

29 January 2004

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MILLENNIUM

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

Re: Draft Guidance for Industry: Pharmacogenomic Data Submissions [Docket No. 2003D-0497, 68 *Federal Register*, 62461-62463, November 4, 2003]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Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance.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.

Separate Considerations for Nonclinical and Clinical Data

We recommend the guidance contain separate sections on pharmacogenomic submissions related to nonclinical and clinical studies in order to reflect the differences in utility and interpretation of data. Identifying the similarities and differences in the regulatory evaluation of nonclinical and clinical pharmacogenomic data will aid sponsors in preparing appropriate and relevant pharmacogenomic submissions.

Biomarkers

The draft guidance defines a “biomarker”, a “valid biomarker” and two subspecies, a “known valid biomarker” and a “probable valid biomarker”. We feel this is confusing, and that the same distinctions could be accomplished more simply. **We propose** the following definitions:

- ❖ *Biological marker* (biomarker) – a characteristic that is measured objectively and evaluated as an indicator of normal physiological processes, pathological processes or pharmacological responses to a therapeutic intervention.

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- ❖ *Established biomarker* – a biomarker that is measured in an analytical test system with externally validated performance characteristics and for which there is a compelling scientific framework or body of evidence that elucidates the biological significance of the test results, and that has been publicly established through the work of multiple investigators. [For purposes of regulatory decision-making, an established biomarker is one that the regulatory authority either has accepted as authentic in the past, or commits to accepting as authentic for the future (see text below).]
- ❖ *Emergent biomarker* - a biomarker that is measured in an analytical test system with externally validated performance characteristics and for which there appears to be a coherent scientific framework or body of evidence that elucidates the biological significance of the test results.

In this scheme, there is no “valid biomarker”, because an “invalid biomarker” would be meaningless, and the “known valid biomarker” and the “probable valid biomarker” of the draft guidance are replaced by the “established biomarker” and the “emergent biomarker”, respectively.

Process for Biomarker Validation

The draft guidance proposes the distinctions between “emergent” and “established” biomarkers, but does not define a process for the former to be recognized as the latter for the purposes of regulatory decision-making. This recognition is, clearly, of critical concern to drug sponsors. The issue is not whether a biomarker has been well supported with evidence and, perhaps, adopted or endorsed by one or more expert groups but, specifically, whether FDA either has used, or will commit to recognize, the biomarker for regulatory decision-making. It is entirely conceivable that a biomarker could be apparently well supported by evidence and endorsed by other groups or institutions, but not be accepted by FDA for regulatory purposes. It is also the case that different biomarkers are used for different decision-making purposes, related to their being validated to different degrees of confidence.

Therefore, **we recommend** that FDA should define a process by which sponsors could prospectively gain a commitment that a particular biomarker would be accepted for regulatory decision-making. The process description should include a list of the data elements that sponsors could use in assembling their submission relating to an emergent biomarker, or an algorithm by which the sponsor could assemble data into a construct that FDA would find persuasive. In addition, **we recommend** that the Agency provide further guidance to help sponsors differentiate validation requirements based on biomarker uses. For example, validation requirements for use of a biomarker for clinical decision making may be different from requirements for the development on an *in vitro* diagnostic.

Ideally, the definition of the biomarker validation process should be included in the next draft of the guidance on Pharmacogenomic Data Submissions, but we



recognize that defining this process might take longer than the Agency would wish to spend before finalizing the current draft. In this case, the definition of a process for establishing biomarkers should be the subject of another guidance at the earliest possible time. In addition, FDA should append to the current guidance a list of all the pharmacogenomic biomarkers that it has already accepted for regulatory decision-making, with the contextual background for each, so that sponsors can regard these biomarkers as “established” or precedented. The list should be updated as additional biomarkers are accepted for regulatory decision-making.

Context and Materiality in Submitting Genomic Data

We suggest that the context and the materiality of genomic information, particularly as regards nonclinical data, be taken into consideration when specifying the submission process for genomic data. Considering the impact of the genomic data can help to avoid confusion in choosing the appropriate submission pathway. For example, if an animal expressing a human gene shows greater response to a drug than wild type animals, this information would be used to support proceeding with human trials, and it would be submitted to the IND under §312.23 (see point 2 on p. 7, lines 287-288). However, one could make an argument that these data could be submitted under VGDS if there are already other compelling arguments to support the biological plausibility of the therapeutic hypothesis being tested in clinical trials (e.g., information resulting from classical toxicology studies). On the other hand, if the gene’s presence were to be used as a stratification variable in a clinical trial, the animal data would be submitted for regulatory review to the IND under point 1 of §312.23, and VGDS would be unacceptable.

The Interdisciplinary Pharmacogenomic Review Group

We recommend that the Agency provide more detail on the composition, processes, role, and objectives of the Interdisciplinary Pharmacogenomic Review Group (IPRG).

Composition

What will be the composition (expertises represented, range of affiliations, etc) and terms of reference of the IPRG?

