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

Subject: Docket No. 2006D-0012
Draft Guidance for Industry and FDA Staff - Pharmacogenetic Tests and Genetic Tests for Heritable Markers

10 May 2006

Dear Sir/Madam:

Thank you for the opportunity to comment on the draft guidance entitled “**Draft Guidance for Industry and FDA Staff - Pharmacogenetic Tests and Genetic Tests for Heritable Markers**” issued February 9, 2006. Genzyme Corporation is in a unique position to comment on this Guidance. Genzyme has always been recognized as a leader in understanding genetic based disorders, and has demonstrated leadership in developing both tests and therapeutics for such disorders. Unique within Genzyme’s corporate infrastructure, are the Diagnostic business unit and the Genzyme Genetics services units, allowing personalized medicine approach to therapies to be more broadly utilized. Genzyme has already differentiated its product offerings based on Genzyme’s understanding of patient disease and the relationship of biomarkers to response. Genzyme also has considerable experience in our expertise in studying rare genetic disorders and small patient populations. We have successfully launched therapies for four rare genetic disorders and provide diagnostics testing to identify those patients.

This guidance is intended to provide recommendations to sponsors and FDA reviewers in preparing and reviewing premarket approval applications and premarket notification submissions for pharmacogenetic and other human genetic tests, and to recommend a basic framework for the types of data and regulatory issues to be addressed in a genetic test submission.

Genzyme commends the Agency on the work that has gone into the development of this guidance and supports the guidance in its intention to shorten development and review timelines. Genzyme also commends FDA for replacing the February 27, 2003 draft guidance “*Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers.*” We note that the draft guidance reflects much of FDA’s recent, successful experience with the regulation of pharmacogenetic and genetic tests and encourage the agency to provide additional guidance to a least burdensome approach to studies for rare disorders and use of published literature to create a bridge between analytical data and clinical validity. Use of published literature has been shown to be an effective tool when there is sufficient pre-existing

scientific knowledge related to the marker. However, the approach proposed in the draft may be overly proscriptive and should allow more flexibility.

Specifically, Page 13, item f – addresses the use of literature to support clinical validity. It states that “when literature is intended to support bridging from analytical to clinical performance, the literature should identify the same technology as the new test and similar patient population.”

We agree that the use of literature to support the clinical performance a biomarker may be limited by differing technologies or patient populations used in the literature compared to the candidate test, but, the use of literature to support clinical validity (utility) is not as dependent on the technology as indicated in these statements. The clinical validity (utility) of a biomarker (analyte) is really dependent on the presence absence or quantity of the analyte and relationship to the disease or condition for which it is intended it is to describe rather than the method for which it was determined. While sensitivity, specificity and predictive value of a positive test, and predictive value of a negative test (all performance descriptors) may be affected by technology and patient populations studied, the link between the biomarker and health condition is not.

Another area of concern is the discussion on enrichment for tests that evaluate for rare events. The draft guidance discourages enrichment for tests that evaluate rare events. Without enrichment or the use of synthetic samples, studies of tests for rare disorders will be overly burdensome requiring an extremely large specimen pool. For example, a study for a test for a rare mutation occurring at a rate of 1 in 5,000 would require 80,000 patient specimens to obtain 10 positive specimens.

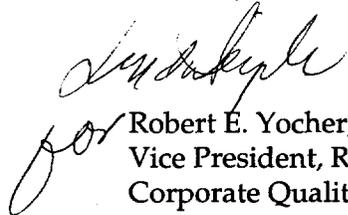
Specifically, Page 4, paragraph 2, bullet 1 – states “Enrichment can be undesirable because sensitivity can be affected by spectrum bias due to irregular retrospective selection of cases and because predictive values are dependent on the prevalence in the intended use population, which cannot be characterized from such a study.”

We agree that an enriched design is not necessarily always appropriate to determine the positive and negative predictive values of an assay. An enriched design may or may not be acceptable within a given study. This may depend upon the purpose of the study in evaluating the analytical or clinical performance characteristics of a pharmacogenetic test. Provided that the enrichment is not biased to select, e.g., one null-allele over another, then the data from an enriched study should be adequate to determine specificity and sensitivity. If the basis for enrichment is included in the submission, then the concern over bias should be addressed.

We also recommend FDA address how enrichment and synthetic specimens may be used to address test for rare mutations, such as those occurring 1 in 5,000 and expand this portion of the guidance accordingly.

Genzyme appreciates the opportunity to comment on this draft guidance. Please contact me at 617-768-6275 or Linda Temple at 617-768-9290 should you have any questions regarding this letter.

Cordially,



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