Dennis M. Erb, Ph.D.
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Merck & Co., Inc.
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June 16, 1999

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

MERCK
Research Laboratories

Re: Stability Testing of Drug Substances and Drug Products Draft Guidance for Industry; Revised Proposal for Site Specific Stability Data for Drug and Biologic Applications

Merck & Co., Inc. is a worldwide research intensive company that is a leader in the U.S. pharmaceutical industry in discovery, development, production and marketing of human and animal health products. Since 1992, we have filed and received approval for thirteen original NDAs, and these products have been successfully launched. Based on this experience, we feel qualified to comment on the FDA draft proposal related to the requirement for site stability data as an integral part of a CMC NDA package.

We have on numerous occasions articulated our position to the Agency that site specific stability data does not provide added assurance of product quality or a successful transfer of technology. The most recent occasion was at the public meeting on March 31, 1999 to discuss the scientific issues related to this subject. At this meeting, we summarized our experience with thirteen recent product introductions documenting that site specific stability has little value in assessing technology transfer.

Attachment 1 is a copy of the position paper on site stability that was submitted to FDA prior to the March 31, 1999 meeting. This document summarizes our opinion that the proposed specific site stability requirement does not provide added value to the quality of products while adding a significant cost to the Sponsor during product development. Further, we believe that validation, not site stability, is the most relevant scientific measure of successful technology transfer. Based on these principles, we offered in Attachment 1 and at the open meeting on March 31, 1999 an alternative proposal to provide a summary of the process validation at least three months prior to the PDUFA due date.

In response to requests for stability data made at the open FDA meeting on Site Specific Stability we have completed a review of products introduced over the past 15 years. Provided in Attachment 2 are stability data for 25 marketed products which were the subject of NDAs submitted between 1983 and 1997. This spreadsheet contains stability data from a representative research batch compared to stability data from a representative production/validation batch for each product. In all cases, the stability results from both research and manufacturing batches were comparable. The results of this comparison further support that site stability data does not provide any added information over that from research batches and process validation.

We trust that these comments and the data provided will be considered in further development of the draft guidance.

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Senior Director, Regulatory Affairs

Attachments
Q/ligi/guidance/294

98D-0362

C68

Attachment I

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March 23, 1999

Ms. Kimberly Topper
Center for Drug Evaluation and Research
HFD-021, Room 1091
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MERCK
Research Laboratories

Re: Scientific Issues Related to "Site-Specific Stability Data for Drug and Biologic Applications" Section of Draft Guidance and Possible Revisions

Merck & Co., Inc., is a worldwide research intensive company that is a leader in the U.S. pharmaceutical industry in discovery, development, production and marketing of human and animal health products. Since 1992, we have filed and received approval for thirteen original NDAs, and these products have been successfully launched; based on this experience, we feel qualified to comment on the FDA draft proposal related to the requirement for site stability data as an integral part of a CMC NDA package. We have worked with the Agency, both through correspondence and meetings in an effort to better define the "value add" of site specific stability during the NDA review process. We have been unsuccessful in defining with the Agency any scientific or technical benefit to be gained in product quality, or patient protection by this new requirement.

Development time for a pharmaceutical product, particularly for a new chemical entity is extremely long, generally 5-7 years. As part of the development, extensive work is done to fully characterize both the API and the drug product, together with stability profiles, and to understand the manufacturing processes, including process parameters and potential environmental sensitivities. The collection and evaluation of in-process test results, release results and stability information associated with all stages of product development are used to demonstrate the integrity of the process and the product. It is also used to determine specific sensitivities which must be controlled during further process scale-up and/or transfer to other manufacturing sites. The validity of this development scheme has been evidenced 13 times in the last 7 years at Merck with the successful transfer of processes and products to multiple manufacturing sites. In none of these cases were there any stability concerns.

The assumption by the FDA that site specific stability data provides an added assurance of product quality or successful transfer of technology is inaccurate. In most cases the

greatest challenges for successful validation are scale up issues, rather than site specific concerns. Site stability is not a scientifically appropriate measure of successful technology transfer. Stability is a function of the intrinsic molecular structure of the bulk substance, the composition of the formulation, the environment and storage conditions; all of these parameters are clearly defined as part of the development program and provide a significant body of knowledge about the product and its manufacturing process. None of these conditions are changed during technology transfer. Validation of a process using pre-defined processing parameters and quality attributes is the most relevant measure of successful technology transfer. Release of the validation lots meeting all critical quality attributes demonstrates that the product to be marketed is comparable to the biobatch and material used in the pivotal clinical studies.

The Agency has provided no scientific rationale as the basis for site specific stability beyond the "difference factor"- potential differences in the site technical staff, SOPs, raw materials etc. It is not logical to assume that technology transfer within a site is more or less rigorous than between sites. At Merck the site technical staff in most cases, reports into a central organization, common consistent SOPs exist between sites, common suppliers of raw materials are used and common specifications, test methods, audit procedures exist to assure control. In all cases representatives from Research & Development are actively involved in all process demonstrations and validation exercises for new product introductions into manufacturing, regardless of site location.