Role/Objectives

- i. In regards to the role of IPRG, FDA should state that the Agency will remain the statutory regulatory authority and the IPRG will function strictly in an advisory capacity. Further, for some of the functions ascribed to the IPRG in the draft guidance (lines 240-242), we believe that there would be advantages to constituting an advisory committee under the Federal Advisory Committee Act of 1972 and 21 CFR Part 14, in that it could include government, academic and, possibly, industrial representation. We believe that this would ensure the highest levels of expertise and transparency, and that this type of body



would be ideal for the horizontal review of accumulated data across many drugs, advising FDA as to the authenticity of pharmacogenomic biomarkers for regulatory decision-making and proposing new guidance and policy in this area. Moreover, it is not clear to us that, due to the highly technical nature of much of pharmacogenomics, these functions could be assumed readily by any of FDA's existing advisory committees. We could envisage such an advisory committee working in tandem with an IPRG constituted from within FDA.

- ii. **We recommend** a more concrete outline be provided of the “deliverables” of the IPRG and the timetable by which they expect to complete their analysis in conjunction with the FDA review divisions. Clarification is also needed on whether the IPRG will communicate to both the FDA review divisions and the sponsor on their assessments of genomic data submissions. If so, what opportunities and process will be put in place for the sponsor to discuss these with the IPRG? We regard it as critical that sponsors should have opportunities to receive and discuss information about new signals or signatures (“emergent biomarkers”) identified by the IPRG. These could be identified in an individual sponsor's data, in which case the discussion with IPRG should probably (but not necessarily in every case) be restricted to that sponsor for reasons of confidentiality but, perhaps more typically, patterns of associations might be identified across submissions from multiple sponsors, in which case the discussion should be open to all sponsors. We feel that this information sharing is an important incentive for industry to participate in the VGDS initiative and that the guidance should contain descriptive language.
- iii. Will there be circumstances in which the IPRG will be able to recommend that data that were submitted voluntarily (or later versions of the same data) be also submitted as part of a regulated submission? The draft guidance is not clear on this point: it states, “*The FDA will not use information submitted through the voluntary process for regulatory decision making on INDs or NDAs.*” (lines 498-499), but then, “*However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted ..., the sponsor must submit the data to the IND, NDA or BLA ...*” (lines 503-505). It is not clear whether the “*additional information*” is intended to mean information relating to the sponsor's own drug (in which case it would be expected that he would know about and understand the significance of the later data) or information derived from (say,) horizontal analyses of data from several sponsors' drugs (in which case any single sponsor could not be expected to know about the other sponsors' data, or their significance for the submission for regulatory decision-making of his own data, previously submitted



voluntarily.) Particularly if the information, whose discovery could result in a sponsor having to submit to a regulated submission data that had been previously submitted voluntarily, could come from horizontal analyses of data from several sponsors, sponsors could be faced with significant regulatory risk or project cost (in, say, a requirement for additional studies) as a result of the voluntary submission of data in good faith. This conclusion is inconsistent with the spirit of the VGDS process, as stated, that FDA will not use voluntarily submitted data for decision-making. It is very important for sponsors that they are able to understand and control any regulatory risk involved in the making a VGDS submission since this is a voluntary process. Therefore, **we recommend** that FDA clarifies in detail the circumstances under which a mandatory submission for regulatory decision-making of voluntarily submitted data would be justified and also describe what dispute resolution procedures would be open to affected sponsors in the event that they might disagree with FDA's judgment in these matters.

- iv. We recommend that the Agency provide more information on how confidentiality of VGDS submissions will be maintained by the IPRG, particularly as the IPRG will review data sets from numerous sponsors. Measures for managing potential conflicts of interest with members of the IPRG (who may not be FDA employees) should also be included in the guidance.

Format, Content and Timing of Submissions

In any final guidance, the Agency should be clear and specific regarding the nature and content of each type of pharmacogenomic report to be submitted: complete report, abbreviated report, and synopsis. The structure of these reports should be clearly defined and agreed upon with industry to promote global harmonization of pharmacogenomic approaches. In addition, the guidance should be clear about the content, format and amount of raw data necessary for a required versus a voluntary (VGDS) submission. As the draft guidance points out, and we agree, a consensus does not exist for presenting and exchanging genomic data. However, the suggested content and format ranges widely from no raw data (as would be the case, for example, for an article submitted to a peer-reviewed scientific journal) to submission of electronic files containing all raw data, images, scatter plots, etc. for all experiments, plus validation data. If reporting clinical genomic data thorough a journal article format is feasible, this would an acceptable way for reporting aggregate results within the limits of many informed consent protocols.

Further, it is essential for sponsors to know, at least in general, how much data the Agency will be expecting in the submission. There are several ways to address this. Initially, any guidance document should be clear about the agency's expectations. Then, as standards evolve and FDA gains more experience with VGDS, new and additional



requirements or expectations may be conveyed to industry through public meetings or dialogue sessions.

