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

**Re: (Docket No. 98D-0362) Stability Testing of Drug Substances and Drug Products
Draft Guidance for Industry; Revised Proposal for Site Specific Stability Data for
Drug and Biologic Applications**

Eli Lilly and Company is pleased to have the opportunity to again comment on the subject draft document. We applaud FDA's attempts to reach a mutually agreeable solution to the issue of site specific stability as well as other issues in the draft guidance on stability.

Attached are detailed comments on the revised proposal for site specific stability presented at the public meeting held on March 31, 1999.

In addition, we would like to note that the recommended uniform storage statements for drug product labeling in the draft stability guidance are inconsistent with guidances issued by other regulatory authorities. Without harmonization of labeling requirements, industry cannot fully realize the advantages of the ICH stability guidance. We therefore strongly suggest that the FDA work with the European and Japanese authorities to harmonize the corresponding label statements.

Please feel free to contact me at (317) 276-0368 for clarification of any comments.

Sincerely,



Tobias Massa, PhD.
Director, Global Regulatory Affairs,
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Comments regarding the draft guidance:

Stability Testing of Drug Substances and Drug Products

The draft guidance, Stability Testing of Drug Substances and Drug Products, was published in the Federal Register in June 1998. It was then revised, and the revision made public in March 1999. This draft guidance would change the current requirements for approval and commercialization of new products by **adding** a new requirement that site specific stability data be submitted prior to approval.

PREVAILING LEGISLATION AND GUIDANCE

Currently there is not a general requirement in current legislation or guidance that site specific stability data be included in NDA or BLA applications. Specifically, Section 124 of the Food and Drug Administration Modernization Act of 1997 states,

“...A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure safety of effectiveness of the drug...”

This intent of the Legislation is clarified by the Senate Report covering this section of FDAMA which states (emphasis added):

- *“...the FDA **review and approve** new drugs and biological products on the basis of **pilot and small-scale manufacturing**,*
- *“and permit the company to scale-up to a large facility **after** the product has been approved.*
- *“Scaling up can be readily undertaken on the basis of **process validation**, without additional clinical trials.*
- *“Only in the **very rare cases** where full-scale production is necessary to ensure the safety or effectiveness of the new drug and biological product prior to approval is FDA given the authority to require such manufacturing as a condition of approval...”*

This view is consistent with the ICH Q1A guidance, Stability Testing of New Drug Substances and Products, which does not require site specific stability data for approval or marketing of a new drug substance or product. ICH requires the sponsor to make a commitment to place the initial commercial batches into a **post-approval** stability program if these data are not included in the initial application; however, submission of this data prior to approval is **not** required under ICH. FDA is a signatory to the ICH guidance, and this guidance was published in the Federal Register September 22, 1994 and effective on that date.

The current ICH guideline is actually consistent with and gives continuity to the previous prevailing guideline on stability published in 1987 which states [emphasis added],

- Regarding drug substance: “... *studies to define the drug substance stability profile need to be conducted only **once** for each drug substance produced **by the same manufacturing process** ...*” [section III.A].
- Regarding drug product: “... *Tested batches must ...be **representative** in all respects ... of the population of production batches of drug product ...*” [section III.C.1] And then goes on to say, “*If research or pilot scale batches are used, they should have **the same characteristics** as production scale batches, ...*” [section III.C.1.a]

Based upon this, one can conclude that site specific stability is not required for the NDS by the 1987 guideline. And contrary to FDA claims, the 1987 guideline does not mandate that site specific stability is required to support a new manufacturing facility for a drug product. The guideline suggests that such data “may be needed”, but it also clearly states that this is dependent upon “the nature of the product, the process involved, and the stability data previously generated”, that is, what is known about the drug product. The guideline states (emphasis added),

*For a change limited to a new manufacturing facility for the identical drug product using similar equipment, 3 months accelerated data **may be needed**, depending on **the nature of the product, the process involved, and the stability data previously generated**. A commitment should be made to conduct stability studies on at least the first three commercial production lots based upon the approved stability protocol. Ordinarily, the already approved expiration dating period may be used under these circumstances.* [section V.D.3]

In light of FDAMA and the ICH guidance, which in our opinion supercede the 1987 guideline and are now the current prevailing guidance on stability requirements, it is inappropriate for the FDA to now **require** site specific or production scale stability data in the registration application for new drug substances and new drug products.

