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



**RE: Docket No. 02D-0237 International Conference on Harmonisation: Draft Guidance on Q1E Evaluation of Stability Data; Availability**

Merck & Co., Inc. is a leading research-driven pharmaceutical products and services company. Merck discovers, develops, manufactures and markets a broad range of innovative products to improve human and animal health. Through a combination of the best science and state-of-the-art medicine, Merck's Research & Development (R & D) pipeline has produced many of the important pharmaceutical products on the market today.

As a global, innovative R & D company, Merck is affected by ICH regulations. Merck Research Laboratories (MRL) scientists have participated in many ICH harmonization discussions and, therefore, are interested in, and well qualified to comment on this Draft Guidance on Q1E Evaluation of Stability Data, hereafter referred to as The Draft Guidance. The Draft Guidance is an annex to an ICH guidance entitled "Q1A (R) Stability Testing of New Drug Substances and Products," hereafter referred to as Q1A (R). We understand that it is intended to provide guidance on how to use stability data generated in accordance with Q1A (R) to propose a retest period for the drug substance and a shelf life for the drug product.

Merck supports the development of The Draft Guidance and, to assist in its further development, we are providing the following general comment, specific line comments and editorial comments for your consideration.

**GENERAL COMMENT**

**Section 2.3, Extrapolation**

**Comment:** The Draft Guidance allows limited extrapolation to extend the retest period or shelf life beyond the observed range of available long-term data. It also provides guidance on the length of time one can extrapolate retest period or shelf life beyond available long-term data for different circumstances. It would be helpful to include in the discussion a reference to Q1A (R) for the minimum time period to be covered by the data at submission.

**SPECIFIC COMMENTS**

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**Appendix B, Section B.1, third paragraph, first sentence.**

***If the above approach is used, the values of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within acceptance criteria through the end of the retest period or shelf life at a confidence level of 95 percent.***

**Comment:** The use of confidence limits for the regression line involves inference on the means, not individual values. We suggest that this sentence should be changed to read:  
*If the above approach is used, the mean value of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within acceptance criteria through the end of the retest period or shelf life at a confidence level of 95 percent.*

**Appendix B, Section B.1, third paragraph, last sentence.**

*If, however, the acceptance criterion for the quantitative attribute calls for individual values, confidence limits for the individual values should be used (e.g., content uniformity for some complex dosage forms).*

**Comment:** It is not clear which products or attributes are referred to in this sentence. Although one ensures that content uniformity is met at shelf life, content uniformity is not routinely tested during stability studies. In most cases, where the acceptance criterion calls for individual values, the tests are multi-stage in nature. The multi-stage nature of the tests calls for a more complicated analysis, often requiring sophisticated methods such as Monte Carlo simulation for computing limits on individual values that account for the sequential data collection. Unless more clarification and guidance is provided on the implementation of this concept, this sentence should be deleted.

**Appendix B, Section B.2.1.1, first paragraph, last sentence**

*Each of these tests should be conducted using a significance level of 0.25 to compensate for the expected low power of the design due to the relatively limited sample size in a formal stability study.*

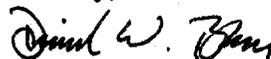
**Comment:** This statement appears to allow the option to use a significance level other than 0.25, as long as the design has sufficient power to detect slope and intercept differences among batches. However, the acceptable level of power needs to be specified for this deviation to be meaningful in context. Although the definition of acceptable power is not critical to section B.2.1.1, it is integral to some of the statistical procedures described in Section B.2.1.2. (See comment below.)

**Appendix B, Section B.2.1.2. Other methods**

**Comment:** Some of the statistical procedures described in this section require one to specify a desired level of power. Guidance on what would be considered an acceptable level of power would be useful. (See comment above.)

We appreciate the opportunity to provide comments and trust that these comments will be considered in further development of The Draft Guidance.

Sincerely,



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