Alternatively or additionally, the Agency could provide a mechanism by which sponsors anticipating making a VGDS may meet with appropriate agency representatives to discuss the planned VGDS. (One option would be to have this take place as part of a Type 'C' meeting.) This would allow sponsors to anticipate when VGDS submissions likely would be made in order to prepare for such a submission. Interaction between the Agency and the sponsor before, during, and after review of the submission by the IPRG is critical, so there will be feedback to the sponsor regarding the agency's understanding of the data. A formal meeting should be held at the request of the Sponsor, at which the sponsor could present the data and its interpretation and the agency can discuss its data needs, including whether it is likely that the IPRG may request additional data. The amount and nature of the information exchange at any such meeting will, of course, depend on the timing of the meeting.

For VGDS in the pre-IND stage, **we suggest** that guidance be provided on whether an IND number should be requested. There is a potential for data much more voluminous than typically occurs with the request for pre-IND meetings.

The desired timing for any VGDS should be outlined to enable the IPRG to evaluate the data most effectively with the appropriate data set. In addition, some guidance as to the preferred format of the reports along with the potential of integration into primary clinical study or non-clinical study reports would be helpful.

Compliance with 21 CFR Part 58

Section IV. D of the guidance (lines 391 – 405) concludes that *“the requirements of part 58 apply to nonclinical studies submitted to support safety findings, including nonclinical pharmacogenomic studies intended to support regulatory decisionmaking”*. However, there are several obstacles to making pharmacogenomic analyses GLP-compliant. Firstly, the technologies that are used to generate pharmacogenomic data are varied and complex and will be inherently difficult to validate. Secondly, pharmacogenomic analyses are not routinely included in toxicology studies and, therefore, it may be difficult and costly for the sponsor to create the facilities and infrastructure required to generate GLP-compliant pharmacogenomic data. Thirdly, at the present time there is no consensus between the industry and FDA as to what constitutes a GLP regime for some pharmacogenomic technologies. Therefore, in order to give sponsors the greatest flexibility in generating pharmacogenomic data from toxicology studies and to maximize the amount of pharmacogenomic data that are available to the FDA, we propose that pharmacogenomic data, in the large part, be treated similarly to other bioanalytical or pharmacodynamic data that are exploratory in nature, or for which significant impediments exist to making such data compliant with Part 58.

Therefore, **we suggest** that the following additional text be inserted in the guidance: *“ Pharmacogenomic analytical techniques may not readily lend themselves to*



full compliance with Part 58 due to their complex nature and difficulties in creating Part 58 compliant laboratories. Therefore, it may not be feasible for the Sponsor to comply completely with Part 58 for pharmacogenomic nonclinical studies. In these instances, the Sponsor will clearly indicate in the study report the areas in which such data do not comply with Part 58 and the rationale for the non-compliance. Such data can still be used in the interpretation of safety findings in nonclinical studies as long as the data can be supported by a strong scientific rationale and evidence of the sponsor's due diligence. For pivotal nonclinical studies, the Sponsor should make all reasonable efforts to comply with Part 58.

The guidance also states that (lines 404-405) “Any studies eligible to be submitted in an abbreviated report, synopsis or VGDS under the algorithms discussed above do not fall under part 58.” The language used here could be made more explicit. **We recommend** the following new text “*Exploratory studies that are not critical to regulatory decision making and that can be submitted in an abbreviated report, synopsis, or VGDS, do not fall under part 58.*”

Extension of Guidance to Proteomic and Metabolomic Data

The draft guidance states (lines 31-33): “*Pharmacogenomics also does not refer to data resulting from proteomic or metabolomic techniques. This document is not meant to provide guidance on pharmacoproteomics or multiplexed protein analyte based technologies.*” The implications of this are that, at least for the time being, sponsors could not submit data from proteomic or metabolomic analyses and have them treated in the same way as data from genomic (DNA genotyping and RNA expression profiling) analyses, particularly with regard to the voluntary submission process. While we recognize that most results from the use of these technologies are still exploratory and that, therefore, there should generally be no requirement to submit proteomic and metabolomic data to INDs, NDAs and BLAs, we believe that there will be situations when it will be no less important or useful to a sponsor to be able to submit proteomic or metabolomic data under the voluntary process than it is to submit genomic data. **We recommend** that FDA reconsiders the scope of the guidance to include the voluntary submission of data from any of the genomic, proteomic or metabolomic technologies.

Submission of Pharmacogenomic Data in a Full Report to an Approved NDA or BLA

The draft guidance states (lines 382-385) that “*the requirements for submitting new scientific information to an approved NDA or BLA are outlined in §§ 314.81(b)(2) and 601.12. Results of nonclinical or clinical pharmacogenomic investigations on known or probably valid biomarkers must be submitted in the annual report as synopses or abbreviated reports (21 CFR 314.81(b)(2)).*” For clarification, we **suggest** the following additional text be added to the guidance when data are submitted as a supplement to an approved NDA or BLA: “*However, if the data will be the basis for new efficacy or labeling claims (as a supplement to and NDA/BLA), the data should be submitted in a full report (per Appendix B)*”.



Sincerely,

A handwritten signature in black ink, appearing to read 'R.G. Pietrusko, Pharm.D.', with a fluid, cursive style.

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