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

**Re: ICH Q5E, Draft Consensus Guideline, Comparability of
Biotechnological/Biological Products Subject to Changes in Their Manufacturing
Process [Docket No. 2004D-0118, 69 *Federal Register*, 16580-16581, March 30, 2004]**

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc., (Millennium), 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Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance.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.

Scope of the Guidance

We recommend that it should be clearly stated that this guidance applies only to changes in manufacturing processes made during drug development or post-approval *by the innovating manufacturer, and not to "biogeneric" or "follow-on" products made by different manufacturers.* In fact, there exists no legal basis in the United States at present for the guidance to be applied to products made by different manufacturers.

Considerations for Post-approval Changes

Lines 108-109 note that *"it might be appropriate to collect data on the drug product to support the determination of comparability even though all process changes occurred in the manufacture of the drug substance"*. This would imply that manufacturing changes

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on the drug substance can be captured on the drug product. If changes are made in unit operations (downstream processing) then only changes in that unit operation need to be assessed via comparability exercise.

The guidance notes (lines 324-325) that *“to support process changes for approved products, data from commercial-scale batches are generally indicated”*. We submit that there can be circumstances in which data from smaller scale batches can be acceptable, provided that the process is validated (e.g., viral clearance), and this should be stated. We note that the following paragraph of the guidance suggests the use of development batches in process assessment.

Lines 358-359 note that *“for approved products, an appropriate number of post-change batches should be analysed to demonstrate consistent performance of the process”*. We would like clarification on what is the "appropriate" number?

Definitions of Comparability, Comparability Exercise and Comparability Bridging Study

We would like to address apparent conflicts in the definitions provided for the terms “comparable”, and “comparability exercise”.

Comparable is defined (lines 427-431) as:

“A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety, or efficacy of the drug product occurred. This conclusion can be based on an analysis of product quality attributes.”

The definition limits the change seen in the drug product to an “adverse impact” on the post-change drug product. However, comparability should also encompass perceived differences in the drug product in terms of quality, safety, or efficacy. For example, a post-change product that may have improved efficacy over a pre-change product should not be considered comparable.

Product quality attributes and nonclinical testing may indicate that a post-change product is “highly similar” to the pre-change product. However, the lack of an “adverse impact on the quality, [human] safety or [human] efficacy” of the post-change product can only be *proven* in humans. Use of the word “*occurred*” in the first sentence of the definition implies that such testing in humans was done, and thus that comparability was demonstrated, permitting use of the term “comparable”. Therefore, the second sentence of the definition, in which quality attributes alone may support comparability, would seem inconsistent with the first, which implies that human testing must be done to demonstrate comparability. Alternatively, we propose the definition would be better expressed as:

*“A conclusion that products are highly similar before and after manufacturing process changes and that no material difference in the quality, safety, or efficacy of the drug product is **anticipated**. This conclusion can be based on an analysis of product quality attributes, **and sometimes nonclinical testing and/or clinical testing.**”*

Comparability Exercise is defined (lines 432-434) as:

“The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.”

By this definition, pre-change and post-change products cannot be considered comparable until after completion of these studies.

Sincerely,



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