Merck recognizes the importance of stability data to support registration of a new drug product and fully supports the ICH recommendations. Prior to approval, we collect probe stability data during early development and generally at least 12 months stability data on three batches, at least two of which are manufactured at $1/10^{th}$ production scale, using the final composition and process. This significant body of data permits a full understanding of the stability profile of the drug product. After approval, stability data are collected on the first 3 commercial scale batches manufactured at each site under accelerated and long-term storage conditions, and a commitment is made in the NDA to continually place on stability at least one batch every year. The Agency's request for 3 month additional site specific stability does not add to our stability knowledge base, nor is this information the appropriate measure for success of technology transfer.

To remain competitive in the global market, Merck frequently uses multiple manufacturing sites for each of its products. However, our Research and Development and pilot plant facilities are limited in number and are not necessarily located at the final site of manufacture. The requirement for three months stability data on drug product made at the final facility with API from the final manufacturing site would have a major impact financially and on our timeline for regulatory filings. In many cases, in order to have API available for the site stability lots, construction of the API facility and the commitment of funds[$5-10 million at risk] for construction would have to begin 6-10 months prior to the beginning of Phase III clinical studies. This timing is before we have the final dose selected, or have even demonstrated full safety and efficacy of the product. Without this acceleration of construction for both the API and the drug product facilities,

filing of the NDA could be delayed 6-9 months beyond completion of the clinical program. In most cases the lots made for the site stability studies would not be saleable, as they would be too close to expiry at the time of NDA approval. The significant economic investment that is required by these proposed regulations does not serve to add any level of assurance that technology transfer has been successful.

Merck strongly opposes the requirement of site specific stability as part of a NDA filing and approval. We believe such a requirement has no scientific justification, does not improve product quality or add to the safety or efficacy of the product to the patient. While we recognize the Agency's need to assure that material to be marketed is comparable to that which is used in the clinic, we would propose as an alternate:

> **At least three months prior to the FDA "PDUFA Due Date", the applicant will provide release data and a summary report of validation on at least three lots of API and three lots of drug product made at production scale in the final manufacturing equipment at the final manufacturing site. These validation lots will be placed on accelerated and long term stability as a NDA commitment.**

In summary, Merck believes that 3 (or 6) months site specific stability data do not provide assurance of product quality or demonstrate successful transfer of technology. These attributes can be demonstrated only through successful validation of the processes at full scale in the final manufacturing equipment at the final facility. We believe that in virtually all instances of purported site-stability failures, the failures actually reflect situations that could and should have been flagged during process validation. We would propose as an alternative that release data and a summary of the validation study be available for review by the Agency three months prior to the PDUFA Due Date.

We appreciate the opportunity to participate in the March 31, 1999 public meeting to further discuss the scientific issues related to "Site-Specific Stability for Drug and Biologic Applications".

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

Q/ligi/guidance/ss331

Attachment II

STABILITY RESULTS - MERCK 25 PRODUCT FILINGS (1983-1997)

	Research Exhibit Batch Stability						Production Validation Batch Stability					
	Months	Assay %	Degs total %	Assay* %	Degs* total %	Diss %LC	Months	Assay %	Degs total %	Assay* %	Degs* total %	Diss %LC
MAXALT MLT	0	101.2	<LOQ	N/A	N/A	103	0	100.7	<LOQ	N/A	N/A	103
	18	99.0	0.5	N/A	N/A	101	18	99.8	0.4	N/A	N/A	103
MAXALT Tablets	0	99.9	<LOQ	N/A	N/A	103	0	101.0	<LOQ	N/A	N/A	103
	18	98.9	0.1	N/A	N/A	101	18	101.0	<LOQ	N/A	N/A	102
PEPCID RPD	0	100.1	0.2	N/A	N/A	101	0	102.6	0.0	N/A	N/A	104
	24	98.4	0.3	N/A	N/A	101	24	101.0	0.2	N/A	N/A	98
AGGRASTAT Pre-Mixed	0	99.1	<LOQ	N/A	N/A	N/A	0	99.1	<LOQ	N/A	N/A	N/A
	9	99.9	<LOQ	N/A	N/A	N/A	9	100.4	<LOQ	N/A	N/A	N/A
AGGRASTAT	0	99.0	<LOQ	N/A	N/A	N/A	0	98.8	<LOQ	N/A	N/A	N/A
	12	101.1	<LOQ	N/A	N/A	N/A	12	99.4	<LOQ	N/A	N/A	N/A
COSOPT (2 actives)	0	100.7	<0.1	99.8	N/A	N/A	0	99.7	<0.1	99.3	N/A	N/A
	9	101.9	0.2	100.2	N/A	N/A	9	101.5	0.2	100.6	N/A	N/A
SINGULAIR Chewable	0	99.8	0.2	N/A	N/A	94	0	100.3	0.4	N/A	N/A	96
	12	100.8	0.4	N/A	N/A	97	12	100.0	0.6	N/A	N/A	95
SINGULAIR FCT	0	101.3	0.1	N/A	N/A	94	0	99.9	0.3	N/A	N/A	96
	12	99.7	0.3	N/A	N/A	97	12	98.5	0.3	N/A	N/A	94
PROPECIA	0	100.1	N/A	N/A	N/A	98	0	98.8	N/A	N/A	N/A	99
	12	99.8	N/A	N/A	N/A	98	14	98.3	N/A	N/A	N/A	97
CRIXIVAN	0	98.8	<0.1	N/A	N/A	95	0	102.6	0.0	N/A	N/A	94
	24	99.4	0.4	N/A	N/A	100	24	98.5	0.2	N/A	N/A	95
FOSAMAX	0	99.9	N/A	N/A	N/A	97	0	98.5	N/A	N/A	N/A	96
	24	99.7	N/A	N/A	N/A	99	24	99.5	N/A	N/A	N/A	93
HYZAAR (2 actives)	0	99.5	<0.1	100.5	<0.1	100(85)	0	99.8	<0.1	99.6	<0.1	100(94)
	36	100.7	0.3	99.2	<0.1	102(86)	36	100.0	<0.1	100.2	<0.1	100(92)