The Senate report, which is based upon discussions with Industry and FDA during FDAMA negotiations, makes it clear that manufacturing data from the site of commercial production should not be a routine requirement for application approval. Furthermore, the Congressional record clearly states the appropriate tool to verify scale-up at the manufacturing site is **process validation**. Process validation is addressed under FDA’s current requirements for pre-approval inspections, which provide for on-site inspection of the actual manufacturing site(s) by FDA personnel prior to approval.

COMMENTS ON THE PROPOSAL FOR SITE SPECIFIC STABILITY DATA

The revised draft stability guidance seeks to add a new requirement, namely, the submission of site specific stability data as a condition for approval. This proposal is inconsistent with the current FDAMA legislation and the Congressional intent.

To require site specific stability data in the registration increases the regulatory burden on industry. According to the Tufts Center for the Study of Drug Development, "For NCEs as a whole, about one-third of the drugs that make it to Phase III testing will not be approved for marketing."¹ In today's pharmaceutical manufacturing environment, most companies do not carry excess manufacturing capacity in anticipation of new products. Even if capacity exists to manufacture the NDS and/or NDP, it would be disruptive and costly to do so in a functioning GMP facility which may not manufacture that material again for years if at all.

If existing capacity is not adequate to support manufacture of the NDS and/or NDP, the sponsor would be forced to make one of two choices:

1. Make expenditures early in Phase III clinical studies, knowing that the product may never be approved to market. This could result in building capacity which is never needed.
2. Or wait until Phase III clinical studies are completed, then proceed to build the capacity if needed, manufacture product, put it on stability, analyze the samples, and compile and analyze the data, all of which must be completed before submission could be made. Even if "only" 3 months of stability data from the specific site are required in the application, logic tell us that the submission will be substantially delayed, possibly for up to 18 to 24 months.

Forcing manufacturers to make such a choice will increase the cost of development either due to the risk of building unused capacity and the cost of manufacturing material which will not be marketed, or it will increase cost due to the delay in submission and therefore product launch.

Site specific stability for the NDS is not necessary given that appropriate specifications are established. NDS **stability** is a function of exposure to temperature, humidity, light, and oxygen. The draft stability guidance itself states (lines 2770-3):

Because chemical stability of a substance is an intrinsic property, changes made in the preparation of that substance should not affect its stability provided the isolated substance remains of comparable quality for attributes such as particle size distribution, polymorphic form, impurity profile, and other physiochemical properties.

The application should include a rationale for the NDP formulation and its packaging. The type of information to include in the application is an area where additional guidance may be useful. We suggest the justification should be based upon development studies and include the following, as appropriate for the specific product:

¹ Tufts University, Executive Summary: White Paper On Four Areas of Relevance To New Drug Development And Review in the United States, **Drug Information Journal**, 29(2), 1995, pp. 357-424.

- choice of dosage form and its composition,
- ingredients and intended function of the excipients,
- overage or overfill,
- formulation and processing aspects that are identified as critical for batch reproducibility,
- choice of container/closure system.

Based upon the results of studies performed during development and the primary stability, both the drug substance and the drug product are characterized; the tests, packaging, and storage conditions are chosen; the critical processing parameters identified; and specifications are defined. These are described in the application and do not vary from site to site. The review staff at the Agency has the opportunity to evaluate these parameters as well as the specifications during review of the NDA or BLA. The actual transfer and validation of the process to a manufacturing site is subject to evaluation through the pre-approval inspection process.

As noted by the vast majority of the industry participants at the March 31, 1999 open workshop on site specific stability, **process validation** is the best marker for assessment of successful scale-up and technology transfer to a new site. Site specific stability is not a surrogate for this.

The examples given by FDA at the workshop to justify their claim that site specific data is necessary, in our opinion, do not provide a convincing case for site specific stability data. In our evaluation of the examples, stability of the material is not the root cause for the problems observed. Rather, the root causes for the problems noted appear related to process transfer and validation issues. Refer to the attachment for a detailed discussion of these examples.

No other major country or region requires submission of site specific stability data as a condition of approval or commercial marketing of a product. The requirement for such data has been opposed vigorously by the EU and Japanese regulators involved in ICH. For the FDA to unilaterally add site specific stability data as a new requirement would result in disharmony in the requirements for approval in the three regions, setting back the progress achieved through the ICH process.

Proposals regarding the draft guidance:
Stability Testing of Drug Substances and Drug Products

We recommend the following with regard to the draft guidance:

1. Consistent with ICH, the application will include a commitment to place on stability commercial batches of both the drug substance and the drug product. The results of these studies will be reported in subsequent annual reports.
2. We suggest that the FDA work with industry to develop guidances on
 - The proper manner in which to validate various aspects of site transfer.
 - Appropriate information to include in the application summarizing the development of the drug product
3. We strongly suggest that the FDA work with the European and Japanese authorities to harmonize the uniform storage statements for drug product labeling. The statements proposed for drug product labeling in the draft stability guidance are inconsistent with the CPMP guidance “Note for Guidance of Storage Conditions for Medicinal Products in the Products Particulars” dated January 28, 1998. Industry cannot fully realize the advantage of harmonization of the stability storage conditions specified in the ICH stability guidance document if the individual regulatory bodies require different label statements for products stored under the same conditions.

Attachment

Site Specific Stability

**Comments On Examples Provided By Dr. R. Seevers (CDER, FDA)
at Public Meeting On 3/31/99**

Site Specific Stability

Comments On Examples Provided By Dr. R. Seevers (CDER, FDA) at Public Meeting On 3/31/99

The general nature of the comments provided in the examples makes it difficult to analyze the context in which problems arose. Therefore, we believe it is inappropriate to reference these situations as “case examples” of where site specific stability data is required to detect a “problem”. We offer the following comments on, and interpretation of, these situations:

Example	Situation	Comments
1	<ul style="list-style-type: none"> • Immediate release tablet with 24 months expiry at original site • 3 tech transfer lots fail or have borderline assay at 15 months • Expiry reduced to 12 months at new site • Biostudy shows material from new site is not bioequivalent 	<p>These observations suggest a case in which product changes become apparent only after prolonged storage. While formulations such as these are encountered occasionally, the underlying principle of accelerated stability testing is the Arrhenius relationship. As a result of this relationship, the stability of the product may be accurately predicted after short term (3 to 6 months) testing. Such a stability database is normally generated during routine validation efforts.</p> <p>From the information provided, the product was granted 24-month expiration dating at the original site. This suggests that the applicant had significant experience with the formulation at the original site of manufacture. This experience should have provided a basis for assessing whether the degradation of the active followed Arrhenius relationships. Since accelerated testing is of limited utility in the absence of an Arrhenius relationship, a conservative approach including longer term stability testing should be considered whenever testing at elevated temperatures has been shown not to be indicative of the situation at room temperature.</p> <p>The observation that the material was (subsequently?) shown to be bioequivalent suggests that the processing of the material at the new site was fundamentally different. This may have been detected immediately by dissolution testing, however, there is no mention whether a discriminating and validated test procedure was in place. Data from such a test may have provided an immediate indication of differences in the product manufactured at the new site.</p>
2	<ul style="list-style-type: none"> • IND capsule packed in non-US facility • NDA drug product packed in US facility 	<p>We have occasionally observed similar behavior for blister packaged materials. Our experiences suggest that these phenomena reflect inappropriate settings, or control, of blister packaging equipment. The defective packaging is usually obvious immediately and stability testing is not required to detect this defect.</p>

