May 10, 2006

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

Re: Docket No. 2006D-0012

Dear Sir/Madam:

The following comments on the *Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers* (the draft guidance) are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the draft guidance.

We applaud the decision of the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health (the Centers) to develop the draft guidance, which is designed to "facilitate progress in the field of pharmacogenomics and genetics by helping to shorten development and review timelines, facilitate rapid transfer of new technology from the research bench to the clinical diagnostic laboratory, and encourage informed use of pharmacogenomic and genetic diagnostic devices" (draft guidance, p. 1). Although there remain many unanswered questions about the regulatory issues associated with these new technologies, we believe the draft guidance represents a significant step toward accomplishing the Centers' stated goals.

INTRODUCTION

Clarity with respect to the regulatory environment for pharmacogenetics and genetics is important to facilitating product development in these fields. To BIO's knowledge, FDA

has not yet completed a comprehensive regulatory analysis that explains the basis for FDA regulation of pharmacogenetic and genetic tests. The letter issued by CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) to Roche Molecular Diagnostics on October 29, 2003, contains some analysis of the regulatory provisions that OIVD believes would apply to a particular type of microarray, but this document does not represent official FDA policy, 21 C.F.R. § 10.85(k). We are aware of various other informal statements by FDA officials in connection with pharmacogenetics and genetics, but neither these pronouncements nor the draft guidance and its 2003 predecessor give a basis for FDA regulation.

We are keenly aware of the complexities associated with pharmacogenetic and genetic tests, and the corresponding difficulty in developing a coherent and comprehensive regulatory approach to them. We also very much appreciate FDA's efforts at transparency in the development of regulatory policy relating to pharmacogenetics and genetics. For example, the Drug-Diagnostic Co-Development concept paper, the Guidance on Pharmacogenomic Data Submissions, and the Guidance on In Vivo Drug Metabolism/Drug Interaction Studies have all provided BIO members with useful public analysis of important regulatory issues.

BIO's comments do not speak to the question of what regulatory framework would be most appropriate for various types of pharmacogenetic and genetic tests for heritable markers. In our comments below we offer both general and section-specific recommendations for enhancing the usefulness of the draft guidance to BIO member companies submitting applications to FDA to market such tests.

GENERAL COMMENTS

We request clarification of the applicability of the guidance to tests for genetic disorders that are not amenable to sequencing, such as large deletions, large gains, large rearrangements, and polynucleotide expansions. In many instances these tests appear to be within the scope of the draft guidance. However, certain of the recommendations in the draft guidance are not applicable to such tests. For example, the use of bi-directional sequencing (pp. 14-18) as a reference or gold standard would not be appropriate. Similarly, the recommendation to demonstrate that an assay can distinguish between hetero- and homozygotes (p. 9) would not be appropriate for these tests. BIO recommends that these tests either be explicitly included within the scope of the draft guidance along with statements that clarify when specific recommendations do not apply, or that such tests be addressed in a separate guidance.

With regard to rare mutations, we are concerned that the approach to enrichment taken by the draft guidance will mean that some valuable studies are not feasible. The draft guidance discourages enrichment, even in the context of rare mutations (p. 4). Yet without enrichment, studies of tests for rare disorders may be difficult or impossible to conduct. For example, a study for a test for a rare mutation occurring at a rate of 1 in 5,000 would require 50,000 patient specimens to obtain 10 positive specimens. We

encourage FDA to provide additional guidance with regard to more feasible approaches to studies for rare disorders. For example we note the statement on p. 6 that "When fresh samples for rare alleles, genotypes, or mutations are scarce, we will … also consider artificially prepared materials, such as plasmid DNA or amplified gene segments," and we request that FDA provide more specific guidance on when the use of synthetic samples may be appropriate in studies of tests for rare disorders.

BIO would welcome the opportunity to work with FDA to resolve these and other outstanding issues.

