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

**Subject: Docket No. 2003D-0497
Draft Guidance for Industry on Pharmacogenomic Data Submissions**

16 January, 2004

Dear Sir/Madam:

Thank you for the opportunity to comment on the "Draft Guidance for Industry on Pharmacogenomic Data Submissions" published in the Federal Register on November 4, 2003. Genzyme welcomes the draft guidance document and believes that it is a positive first step toward a collaborative context to advance the positive impact that pharmacogenomics may have on the drug discovery and development process as well as public health. However, we have some concerns about this proposed guidance document. Below are Genzyme's comments for your consideration.

1. We agree that it is important for the FDA to have a role in the evaluation of pharmacogenomic (PG) tests to ensure that policies evolve based on the best science, and to foster public confidence in the field. We also agree on the importance to have FDA policy facilitate the use of pharmacogenomic testing during drug development and encouraging open and public sharing of data and information on pharmacogenomic test results while protecting proprietary information. We are concerned about the volume of data that might be generated from Voluntary Genomic Data Submissions (VGDS). We recognize that the Agency's scientific and review staff possess limited time and resources, and wonder what impact this program may have on already strained resources.
2. We note that there are substantive differences in use, standards, processes, interpretation, and impact associated with the generation of pharmacogenomic data during the various phases of drug discovery and development, and recommend that FDA develop three separate guidances for non-clinical pharmacogenomic, clinical genomic and clinical pharmacology genomic data. The guidances should clearly differentiate between data used in the design of a development program that could be submitted voluntarily, and from data used in specific clinical trial design or as a criterion for patient enrollment that would be required to be submitted under an IND. In addition it would be useful for FDA to describe any process between the Agency and sponsors under which the data submitted voluntarily might be reclassified as a required by the Interdisciplinary Pharmacogenomic Review Group (IPRG). The sponsor's responsibilities and recourses should be clearly delineated for such a situation.

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3. Definitions of "known valid biomarker" and "probable valid biomarker" need further development. The guidance defines a "known valid biomarker" as "*(a) biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.*" (lines 596-599) We note that there can be honest disagreement about the validity of a biomarker where a biomarker might be well accepted by many scientists and some physicians while the medical community in other therapeutic areas may question its validity. In lines 128-131 the guidance states "*(f) or purposes of this guidance, a pharmacogenomic test result may be considered a valid biomarker if (1) it is measured in an analytical test system with well established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.*"

Likewise, *probable biomarker* is defined in lines 600-612 as: "*(a) biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacology, or clinical significance of the test results. A probable valid biomarker may not have reached the status of known valid biomarker because, for example, [1] the data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny. [2] The data elucidating its significance, although highly suggestive, may not be conclusive. [3] Independent replication of the results may not have occurred.*" (numbers added) Further in lines 139-141 the guidance states "*When a sponsor generates, or possess, data sufficient to establish a significant association between a pharmacogenomic test result and clinical outcomes, the test result represents a probable valid biomarker.*"

A recent example of a non-pharmacogenomic biomarker is "Troponin t." Troponin t is measured by a well established analytical system and is used by many physicians to alter their practice of medicine, yet there is not widespread agreement in the medical community. It seems the area between a "body of evidence" or "significant association between a pharmacogenomic test result and clinical outcome" and "widespread agreement" is both subjective and ominously large. Would Troponin t be considered a known or probable biomarker? We ask FDA to carefully consider the definition of "valid biomarkers," as the term is crucial to compliance with the reporting algorithm presented in the guidance.

Closely related to these concepts are the work both CDRH and NCCLS are doing on defining criteria for clinical validity and clinical utility. (see NCCLS MM15-P "Determining the Clinical Utility of Genetic Tests-Proposed Guideline" [ISBN1-56238-000-0]) We suggest the terminology, definitions and concepts should be coordinated or standardized among these efforts. Clearer definitions are needed for concepts which may be viewed differently by the various centers (e.g. CDRH/OIVD and CDER).

4. Please specify the desired timing for submission of Voluntary Genomic Data Submission (VGDS) to best enable the Interdisciplinary Pharmacogenomic Review Group (IPRG) to evaluate the data 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. We note that the current guidelines for the format of abbreviated reports or synopsis is not optimal for the submission of pharmacogenomic data, especially in support of non-clinical studies. Providing greater detail as to the Agency's expectation format would be extremely useful, and should preferably result from collaboration between regulators and sponsors.

5. Reporting clinical genomic data thorough a journal article format is feasible and appropriate for reporting aggregate results within the limits of many informed consents. We believe that VGDS should be limited to group rather than individual records of clinical genomic data. The sponsor should be able to refute or abate conclusions drawn by independent or third parties who may not have the breadth of knowledge possessed by the sponsor.
6. The draft guidance discusses the educational benefits to be gained by the IPRG. Genzyme believes that this cutting-edge scientific information would also benefit the entire pharmaceutical industry as well as regulators, and public health. We would welcome a mechanism to share this information among FDA and sponsors but proprietary information must be honored where claimed. We also recommend creation and implementation of standardized reviewer training across the Centers so that implementation of the final guidance is applied consistently.
7. The phrase "decision making" is concerning. We request that FDA differentiate reporting requirements between pharmacogenomic results that drive decisions in a clinical trial or in animal trial to support safety or efficacy versus decision making in a clinical development program such as selection of promising compounds during candidate screen. We believe that genotype results used to screen or select subjects in a clinical trial, or to stratify the primary analysis, should be reported. We respectfully suggest that FDA limit reporting of full data sets to circumstances when test results influence clinical study conduct or are integrated into the primary analysis of any clinical study, or in an animal trial used to support safety.
8. We do not recommend that submission of full pharmacogenomic data sets generated with the microarray technology when a limited subset of genes is actually used by investigators to make interpretations based on previous validation experiments. In such situations, submission of data related to this subset of genes is more appropriate and informative.

The field of genomics is relatively new and as such, in a state of evolutionary flux. As FDA notes in the background of this guidance, the scientific framework may not be in place to appropriately evaluate scientific or clinical significance of certain experimental results. There are technical issues as well, ranging from inconsistent laboratory techniques to under-tested microarray technology. Genzyme applauds the effort of the agency in enlisting stakeholders in the development of these guidances and especially feels the industry workshops have been a very useful forum. We generally agree with PhRMA's position on this guidance and in particular with their proposed biomarker definition section. We also suggest some of the examples in the recent DIA workshop materials be incorporated into the next drafts. While Genzyme appreciates FDA's efforts, we respectfully suggest that it may be premature to formalize a comprehensive guidance

for a field in its infancy and, as noted in 2 above, suggest three separate guidances each using more extensive definitions and examples. Genzyme appreciates the opportunity to comment on "Draft Guidance for Industry on Pharmacogenomic Data Submissions." Please contact me at (617) 768-6275 or Juliette Shih at (617) 768-6929 should you have any questions regarding this letter.

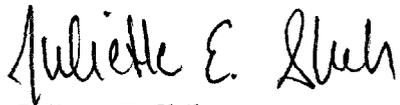
Cordially,



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