



NATIONAL PHARMACEUTICAL ALLIANCE

SUITE 222 • 421 KING STREET • ALEXANDRIA, VIRGINIA 22314 • (703) 836-8816 • FAX (703) 549-4749 • EMAIL: NPA@EROLS.COM

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

June 14, 1999

D
Docket No. 98~~B~~0362

Gentlemen:

Attached are two copies of the NPA's Technical Committee on the revised Site Specific Stability Guidance (SSS) issued March 31, 1999. The closing date for comments is today.

Very truly yours,

R. A. Jewssi for
Christine Sizemore
President

0173 JUN 11 2000

98D-0362

C67

COMMENTS BY THE NPA'S TECHNICAL COMMITTEE ON THE FDA'S REVISED SITE SPECIFIC STABILITY (SSS) GUIDANCE DISTRIBUTED MARCH 31, 1999

June 14, 1999

Docket No. 98~~B~~^D 0362

General Comments

In our opinion, there is no need for site-specific stability data when the manufacture of a drug substance or drug product is transferred to a new site as long as the manufacturing process does not differ materially from that in the former establishment and the process in the new facility is validated. This is true whether the new site is within a single facility, a contiguous campus or a different campus. The stability of a drug substance or drug product is not dependent on the geographical location in which it is manufactured but only on the nature of the drug substance, the drug product, the manufacturing process, and the container/closure system in which it is packaged. If properly manufactured under GMP conditions and using a validated process which equalizes environmental factors, mere geography will have no impact on stability. Temperature and humidity of a physical location could have an impact on stability but these can be controlled during the manufacturing process. The type of dosage form also obtains no impact from geography. Based on the aforesaid, it is difficult to understand why FDA considers the stability requirements in this draft proposal to be so dependent on the physical properties of drug substances and type of dosage form when moving from one location to another. No doubt, stability does depend on those fundamental characteristics of drugs that allow them to react with air, water, oxidants, etc. but these are properties of drug substances and formulations and not of the physical locations.

One problem with this draft guidance is that it states that "site changes involving the final intermediate and/or drug substance, the recommendation for additional information may be similar to those in BACPAC II". Unfortunately, the BACPAC II draft guidance is not out yet thus preventing real comments on the SSS data involving the drug substance. Most site specific movements involving the drug substance or its intermediates will be for the drug substance rather than for any intermediate. The absence of any reference to SUPAC-IR and SUPAC-MR leaves one to wonder if the recommendations provided in the March 31, 1999 revised guidance will replace those for SSS data described in those two guidances.

At the March 31, 1999 meeting on this topic, the Agency presented ten examples of site-specific problems. Of the ten, eight can be attributed to GMP and/or technical transfer insufficiencies. In addition, only two of the ten problems would have been discovered with the proposed required SSS data.

Specific Comments

1. Table 2: Site-Specific Stability Data for a Drug Substance for an Original Application

We disagree with the Major Example given in this Table. As written, if a drug substance's polymorphic form or particle size is critical to the performance of the drug product, a significant (Major - up to three batches) amount of stability data must be presented at the submission of the application. If both of these properties are controlled at the new site and match those at the former site, where is the Major potential to have an adverse effect on the stability? How will the required stability data predict the performance of the drug product? Additionally, will a firm have to generate data to indicate that particle size and/or polymorphic form are not critical to product performance? That entails a research project if it isn't already known and would block use of the new facility for an extended period.

Under the Moderate Examples, those given are not sufficient to indicate what is really meant by "Drug substances susceptible to manufacturing conditions, technology or site transfer". What drug substance is susceptible to site transfer per se? How would one know that if the change involved is the first site transfer for that particular drug substance? One could argue that every drug substance is susceptible to site transfer if the latter is not carried out carefully and correctly. As for the manufacturing conditions, one would hope that the drug substance is susceptible to them since if it were not, another substance may be produced or the drug substance would be contaminated with a number of impurities.

Both these categories, Major and Moderate, are not supported by the examples given. We believe that our comments support the position that SSS data is not needed when the drug substance is manufactured under the conditions described in the General Comments.

2. Table 3: Site-Specific Stability Data for a Drug Product for an Original Application

With the possible example of liposomal formulations the Major Examples given in this table are already approved generic drug products. If this draft is finalized as is, to get a generic drug approved for a site transfer, the amount of SSS data that will be required involves three batches. The already approved generic products in the Examples were likely approved with one batch. FDA should share the experience with these products for a site transfer before expanding the stability requirements from one to three batches for any such site transfer. Where there problems? Why does the Agency feel that there is as potential to have an adverse effect on the drug product stability for these dosage forms? If the transfer is done properly there should be no greater potential for the listed Example dosage forms than for any others.