* second active

STABILITY RESULTS - MERCK 25 PRODUCT FILINGS (1983-1997)

	Research Exhibit Batch Stability						Production Validation Batch Stability					
		Assay	Degs	Assay*	Degs*	Diss		Assay	Degs	Assay*	Degs*	Diss
	Months	%	total %	%	total %	%LC	Months	%	total %	%	total %	%LC
COZAAR	0	99.1	<LOQ	N/A	N/A	93	0	100.4	<LOQ	N/A	N/A	92
	24	99.1	<LOQ	N/A	N/A	97	24	100.1	<LOQ	N/A	N/A	97
TRUSOPT	0	100.1	<0.1	N/A	N/A	N/A	0	101.3	<0.1	N/A	N/A	N/A
	24	108.2	1.1	N/A	N/A	N/A	24	104.3	1.1	N/A	N/A	N/A
PEPCID Premixed Inj	0	100.0	0.2	N/A	N/A	N/A	0	100.0	0.3	N/A	N/A	N/A
	18	97.5	3.9	N/A	N/A	N/A	18	95.0	4.2	N/A	N/A	N/A
TIMPOTIC XE	0	100.6	<LOQ	N/A	N/A	N/A	0	98.0	<LOQ	N/A	N/A	N/A
	24	101.1	1.4	N/A	N/A	N/A	24	100.2	0.8	N/A	N/A	N/A
PROSCAR	0	100.0	N/A	N/A	N/A	97	0	101.1	N/A	N/A	N/A	98
	12	101.0	N/A	N/A	N/A	102	12	98.9	N/A	N/A	N/A	98
ZOCOR	0	100.0	N/A	N/A	N/A	98	0	98.4	N/A	N/A	N/A	96
	24	98.0	N/A	N/A	N/A	94	24	97.5	N/A	N/A	N/A	88
NOROXIN	0	100.0	N/A	N/A	N/A	99	0	97.7	N/A	N/A	N/A	101
	24	92.8	N/A	N/A	N/A	100	24	98.5	N/A	N/A	N/A	102
PRIMAXIN I.M.	0	100.0	N/A	100.0	N/A	N/A	0	103.9	N/A	N/A	104.6	N/A
	24	93.1	N/A	101.0	N/A	N/A	24	102.3	N/A	N/A	104.2	N/A
PRINZIDE (2 actives)	0	100.0	0.0	100.0	0.5	105 (99)	0	99.3	0.0	101.0	0.0	102(99)
	24	94.8	0.2	100.0	0.6	104(103)	24	98.1	0.0	98.5	0.2	98(96)
PRINIVIL	0	100.0	0.0	N/A	N/A	100	0	100.0	0.0	N/A	N/A	103
	24	96.3	0.4	N/A	N/A	95	24	101.0	0.0	N/A	N/A	99
MEVACOR	0	100.0	N/A	N/A	N/A	100.0	0	100.0	N/A	N/A	N/A	99.0
	24	97.1	N/A	N/A	N/A	95.0	24	97.0	N/A	N/A	N/A	100.0
PEPCID OS	0	100.0	0.0	N/A	N/A	N/A	0	99.0	0.0	N/A	N/A	N/A
	24	98.9	0.0	N/A	N/A	N/A	24	99.4	0.0	N/A	N/A	N/A
VASOTEC	0	98.3	0.2	N/A	N/A	102	0	97.6	0.0	N/A	N/A	96
	24	96.5	0.7	N/A	N/A	97	24	98.1	0.2	N/A	N/A	100

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