



January 9, 2003

Docket #: 2003D-0497, CDER 2003163
Division of Dockets Management (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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Dear Drs. Lesko, Puri and Gutman:

Affymetrix respectfully submits the following comments on the Draft Guidance, "*Pharmacogenomic Data Submissions*". We are pleased that the FDA recognizes the need and value for pharmacogenomic data in drug discovery and development. We believe this data has the potential to transform medicine and improve human health. The Agency's willingness to maintain an open dialogue with industry regarding pharmacogenomics issues and opportunities is particularly laudable.

Overall, we find the guidance document to be informative and extremely well written. However, there are several areas on which we wish to comment.

First, the differentiation between valid and probable biomarkers warrants further elaboration and definition. Specifically, what criteria will be used to decide when a biomarker moves from the probable category into the valid category? How will decisions regarding new valid biomarkers be communicated to industry, and importantly, to clinicians? It is also worth noting that the validity of a biomarker may vary depending on the specific intended use and the existing body of literature for that intended use; in other words, the categorization of a biomarker is likely to be context-specific.

Second, we suggest that the Agency contemplate the idea that some of the best biomarkers should be thought of as gene expression or SNP patterns rather than as a collection of individual markers. For example, many peer-reviewed publications (reference Affymetrix MAF-1241 volumes 2-4) indicate that the confidence level of classification using gene expression patterns is enhanced when the patterns comprise more transcripts; in these cases, the presence or absence of any particular transcript should not affect the classification result. Thus, we propose that the appropriate validation for gene expression patterns may be to validate the performance of patterns rather than deconstructing a pattern into individual transcripts. If validation is required for each individual transcript as is currently suggested, the tendency may be to validate smaller, often less informative and potentially less statistically significant patterns. For some applications, expression patterns or "metagenes" may provide better predictive accuracy than individual markers (e.g., Nevins, J.R., et al., *Human Molecular Genetics*, October 2003, 12 Spec No 2: R153-7, Epub 2003 Aug 19; Huang E., et al., *Nature Genetics*, June 2003, 34(2): p. 226-30). Also, we believe this consideration will better align with the Agency's stated goal of ensuring the least burdensome regulatory approach.

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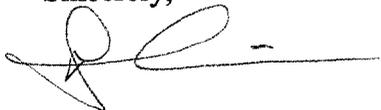
Third, we believe that data submission requirements need to be examined in several contexts. For example, measurement of specific transcripts serving as biomarkers may be quantitative whereas application of gene expression patterns to categorize samples or patients may be qualitative. The data submission requirements should reflect the context of genetic information used in the particular study as well as the nature of the genetic information's intended application. In many cases for gene expression information, we believe that average intensity data for a given feature (.CEL files) will be sufficiently informative and less-burdensome than raw intensity (.DAT files) which are very large (for our new U133 Human Genome Array greater than 140mb) and may be difficult to manage.

Fourth, we feel that bullet point 4 on page 2 "the transmission, data processing and storage of large amounts of highly dimensional data generated from microarray technology has not been well validated nor widely tested," warrants reconsideration (*cf.* Affymetrix MAF-1241). Although this statement may be true for some platforms, there are over 1,500 peer-reviewed publications using our GeneChip® technology and many examples of database construction and sharing across and among organizations. Our fear, of course, is that generalizations lead the Agency to a "least common denominator" approach rather than one cognizant that performance and the capability for standardization differ among technologies.

Finally, in reference to bullet point 1 on page 2 and bullet point 3 on page 11, we would like to call attention to the rapid and recent progress being made in the development of a set of universal RNA spike-in controls for use on commercially available microarray platforms and by RT-PCR. The External RNA Controls Consortium (ERCC) is an open community-wide effort with participation from pharmaceutical, diagnostic, biotechnology, academic, national laboratory and regulatory agency scientists (www.nist.gov). The ERCC is developing and testing a set of standard RNA controls aligned with the recommendations put forth at a NIST sponsored meeting at Stanford University, March 2003 (M. Cronin *et al.* Clinical Chemistry in press). We hope that the agency will continue to encourage and participate in the ERCC and related efforts and when standard controls are established, that the agency will recommend the inclusion of control data in pharmacogenomic data submissions.

We would like to reiterate that we deeply appreciate the Agency's approach to submission of pharmacogenomics data and see the development of the VGDS approach as an excellent concept. We intend to continue working with FDA as well as with our pharmaceutical and diagnostic partners to define least-burdensome paths to bring array technology to clinical trials and clinical settings.

Sincerely,



Thane Kreiner, Ph.D.
Senior Vice President, Corporate Affairs