Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
Tel 617 679 7000
www.millennium.com

MILLENNIUM

7 November 2003

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

Re: Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing. [Docket No. 2003D–0382, 68 *Federal Register*, 52782-3, 5 September, 2003]

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Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance. We are pleased to have the opportunity to comment on it, as follows.

Page 18, Lines 574-575: *"Containers and closures should be rendered sterile and, for parenteral drug products, pyrogen-free."*
This is the first time the term "pyrogen-free" is used in the document. The phrase is not defined with respect to a test method or endotoxin level. We suggest that a standard test method and an acceptable logarithmic reduction of endotoxin concentration, required for the product to be considered pyrogen-free, should be stated (see lines 668-669).

2003D-0382

Continued .../ C33

Page 19, Lines 629-630: *"A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product."*
Air can diffuse through some rubber stoppers without compromising the sterility of the product.

Suggestion: Remove the word "air" from the sentence. The new sentence should read: "A container closure system that permits penetration of microorganisms is unsuitable for a sterile product."

Page 23, Lines 783-785: *"In any study protocol, the duration of the run and the overall study design should adequately mimic worst-case operating conditions and cover all manipulations that are performed in the actual processing operation."*
The definition of "worst-case" is ambiguous. We suggest that the following sentence is substituted: "In any study protocol, the duration of the run and the overall study design should adequately mimic the process at the extremes of identified critical variables and cover all manipulations that are performed in the actual processing operation."

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

Sincerely,

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