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07 June 2005

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

**Re: Draft Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics** [Docket No. 2005D-0112, 70 *Federal Register*, 17095, April 4, 2005]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc., a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN® (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE™ (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance. As a company with a heavy investment and a particular expertise in the development of new cancer therapies, we are pleased to have the opportunity to comment, as follows.

1. Section III.B.3 – Time to Progression and Disease Free Survival

It would be beneficial if there were a separate section for “Time-to-Progression” as there are separate sections for all other endpoints.

2. Section III.B.3.c – Progression-Free Survival (PFS) Trial Design Issues

As stated in the Guidance, the definition for tumor progression varies widely. Standard regulatory criteria for assessing tumor progression would be ideal, however, we do understand that it would be difficult to provide a standard set of

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criteria for all tumors because response criteria differ among tumor types and the measurements can be different from tumor to tumor. We feel that the Agency should consider developing regulatory criteria for assessing tumor progression for each cancer. Standard criteria for each cancer would aid the sponsor in developing details in the protocol and the analysis plan thereby facilitating the collection of more robust data to conduct a sufficient evaluation of the correlation between effects on survival and PFS and/or time to progression (TTP).

### 3. Section III.C – Endpoints Involving Symptom Assessment

The Guidance indicates that Quality of Life (QOL) as a symptom endpoint provides more direct evidence for clinical benefit than overall response rate (ORR). However, QOL is not mentioned in Table 1: A Comparison of Important Cancer Approach Endpoints. Instead, ORR is listed. We recommend that the Agency provide clarification earlier in the Guidance to address this distinction.

### 4. Section IV.B – Studies Designed to Demonstrate Noninferiority (NI)

A. The guidance states that the NI margin is often set to be some fraction (i.e. 50%) of the control drug effect. However, it is not clear whether the NI margin is 50% of the point estimate of the control drug effect or 50% of the lower or upper limit of the confidence interval of the control drug effect. The latter has been generally accepted. We recommend that the Agency provide clarification on this issue.

B. Since NI trials rely on historical data to establish the expected size of treatment effect of the active control, and in many situations adequate historical data for the control do not exist, we recommend that FDA encourage the development and use of registries for retrospective data collection in order to provide usable historical data.

### 5. Section IV.D – Isolating Drug Effects in Combinations

It is suggested that this section be clarified to state that “An add-on study design should be sufficient to demonstrate the individual contribution of a new drug in such a regimen when the study is adequately designed and powered to detect a statistically significance difference for superiority of the new drug in the combination”. It is unclear from the current regulations that the effectiveness of a new medication has to be isolated for regulatory approval. Fixed dose combination product regulations require this isolation of such an effect but these



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regulations would not be applicable to this situation. Also, the add-on effect being superior should be sufficient and not require additional single agent studies that may not show efficacy when used alone in cancer populations.

6. General Comments

- A. The multiple-endpoint study is a frequently used design, but was not mentioned in the Guidance document. It would be helpful for the Agency to provide guidance on the utilization, design and statistical analysis surrounding the use of multiple endpoints in oncology clinical trials.
- B. We recommend the Agency provide clarification on the issue of treatment crossover as a separate section in the Guidance. Survival is the gold standard; however, most oncology trial protocols allow patients who failed one treatment to switch to an alternative therapy. In this case, it is almost impossible to detect a treatment difference in survival due to the huge sample size required, which may lead to denying the approval of an effective treatment.
- C. A general statement should be made that if there is an agreement with the FDA on the protocol design endpoints through a Special Protocol Assessment (SPA) that this should be sufficient for approval (accelerated or full approval) and not be subject to an Advisory Committee review. Although it is recognized that the decisions of the Advisory Committee are non-binding, FDA usually follows these recommendations. Such Committee "votes" have fluctuated markedly over time as noted in the guidance document. Approvals generally should not be decided by an Advisory Committee post-submission after the endpoints have been achieved with full agreement by the Agency.

We trust these comments will be helpful in evolving the final guidance.

Sincerely,

Robert G. Pietrusko, Pharm.D.  
Senior Vice-President,  
Worldwide Regulatory Affairs  
Millennium Pharmaceuticals, Inc.