

Bristol-Myers Squibb Pharmaceutical Research Institute

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

**Re: Docket No. 02D-0237; Draft Consensus Guidance, *Evaluation of Stability Data*,
Federal Register, Vol. 67, No.115, p. 40949 (June 14, 2002)**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, and nutritionals. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated \$2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in, and well qualified to comment on, this FDA guideline for the evaluation of stability data.

We commend the U.S. FDA for bringing forward this guidance. We found it to be both clear and well-written. In terms of improvement, we agree with PhRMA statistics working group, that three items require some clarification. These items are listed below.

Appendix B, section B.1, paragraph 3, 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."

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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



Appendix B, section B.1, paragraph 3, 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).”

It is not clear as to which products or attributes this sentence refers to. Although one ensures that content uniformity is met at shelf life, content uniformity is not routinely tested during stability studies. And 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, possibly with no closed forms for computing limits on individual values. Unless more clarification and guidance is given on the implementation of this sentence, this sentence should be deleted.

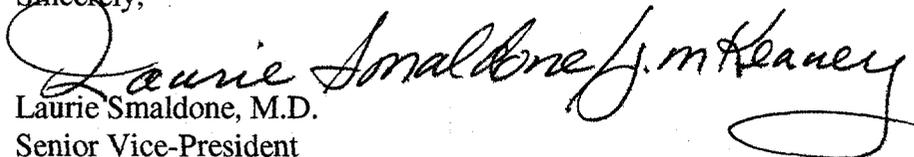
Appendix B, section B.2.1.2

“Statistical procedures other than those described above can be used in retest period or shelf life estimation. For example, if it is possible to decide in advance the acceptable difference in slope or in mean shelf life among batches, an appropriate procedure for assessing the equivalence in slope or in mean shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, and justified and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate the appropriate statistical properties of the alternative procedure selected.”

Some of the statistical procedures described in this section require one to specify a desired level of power. Some guidance is needed on what would be considered an acceptable level of power.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



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