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MILLENNIUM

October 14, 2003

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

RE: Docket No. 00N-1484. Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products (68 FR 12406)

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.

We are grateful to the Agency for this opportunity to provide input on the Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products, and commend the Agency on the intent to harmonize U.S. requirements with those recommended by the International Conference on Harmonisation (ICH) and by the Council for International Organizations of Medical Sciences (CIOMS). In particular, we agree with the new focus on Suspected Adverse Drug Reaction (SADR), which is consistent with information contained within ICH E2A (Clinical Safety Data Management – Definitions and Standards for Expedited Reporting).

The new focus on SADR is consistent with how safety information for a product evolves,and will enhance management of product labeling within the pharmaceutical industry. Initially, adverse events are temporally associated with the administration of a drug, and thus at the time of observation, it is not necessarily known with certainty whether the event is causally related to the drug. The relationship of the event to the drug is considered "suspected" until definite drug causality can be established. If the cause of the adverse event is ultimately determined to be due to the drug (populational analyses), at that time the reaction is no longer "suspected," but becomes a known Adverse Drug Reaction, and should be added to the Company Core Safety Information. Finally, the use of the term "suspected" is consistent with how adverse events are reported in product

labeling. For example, the European Commission's Guideline on Summary of Product Characteristics states that Section 4.8, Undesirable Effects, should contain comprehensive information on "all adverse reactions attributed to the medicinal product *with at least reasonable suspicion*" and "adverse events, without at least a *suspected* causal relationship, should not be listed in the SPC." (*Emphasis added*). The focus of "suspected ADRs" is also consistent with the FDA Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (May 2000), which states: "In general, the ADVERSE REACTIONS section should include only information that would be useful to clinicians when making treatment decisions and in monitoring and advising patients. Long and exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy, should be avoided."

Millennium also agrees with the Agency's decision to require a new category of expedited reporting for medication errors. In the 1999 report of the FDA Task Force on Risk Management, medication errors are identified as a major source of preventable adverse drug reactions. As we note in comments below, however, we find the proposed definitions for actual and potential medication errors to be confusing.

We also agree that SADRs reported as part of class action lawsuits should not be subject to expedited reporting. In general, these reports have not contributed to the identification of safety signals or the communication of important new safety information.

We have organized our comments by the subsections outlined for Section III, Description of the Proposed Rule, in the Table of Contents to the Supplementary Information.

Section III. A. 1: Suspected Adverse Drug Reaction

The Agency defines "reasonable possibility" as synonymous with "the relationship cannot be ruled out." Although this definition is technically consistent with the definition provided in ICH E2A (Clinical Safety Data Management – Definitions and Standards for Expedited Reporting), adoption of this definition will result in a significant increase in adverse event (AE) reports being assessed as SADRs. This will increase the volume of expedited safety reports with potential impact on the ability to differentiate signal from noise within the compliance system. Investigator sites would also be overwhelmed with IND safety letters which would be of questionable value with regard to informing investigators of new important safety information. The focus of the definition for SADR should be on suspicion of an ADR (reasonable possibility) and not on whether or not a causal relationship can be ruled out. Ruling out a causal relationship is a situation which is impossible in almost all circumstances involving temporal drug-AE association unless there is a definite alternative diagnosis for the AE. Identification of an SADR should therefore involve active evaluation of all aspects surrounding the occurrence of an AE in a patient rather than a passive process of exclusion.