Under the Moderate examples is given drug substances with low solubility and either low or high permeability. Apparently, this is referring to the solubility definition given in SUPAC IR and if that is so it should be referenced therein. A question is why would the low solubility of a drug substance compared to high solubility have a greater potential to have an adverse effect on the drug product stability? One of the theories of

oxidation/degradation in a solid oral dosage form is that small amounts of the drug substance dissolves in the small amounts of water associated with the dosage form and that oxidation/degradation occurs in this solution. If this theory has any validity, the more soluble drug substance would be at greater risk than the least soluble one.

Reference is made to our previous comments under #2. about drug substances potentially susceptible to manufacturing conditions. This appears for both drug substances and drug products under the Moderate potential to have an adverse effect on stability.

3. Under "FDA's Revised Proposal on Site-Specific Stability Data"

"I Drug Substance, A. Additional Information".

The first sentence of this section indicates that up to but not including the final intermediate, no additional stability information are recommended if the impurity profile does not change. This requires knowledge of the impurity profiles of intermediates. The latter will have no consequence if they are removed during the rest of the manufacturing process resulting in the drug substance. It is the stability of the drug substance that is critical, not that of any intermediate. Site-specific stability data is recommended for a complex drug substance. Why is a change in manufacturing site more critical for a so-called complex drug substance than for a non complex drug substance as long as the same process is used and it is validated?

"II. Drug Product, A. Additional Information"

This section states that site-specific stability data is recommended for non-SUPAC dosage forms. Why? If these haven't already been covered in the Examples section of Table 3., then they should be either added to that Table or this sentence eliminated. Sterile products are the big missing dosage forms not covered by a SUPAC document and they are already covered in Table 3. However, the same arguments we have advanced for the absence of need for SSS data also applies to sterile dosage forms.

"IV. Further research"

We agree that data mining and/or prospective research should be performed in this area to determine whether or not site specific stability data is really needed. Attached are two tables which indicate drug products can be manufactured at different plant sites and not lead to stability problems. The first is for 22 Captopril approvals at presumably 22 different sites. This data was originally introduced by Dr. Sidney Goldstein of Duramed Pharmaceutical, Inc. at the special meeting on SSS held at FDA in July, 1998 and presented again at the March 31, 1999 FDA meeting on this topic by Dr. Robert Jerussi of Jerussi Consulting, Inc. At the same meeting, Dr. Jerussi also presented data provided to him by Dr. Goldstein on multiple approvals for other generic drugs that appear in the

second table which further reinforce the point that the same drug can be manufactured at multiple plants without stability problems. Searching FDA's own published data indicated that through the end of February, 1999, only one batch of one drug in the two charts had a recall due to stability problems and that was Cimetidine tablets, 800 mg and the failure was for dissolution. It would seem that it is would be more difficult for two different firms to make the same drug product with potential different formulations, processing schemes and sources of the drug substance than for the same firm to make the same drug at two different facilities.

Note that in the second table one drug is a delayed release product, Diclofenac, and another is an insoluble one, Acyclovir, as per the SUPAC-IR definition. Both of these drug products are considered Major and Moderate respectively as to potential to have an adverse effect on the drug product stability in site transfer in Table 3 of the revised SSS draft document. Yet neither has had a recall through February, 1999 based on stability considerations and the multiple generic applications approved for these product were conducted probably with one batch and 3 months accelerated stability data.

SAME DRUG PRODUCT MANUFACTURED AT DIFFERENT SITES

Sidney Goldstein, D. Sc., Duramed Pharm.

Captopril 22 ANDA approvals

Sites 22 possible different manufacturing plants

Components/
Composition 22 possible different

Container/
Closure How Many Different Materials/Sizes?

Bioequiv. 22 studies

NDS Sources How Many Different Manufacturers?

ADDITIONAL EXAMPLES OF MULTIPLE GENERIC APPROVALS

<u>DRUG</u>	<u>NO. OF APPROVALS*</u>
Acylovir Caps.	Eight
Acylovir Tabs.	Five
Cimetidine Tabs.	Nine
Etodolac Tabs.	Ten
Ranitidine Tabs.	Twelve
Selegiline Tabs.	Seven
Diclofenac Delayed Release Tabs.	Seven

* Approvals after January, 1995