Data for Drug and Biologic Applications as a result of the public meeting held on March 31, 1999, at the Holiday Inn Bethesda, 8120 Wisconsin Ave., Bethesda, Maryland.

The position expressed in our December 7 response remains essentially unchanged. Nevertheless, we believe it is important to comment on the proposed site specific guidance in the event FDA implements the guidance as written.

General Comments

PDA still questions the value of and scientific rationale for site specific stability data. We believe modern process validation practice, which is largely evaluated under FDA's GMP inspection program, provides the necessary assurance of successful technology transfer between manufacturing sites. Site specific stability data should not be a preapproval requirement. Filing requirements should be changed to the standard stability commitment with data submitted in the annual report.

We believe FDA's position on the need for preapproval stability studies is inconsistent in view of the fact that for scale-up batches the agency has accepted the concept of post approval stability data as defined in ICH Q1A.

Specific Comments

The Drug Substance (DS) Table lacks scientific basis for the differentiation of "Major" vs. the other categories. Whether or not polymorphic form or particle size of the DS are critical to the performance of the drug product, any differences in these properties related to the site of manufacture should be easily observed at the time of release testing of the DS. Since neither of these properties is likely to change over time, stability testing should not be required.

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The Drug Product (DP) Table lacks scientific basis for its classifications. For example, IR tablets are placed in either the Moderate or Minor category based on DS solubility/permeability. If the DS has low solubility, it is categorized as Moderate (for either low or high permeability) and if it has high solubility, it is categorized as Minor (for either permeability). This categorization is confusing. Permeability should be the differentiating factor for how critical the stability of the formulation might be. For a drug substance with high permeability, the dissolution of the tablet is more likely to be rate-limiting for bioavailability. Another example is the classification of solutions by whether they are sterile or non-sterile; sterility is unlikely to affect stability.

PDA is pleased with the addition of the provision that "alternative approaches may be justified." Because we believe that process validation and appropriate technology transfer obviate the need for site specific stability, we request that this be listed explicitly as an alternative approach in the final text.

Comments on Robert H. Seevers's Presentation

The following comments address the presentation "Site-Specific Stability: Scientific Issues and Examples," by Robert H. Seevers, Ph.D., which was given at the March 31 public meeting (copy attached).

We reviewed the ten examples that the FDA presented at the meeting. These examples presented situations where manufacturing changes impacted the stability performance of drug products. However, many of the manufacturing changes described are not specifically related to manufacturing site changes and do not support a requirement for pre-approval, site specific stability data.

Although not enough information was included on most of the slides to identify the root cause of the problems, inadequate understanding of key process parameters and inadequate process validation appear to be consistent features in these examples.

In examples 1 and 3, the outcomes suggest that there were fundamental changes in the processing of the material between the two sites. Appropriate technology transfer or validation practices should detect such changes or avoid them.

In examples 2, 6 and 8, it appears that the packaging or processing equipment was not properly qualified and/or validated prior to use. If appropriate in-process and release limits were in place, these problems should have been detected during initial release or validation testing. Example 8 emphasizes the importance of communication.

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The remaining examples demonstrate the importance of thoroughly understanding a drug product's manufacturing process. Parameters such as humidity levels, equipment specifications, polymorph behavior and coating specifications, if important to the successful processing of the drug product, must be identified and validated as part of a technology transfer activity.

In these examples, stability results from product made after a site transfer may have identified a problem with the transfer. However, it is our belief that site specific stability data should not be used as a "safety net" to catch problems associated with inadequate process validation and site transfer.

Conclusion

PDA is convinced that preapproval site specific stability data should not be a requirement. The usual stability commitment and annual reporting should be sufficient to capture site specific stability changes, if any. If FDA insists on going forward, we have the following additional comments:

- There is no need for three categories (field alerts will capture anomalies).
- If categories are retained, simple sterile solutions should be classed as "minor." In addition, other product categories should be based on sound scientific rationale.
- Accelerated stability studies should be optional for biotech/biological products.
- There is no scientific rationale for requiring three-batch site specific stability data; a single batch at the new site followed by a standard, ongoing stability program is sufficient.

We appreciate the opportunity to contribute to the development of this important guidance for industry. Please contact me if you have any questions.

Sincerely,



Edmund M. Fry
PDA President

cc: Jennie Allewell, Cell Therapeutics Inc.
Eric Sheinin, Ph.D., CDER
Kathryn C. Zoon, Ph.D., CBER