Example	Situation	Comments
	<ul style="list-style-type: none"> • Delamination of blister packaging: stability compromised • Cause attributed to heat sealing at US facility 	
3	<ul style="list-style-type: none"> • Injectable combination drug with epinephrine • At new site, firm adds 8%, then 11% epinephrine overage • Stability failures trigger reduction in expiration dating: 36 months to 24 months, then 18 months 	<p>No mention is made of whether an overage was used at the original manufacturing site. If no overage was necessary at the original manufacturing site, and manufacturing overages of the magnitude stated are required at the new site, fundamental differences in the manufacturing process between the sites are clearly indicated and warrant investigation. These differences should be immediately obvious, even upon initial assay and raise concerns relative to the state of validation of the process at the new site. Long term stability data would merely confirm the initial observations. From the limited information provided, we are inclined to agree that the manufacturing process at the new site has not been optimized. Additional study is clearly warranted to determine areas for increased attention. Site specific stability, however, is not required to reach this conclusion.</p>
4	<ul style="list-style-type: none"> • Pre-approval site change for IR tablets: hygroscopic • Supplement for manufacturing sites in PR and PA • Stability testing shows that product manufactured in PR has significantly shorter projected expiry • PR site withdrawn 	<p>In process and release testing for drug products containing a hygroscopic drug substance should obviously include LOD and, perhaps, Karl Fischer testing. This is even more important in those cases where the drug substance is moisture labile. No mention is made of whether initial assessments of moisture content at the PR site were performed, or whether the data generated varied from experiences at the PA site. Such initial testing might provide an immediate indication of the comparability of the manufacture at the two sites.</p> <p>An additional element in the successful production of such a product is the adequacy of the packaging. If the applicant changed the packaging materials or the packaging equipment in the process of effecting the site change, careful evaluation of the suitability of the new commodities (and process) should be conducted. This evaluation might include studies of moisture vapor transmission rates, as well as stability testing of the product (at elevated humidity conditions). These evaluations are secondary to the site change however and are not mandated due to a site change per se. The studies would not necessarily require the use of materials manufactured at the proposed site, as long as the packaging supplies and process are recreated. If the moisture content of the product manufactured at the PR site is maintained at levels equivalent to those previously observed at the PA site, it is unlikely that stability testing will reveal critical differences in the products. Whenever the packaging for a hygroscopic product is changed stability testing must be conducted to establish the adequacy of the proposed package. This is true whether or not a site change is also being effected.</p>
5	<ul style="list-style-type: none"> • Site renovation • Tablets in blister package • Satisfactory data on several lots -6 month accelerated/60 month 	<p>There is little information on which to comment. It is not clear from these remarks whether there were some formulations that were made in the renovated facility that subsequently failed during stability testing as well as some products that were successfully manufactured in the new facility. If this were the case, a critical evaluation of the facility modifications and product characteristics might provide insights on what types of products are most</p>

