MILLENNIUM

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

RE: Docket No. 2003D-0412.
Draft Guidance. Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D). 68 FR 53983.

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.

Thank you for the opportunity to provide comment on the proposed definitions and standards for expedited reporting in the post-approval stage, drafted by the International Conference on Harmonisation (ICH) and released for consultation. We agree with the intent to create international standards for post-approval safety data management that will align with the standards adopted in ICH E2A for pre-approval safety data management.

We have organized our comments by the section numbers of the document.

Section 2.1.2 Adverse Drug Reaction (ADR)

The actual relationship of the event to the drug in a spontaneous report is irrelevant for safety reporting purposes. Causality is implied, and must be assumed. Therefore the last sentence of this section is unnecessary and should be omitted as it is potentially misleading.

Section 2.3 Unexpected Adverse Drug Reactions

The phrase "official product information" is used in this section instead of the more commonly used and precise terminology of "approved product labeling/prescribing information" used later in Section 3.1.2.1. We recommend that this latter terminology is used consistently throughout the Guideline. "Official product information" is vague and open to interpretation.

Also in this section, the Guideline stipulates that "An ADR with a fatal outcome should be considered unexpected, unless the official product information specifies a fatal outcome for the ADR." We believe this interpretation of expectedness will have a significant impact on product labeling by encouraging the addition of terminology such as "associated with death" to ADRs on the label. We assume this is not intended. Death is already defined as a possible outcome associated with serious adverse events. Adding this outcome as a "subcategory" to potentially numeous ADRs (e.g. myocardial infarction, renal failure, cardiogenic shock, etc.), which are commonly associated with fatal outcome as part of their natural history, does not add value to the safety information communicated, and will decrease the usefulness of the label as a primary source of safety information for health care professionals.

Section 2.5.1.2 Literature

The Guideline states that Marketing Authorisation Holders (MAHs) "should search the literature according to local regulation or at least once a month." Since the EU requires literature searches to be conducted weekly, we recommend that the phrase "once a month" be replaced with "weekly" in order to ensure that MAHs are able to comply with all regional and/or local requirements. Weekly searches are the current minimum standard that must be met by MAHs operating in the EU (ICH region).

Section 4. GOOD CASE MANAGEMENT PRACTICE

We recommend that a similar section be added to ICH E2A, so that the two Guidelines are consistent and equally comprehensive in their scope and content.

Section 4.1 Assessing Patient and Reporter Identifiability

We note that this section provides guidance on the "identifiability" of patients, but not on the identifiability of reporters. Similar guidance should be provided to assist MAHs in developing procedures to ensure the integrity of reports received and protect against fraud in safety reporting. In particular, guidance for determining the identifiability of reporters who use electronic means of reporting such as the Internet would be particularly welcome.

Section 4.2 The Role of the Narrative

The Guideline stipulates that the availability of supplementary records should be mentioned in the narrative, and that autopsy or other post-mortem findings should be provided when available. The listing of available supplementary records and reports, and routine inclusion of autopsy and similar records, adds an administrative burden to safety reporting, but does not add any value to

the "medical story." All relevant information from these supplementary sources should already be included in the narrative.

Millennium strongly supports the International Conference on Harmonization in its mission to develop and promote the adoption of global standards in the evaluation of the safety and efficacy of human medicines, and we are grateful for the opportunity to comment on this draft Guideline.

Sincerely,

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