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MILLENNIUM

12 August 2003

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

Re: Draft Guidance for Review Staff and Industry – Good Review Management Principles for PDUFA Products [Docket No. 2003D–0317, 68 *Federal Register*, 44345, 28 July, 2003]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. ("Millennium") is a global research-based biopharmaceutical company and leader in genomic drug discovery based in Cambridge, Massachusetts with a European affiliate in London, UK. Millennium's research, development and commercialization activities are focused on genomic approaches to the innovation of breakthrough products to treat cancer, metabolic, cardiovascular and inflammatory diseases.

Millennium recognizes the extensive effort that went into preparation of these Good Review Management Principles and commends the Agency on a fine effort. We are pleased to have the opportunity to comment on the draft guidance, as follows.

Page 4, Line 158 – *"It has been FDA's experience that submission of a complete application leads to the most efficient review process and shortest approval time."* We suggest that the following sentence be added: *"This does not imply use of a rolling submission for 'Fast Track' designated products may be less efficient."*

Page 6, lines 232 – 235 - The Review Division should strive to provide written responses or verbal feedback to the sponsor's questions before the meeting

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actually takes place. This can to lead to a more focused meeting or cancellation of the meeting if the answers are clear and there is no further need for the meeting. This is done routinely by the Oncology Division.

Page 7, Line 284 – *"The applicant is strongly encouraged to describe both the strengths and the weaknesses of a proposed application."* To provide more relevant information by the applicant, the following changes are suggested. *"The applicant is strongly encouraged to describe both the strengths and the difficulties encountered in development. Sponsors should point out development issues they faced in addressing the regulations and guidelines for approval and how these difficulties were addressed. Unexplained results or findings, based upon primary or secondary endpoints, safety assessment or subset analyses should be identified with a provision of the sponsor's assessment of their relevance."* Also, a post-NDA submission meeting should be considered. This type of meeting has been utilized by the Oncology Division.

Page 8, Line 308 – *"In addition, the applicant should provide the review division with updates regarding the timing of the planned submission"*. For rolling submissions, the guidance should detail the information that the sponsor should provide to FDA regarding submission strategy (which parts of the application will be submitted, in what sequence and when they will be submitted), how they will be processed within FDA, how a "complete application" will be assessed and what differences there may be in this process from that for assessing a non-'Fast Track' submission. Cross-references to other relevant guidances would also be helpful.

Similarly, with the current trend towards the submission of electronic applications, we suggest that there should be some mention of the particular contingencies and differences from paper applications in the submission acceptance and review processes, with cross-referencing to specific guidances.

Page 11, Lines 430 – 431 – Requests for Inspection *"Requests for inspections of manufacturing facilities and research sites should be made early in the review cycle and optimally, prior to the filing date."* We believe this should be clarified as *"prior to the acceptance of the file"* or *"before the 60-day filing acceptance date"*.

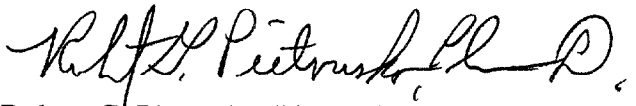
Page 11, Lines 454 – 455 - Designation of Review Priority – *"Agency manuals delineate for FDA review staff the current policy and procedures for assigning review priority."* In the review of the criteria for priority review, the Centers differ on what is considered to merit a priority review. We strongly suggest uniformity between the Centers and recommend use of CDER's definition which is as follows: *"The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation."*

Page 11, Lines 457 – 458 – Designation of Review Priority – *"in some instances, a preliminary designation of review priority may be made prior to submission."* The Guidance document should provide additional information regarding under what circumstances the Review Division may make a preliminary designation. How will this designation be conveyed to the sponsor? Does the sponsor have to make a specific request for the preliminary designation? If so, at what time point should the request be made by the sponsor for a preliminary designation?

Page 20, Line 820 – *Interdisciplinary Communication.* We note that there is no specific mention of interdivisional consultations in this section. Given the concerns expressed about the need to integrate the reviews of different disciplines within a single division, we believe that there should be specific mention of the need to be diligent in obtaining any necessary expert opinions from outside the division, since these opinions may have important implications for the conduct of the review and/or approval, yet may be procedurally more difficult to obtain and integrate with the reviews conducted by staff within the review division.

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

Sincerely,



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