Section III.A.5: Minimum Data Set and Full Data Set for an Individual Case Safety Report

We note that while the definition of "minimum data set" is consistent with ICH E2A, the proposed definition for "full data set" is not. The full data set as defined would require the completion of all elements of FDA Form 3500A (or the equivalent VAERS form for vaccines), or of the CIOMS I form if a foreign SADR. The full data set would be required for certain categories of Individual Case Safety Reports submitted postmarketing. This new definition sets an unrealistically high standard, given the very nature of "spontaneous" reporting in the postmarketing phase. It will be difficult, even with active query, to obtain sufficient information to complete all elements of these forms. We believe that the focus of case documentation should be directed towards the narrative content with clear documentation that the event (AE terms) as reported actually happened (satisfy case definitions) and that all potential causal/contributory risk factors for the event are captured. The CIOMS V narrative format with eight (8) paragraphs enables quality of case narratives to be objectively measured, e.g. completeness of documentation of paragraph 2 (risk factors).

Section III.A.6: Active Query

The proposed regulations state that active query should be conducted by a health care professional at the time of initial contact with an initial reporter. Millennium would be able to meet this standard as our Medical Information bureau -- which receives all spontaneous reports of adverse events involving Millennium products -- is staffed by healthcare professionals. We question, however, whether all companies could practically meet this standard. We would propose instead that all follow-up contact with reporters should be conducted by health care professionals using active query. This places the emphasis for professional involvement more appropriately on those reports that require greater attention.

Section III.A.8: Medication Error

The proposed definitions for "actual medication error" and "potential medication error" are confusing because their distinction is not based on whether an error occurred -- as one would expect from the terms used -- but on whether an "identifiable patient" is involved. We would propose that the distinction should be based on the presence of an actual error. (Note that under this proposal actual medication errors would necessarily always involve an identifiable patient, since an error would have occurred). The error would not necessarily have to lead to an adverse event to be reportable. Potential medication errors would consist both of those errors averted in patients before drug administration and general complaints regarding packaging, similarity of drug names, etc.

Section III.B.2.b: Written IND Safety Reports: Serious and Unexpected SADRs

In the proposed rule, sponsors are required to submit a written IND safety report for a serious, unexpected SADR within 15 days of receipt of the minimum data set. Sponsors are expected to use due diligence in determining the outcome (whether serious or nonserious) and expectedness of an SADR. Sponsors are being asked to include in any

written IND safety report subsequently filed "a chronological history of their efforts" to acquire this information, if there is a delay in obtaining it.

Millennium questions the purpose of having to report the chronological history of efforts used to obtain complete information. If it is to ascertain whether sponsors are practicing due diligence, we suggest that an evaluation of sponsors' efforts to obtain complete safety information is more appropriately undertaken during agency inspections. The administrative burden imposed by additional documentation of processes takes time and effort away from fulfilling the primary purpose of safety reporting, which is "to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions" (ICH E2A, Section II.C.).

Section III.D.3: Postmarketing Expedited Reports: Unexpected SADRs with Unknown Outcome

Millennium differs with the Agency's presumption that manufacturers and applicants will not be able to determine the outcome for SADRs in only a few cases. Again, due to the very nature of spontaneous reporting in the postmarketing phase, it can be difficult to obtain sufficient information, even with active query, to determine the seriousness of an event.

Millennium also disagrees with the introduction of a new timeframe (45 days) for expedited reports of unexpected SADRs with unknown outcome. This new timeframe differs from ICH recommended timelines for expedited reports of 7 and 15 days, depending on the severity of a serious, unexpected reaction. To introduce an additional reporting timeframe, particularly one that differs from international guidelines followed in other jurisdictions, introduces more complexity into safety reporting systems. We recommend instead a 15-day deadline for reporting an unexpected SADR with unknown outcome. The new category of "always expedited events" involves medically significant events and missing information on outcome will have no impact since these events will automatically be subjected to expedited reporting. Other events should be expedited within 15 days on a case by case basis as determined by the manufacturer. If additional information were obtained after this initial report, it would be submitted in a follow-up report.

Finally, as we note in our remarks above regarding written IND safety reports, we question the value in requiring sponsors to include a chronological history of attempts to obtain complete information. Again, we believe the evaluation of whether sponsors are practicing due diligence and active query is more appropriately and efficiently conducted during agency inspections, and not by review of individual case safety reports. We believe that imposing additional administrative requirements will detract from the Agency's intent to ensure that important product safety information is identified and reported.

