



Bristol-Myers Squibb Company

Joseph F. Lamendola, Ph.D.
Vice President
Global Regulatory Strategy
Pharmaceutical Research Institute

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-3781 Fax 609-252-7781
Joseph.Lamendola@bms.com

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

Re: Docket No. 2004D-0484; Draft Guidance, Role of HIV Drug Resistance Testing on Antiretroviral Drug Development," *Federal Register*, Volume 69, No. 228, Pages 69374-69375 (November 29, 2004)

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the draft guidance on the *Role of HIV Drug Resistance Testing on Antiretroviral Drug Development*. We appreciate the opportunity to comment on this important new guidance, which provides detailed recommendations regarding HIV drug resistance research to support the development of new antiretroviral medications. Our comments are set forth below.

BMS General Comments:

1. This guidance is based on experience from resistance studies which have been conducted primarily using drugs which impact relatively homogenous HIV targets in wild-type virus. Future antiretroviral agents, specifically entry inhibitors may target substantially more heterogeneous regions of the virus. This guidance should highlight that resistance investigations should be adapted to address the characteristics of the drug target.
2. We agree with the guidance recommendations to use consistent assays throughout the drug development program; however, the guidance should also reflect that the validation of new assay methods may occur during the development time frame. To address this consideration, we recommend that the guidance advise that samples be obtained and banked for future testing as appropriate should resistance testing substantially change during the clinical development program.
3. While we agree with the general principles of resistance testing as presented in lines 337-346, we think that the most relevant aspect of resistance is related to "virologic failure" rather than overall responses. We recommend that a standard definition of "virologic failure" be set forth in the guidance and include both failure to suppress to a specific threshold at a consistent time point, as well as confirmed rebound above the same threshold. This definition should be consistently used for study outcome determinations as well as interpretation of resistance analyses.

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Specific Comments (Items that Need Clarification & Recommended Actions)

- **Lines 143-145** While we appreciate the Agency's comment and acknowledgement that the draft guidance focuses on characterization of resistance during drug development we are, however, concerned by the Agency's recommendation that the principles of this guidance apply to currently marketed antiretroviral agents as well. The principles existing at the time of the initial approval of each currently marketed antiretroviral agent and applied to those currently marketed antiretroviral agents vary substantially in the requisite amount and quality of work making it difficult to bring these older products to the standards provided in this guidance. Thus, we ask that you consider deleting the recommendation that the principles be applied to currently marketed antiretroviral agents.
- **Line 411** The Drug X vs. Control comparisons proposed in Tables 1, 2A, 2B, 4 and 5 are most relevant when the control is an alternative active agent from the same drug class as Drug X. We request that the Agency include a statement in line 411 that comparisons to either placebo or agents from other classes should be discussed with FDA in advance.
- **Lines 681-684** We recommend revising this line to state that the "definition" of virologic failure should be consistent between the clinical or virologic endpoint in outcome analyses and the patients identified for resistance testing. Confirmed virologic failures should be consistently identified throughout the dataset for a study.

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,



Joseph Lamedola, Ph.D.
Vice President
Global Regulatory Sciences