SPECIFIC COMMENTS

III. A. Intended Use of a Device

Page 4, paragraph 2 reads (underlining ours): "In this document, "screening" as an intended use is considered to be an indication to test patients regardless of symptomology, background, or clinical need for test information before therapeutic intervention. We recommend that if you are presenting data to support this type of intended use, you carefully consider the issues listed below. The following issues also apply to any test that evaluates rare events, such as mutations or variants, within the indicated population(s)."

Page 4, the first bullet reads (underlining ours): "… 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."

Page 4, the second bullet reads: "When many samples are tested for rare events, false positive results could become problematic in that they may be more common than true positives, due to test error and low prevalence."

Comments

BIO recommends that "screening as an intended use" be defined as an indication to test patients regardless of symptomology.

We also have the following comments and requests for clarification with respect to the recommendations in the draft guidance for screening applications and tests for rare variants.

First, the statement pertaining to enrichment implies that enrichment for *rare* alleles can be undesirable. We agree that an enriched design is not always appropriate to determine the positive and negative predictive values of an assay. However, 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 a scientifically valid basis for enrichment is explained in the submission, then the concern over bias should be addressed.

Second, there are applications in which both common and rare alleles give rise to a common phenotype. CYP2D6 is a good example of this. The *4 allele (which has a frequency of approximately 20% in Caucasians) shares the poor metabolizer phenotype with a number of rare alleles that have been detected in as few as one individual among thousands. Under these circumstances, there should be an opportunity to bridge between phenotypic data and clinical validation by genetic association.

Third, we note that a multiplex test might have the ability to detect many alleles that are not detected in clinical trials. For example a CYP2D6 multiplex test might have the ability to detect 40 poor metabolizer alleles, but during clinical trials it is likely that most of those alleles will not be (or will only rarely be) detected. Thus, it would require large amounts of extra work and resources to evaluate sufficient samples containing rare alleles, and collecting these data will not substantially influence the test sensitivity or specificity. A solution to this is for FDA to allow evaluation based on a molecular phenotype shared by multiple alleles. Alternatively, we suggest that FDA explicitly permit the use of synthetic samples.

Fourth, we note that the concern with false positives associated with rare events (the second bullet point) could be addressed by running a specificity arm.

Fifth, BIO suggests separating, within the guidance document, the recommendations pertaining to screening for common alleles from the recommendations pertaining to tests for rare variants. As we note in our General Comments above, and in accordance with the least burdensome approach endorsed on p. 3 of the draft guidance, we also recommend that the guidance address how enrichment and synthetic specimens may be used to address rare events.

III. B. Device Design

Page 5, the fourth bullet reads: "sequence or identity of oligonucleotides, primers, probes, or other capture elements"

Comments:

Please clarify what it is meant by the term "identity" in this bullet, especially in regard to large probes (e.g., 500 KB)

Page 5, the twelfth bullet reads (underlining ours): "for multiplex tests in which the target molecules will contact a number of different probes, the design and functional testing to address the potential for specific and non-specific probe cross-hybridization."

Comments:

> We note that Quality Control (QC) functional testing of larger genome microarrays is inconsistent with the least burdensome approach the draft guidance endorses on p. 3.

III.C. Analytical Studies

Page 6, subsection 1 "General analytical performance considerations" reads: "…You should demonstrate that your assay can distinguish between hetero- and homozygotes, since this is one of the critical aspects in assessing analytical performance of a genetic assay."

Comments:

> The demonstration recommended in this subsection may be important in some cases, such as single nucleotide polymorphisms (SNPs). However, there are a number of situations in which it is not appropriate, such as for large deletions, large gains, large arrangements, and polynucleotide expansions, for completely dominant sequences. Unless tests for genetic disorders involving these situations are exempted from the scope of the guidance (one of the options we offer in our General Comments above), we request insertion of "If appropriate" at the beginning of the sentence.

Page 6, subsection 2 "Sample characterization and specifications" reads: "If your sample preparation method involves preparation of an RNA intermediate, you should evaluate your procedure to ensure that there is no residual contaminating genomic DNA."

Comments:

> We request insertion of "if applicable" at the end of the sentence. For common platforms extracting DNA and RNA one would not want to introduce enzymes that would degrade either DNA or RNA.