Example	Situation	Comments
	long term <ul style="list-style-type: none"> • Manufacturing site renovated • Several lots made after renovation fail dissolution at 2 months accelerated test station 	suspect when changes are made to the manufacturing process as well as what types of facility modifications require careful qualification before initiating routine production.
6	<ul style="list-style-type: none"> • Inhalation solution in Blow-Fill-Seal ampoules • Met all specifications at release • Stability samples darkened over time • Problem traced to a change in one of the head fillers on the ampoule fill line 	Again, there is little information on which to base a comment although this seems to be an issue associated with oxidation and subsequent discoloration. For materials subject to such degradation routes, appropriate specifications should be established for headspace oxygen content. With in process and release testing in place, the performance of the filling equipment, as well as the acceptability of the product, may be assessed. Short term stability testing, performed in conjunction with scale up and validation, might potentially confirm the suitability of the new equipment.
7	<ul style="list-style-type: none"> • Antibiotic drug substance • Assay failures on stability • Problem traced to stainless steel solvent holding tank • Tank leach heavy metals that catalyzed degradation 	In this case, it is not clear if the problem is related to a site transfer. However, it is clear that equipment requirements were not properly communicated, and the compatibility of the reaction solvent with stainless steel was not adequately assessed. A degradation pathway catalyzed by heavy metals could have been detected by Stress testing during development. If an appropriate specification for heavy metals had been set, this situation could have been avoided.
8	<ul style="list-style-type: none"> • New facility had several lots recalled for sub-potency and low preservative • Investigation showed that active and low preservatives adsorbing to PVC tubing • Problem previously detected at former manufacturing site • New site was never apprised of the problem 	This example emphasizes the importance of communication. What is not clear is why the materials were released at all. Adsorption of drug or excipients onto product contact surfaces should have been detected during routine release testing. The sub-potency and low preservative levels would be observable immediately upon completion of the manufacturing process and would not be expected to change (appreciably) during stability testing. Hence, it is unlikely that site specific stability testing would add any information beyond what would reasonably be expected to come from routine validation testing at the proposed manufacturing site.
9	<ul style="list-style-type: none"> • Manufacturing suspended at 	This example again emphasizes the importance of communication in technology transfer. The information

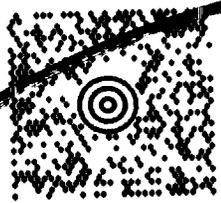
Example	Situation	Comments
	<p>original site after polymorph detected.</p> <ul style="list-style-type: none"> • Manufacturing transferred to contract facility • In a few years polymorph also detected during stability testing of product manufactured by contractor 	<p>suggests the applicant was formulating the product with a metastable polymorph. It is not clear whether the initial development pharmaceuticals work for the product identified multiple polymorphs for the NDS or not. It is also not clear whether the polymorph that was detected upon stability testing had been observed prior to this time. While polymorphic screens and existing analytical techniques can identify multiple polymorphs and assess the relative stability of the polymorphs identified, there cannot be complete assurance that every polymorph has been isolated. In this example one must assume that the new polymorph was more thermodynamically favored than the polymorphic form used for routine manufacture up until that time. A more prudent course of action might have been to study the new form, assess the suitability of using that form in the product, and establish proper process controls and release tests. It is not surprising that the (thermodynamically favored) polymorph also was detected at the new manufacturing site. In this case, site specific stability, would confirm that additional characterization work was warranted. Such a stability study would do nothing to prevent the issue or even alter the need to address the issue at the initial site of manufacture.</p>
10	<ul style="list-style-type: none"> • Enteric coated tablet: site transfer from pilot to production • Pilot stability studies established 18 months expiration dating period • Production lot failed dissolution at 3 months 	<p>We assume the subject product failed the enteric portion of the dissolution test. This may occur when an assumption of a constant coating efficiency is made between sites, equipment, and manufacturing scale. We have found that this assumption may not be appropriate, especially during product scale up or transfer. Calculations of coating efficiency (defined as the fraction of coating solids adhering to the tablet surface relative to the total amount of coating sprayed at the tablet bed) and microscopic assessment of coating thickness can predict when such failures are likely. During scale up or product transfer of enteric-coated products it is important to maintain the target coating thickness that has been previously demonstrated to be required to provide enteric protection.</p> <p>Stability testing of enteric-coated products is useful to assess time dependent changes in the coating like brittleness and cracking. Such changes are primarily indicative of the plasticization of the film and are not likely to be dependent upon the manufacturing location. While these studies are critical during development of the product, it is not obvious that repeating these studies in connection with a product transfer to a new manufacturing site provides any value.</p>

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