Section III.D.3: Postmarketing Expedited Reports: Always Expedited Reports

We agree with the Agency that the medically significant SADRs listed for "always expedited reports" require a heightened level of due diligence in reporting. We would suggest, however, that "always expedited" reports should no longer be necessary after a product has been on the market for a certain period. After this specified period, the incidence and severity of these events will be known with some level of confidence, and should be incorporated into the Core Safety Information for the product as appropriate. We would propose that the always expedited reports listed in this section should be subject, in most cases, to expedited reporting only during the first 2 years post-approval, after which time they should be reported in periodic safety reports. It is possible that in some situations, the severity and/or frequency of one or more of these events may necessitate continued expedited reporting – this should be determined on a product-by-product basis.

Section III.D.6: Postmarketing Expedited Reports: Followup Reports

In this section, the Agency is proposing to introduce a "30-day follow-up" report, which would be submitted for certain expedited report categories, ***even if no new information is available*** *(emphasis added).* As we note in our comments above regarding reporting for unexpected SADRs with unknown outcome, this new reporting requirement and timeframe is not consistent with ICH guidelines, and will introduce additional complexity into safety reporting systems. We also question the value of submitting a report even when no new information is available, and the requirement to include an explanation of why no new information is available and the attempts made to obtain more information. Imposing additional administrative tasks like these will interfere with the primary responsibility of pharmacovigilance departments to identify, characterize, and report new and important safety information associated with use of a company's product(s). We believe the current requirements to submit follow-up reports within 15 days of receipt of new information, or as requested by FDA, are sufficient.

Section III.D.7: Supporting Documentation

Millennium questions the benefit of the proposed requirements for regular submission of supporting documentation such as autopsy reports, death certificates and hospital discharge summaries. Relevant information from these sources, if received by the sponsor, would already be summarized in the narrative of the individual case safety report (ICSR). We also question how this new requirement aligns with the move towards electronic submission of ICSRs. These types of documents are not necessarily available in electronic format. Conversion of documents to PDF format and completing the Document Information fields -- as proposed in the "Draft Guidance to Industry on Providing Regulatory Submissions in Electronic Format - Postmarketing Expedited Safety Reports" -- is not a trivial task, and imposes another administrative burden on product safety departments. Instead, we propose that these documents, when received, should be kept on file by sponsors, and available on a case by case basis to the FDA upon request. The availability of such documents would be listed in the report narrative, as proposed by the FDA.

The proposed rule currently proposes a turnaround time of five calendar days for sponsors to submit supporting documentation to the FDA upon its request. Five calendar days, however, means that in some cases a sponsor may only have three business days or less to respond, depending on when the FDA request was made. For older reports that may be archived off-site from the sponsor's location, for example, this timeframe is not realistic. We would suggest instead that the timeframe for turnaround of these types of documents should be 15 days, to align with the 15-day turnaround required for expedited reporting.

Conclusion

Millennium applauds the Agency on the changes proposed in this rule that will align U.S. safety reporting requirements with international requirements, improve data quality of AE reports and lead to greater protection of public health. We particularly note the new focus on Suspected Adverse Drug Reactions, which is consistent with ICH E2A and with the way in which safety information for a product evolves. We also believe the new requirement for reporting of medication errors should aid in efficient identification and reduction of a major source of preventable adverse events.

Our primary concerns with the Proposed Rule lie not with its intent, but with new requirements that are not consistent with international guidelines, would increase the administrative burden of reporting, and would add complexity to safety reporting systems. These requirements would detract pharmacovigilance professionals from their primary responsibilities to identify and characterize safety signals, and report new and important safety information.

Thank you for the opportunity to comment. We look forward to working closely with the Agency on our common goal to provide safe and efficacious treatments to patients.

Sincerely,

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