III.E. Comparison Studies Using Clinical Specimens

Page 11, subsection 2 "Comparison to another device" reads (underlining ours): "You may choose to describe comparison studies with another well characterized or predicate device, in addition to comparison with the reference method. …"

Comments:

BIO requests that this sentence should be changed to: "Unless comparison to a particular gold standard method is required, you may choose to describe comparison studies with another well characterized or predicate device, instead of comparison with the reference method." For example, the use of bi-directional sequencing as a reference or gold standard would not be appropriate for large deletions, large gains, large arrangements, and polynucleotide expansions. As we note in our General Comments above, BIO recommends that the guidance clarify that sponsors would not be expected to use bi-directional sequencing as a reference method for such tests, or that such tests be excluded from the scope of the guidance.

III. F. Clinical Evaluation Studies Comparing Device Performance to Accepted Diagnostic Procedure(s)

It would be helpful for the guidance to address the situation in which the clinical endpoint is a continuous rather than categorical parameter. This will often be the case for efficacy pharmacogenetics. For example, the response rate for H. pylori eradication by amoxicillin + a proton pump inhibitor in peptic ulcer differs according to CYP2C19 phenotype. However CYP2C19 extensive metabolizers are not necessarily non-responders, and poor metabolizers aren't necessarily responders. Similarly, the mean change on a depression rating scale for patients dosed with an SSRI might differ according to serotonin transporter genotype. In this situation, the clinical claims for a test might be along the lines of predicting a mean response according to genotype, which a psychiatrist might use to benchmark how an individual patient is doing relative to expectations.

Page 12, subsection b) reads: "We recommend that you validate genotype/phenotype correlations, if necessary, on a statistically determined number of specimens for each intended use. You should include the following information, when defining the population(s) used …"

Comments:

We suggest that the guidance note that in defining the populations used for clinical evaluation, there should be an effort to assure uniformity of genetic background between the normal population and the cases, so that the normals are not drawn from (for example) one ethnic group while the cases are drawn from another.

III.F. Clinical Evaluation Studies Comparing Device Performance to Accepted Diagnostic Procedure(s) and III.G. Clinical Effectiveness of the Device

Pages 12-14, throughout.

Comments:

We request that the guidance more clearly distinguish the requirements for tests that have a clinical outcome (such as PathVysion™) from those that do not (such as the CYP AmpliChip™).

III.G. Clinical Effectiveness of the Device

Page 13, subsection 1 "New Markers" reads: "Clinical performance validation of your new markers, mutations, patterns and other outputs of pharmacogenetic and genetic tests must meet the rules for determining safety and effectiveness for the tests' intended use, as outlined in 21 CFR 860.7."

Comments:

Clinical performance validation is an important aspect of test validation. We suggest that the guidance not only refer the reader to the Code of Federal Regulations (CFR) but also summarize the key points of the cited CFR section.

IV. Labeling

Page 14, subsection "Interpretations and Precautions" reads (underlining ours): "We recommend that you provide the key for interpretations of results and specify the language to be used in reporting results. We recommend that you use standard nomenclature to describe alleles, genotypes, and mutations, and that you state the source of the nomenclature system. If you do not use standard nomenclature, you should provide a translation to standard nomenclature."

Comments:

"Standard nomenclature" is undefined in the draft guidance. We request that the final guidance clarify that the Human Genome Organization nomenclature is the "standard nomenclature." Further, we note that it is not necessarily appropriate for commercial organizations to specify/detail how clinicians are to interpret and report results, and that this activity is often better left to professional organizations. It would generally be more appropriate for sponsors to reference accepted third party standards or guidance, where these are available.

Page 15, subsection "Performance" reads: " … Failed assays (e.g., inability to sequence the sample) should be considered disagreements for the purposes of reporting performance characteristics."

Comments:

We request that the guidance clarify why no result is equivalent to disagreement.

CONCLUSION

BIO appreciates the opportunity to comment on the Centers' *Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers*. We look forward to additional opportunities to discuss the issues outlined above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs