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PhRMA

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

May 10, 2006

Re: Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers. [Docket No. 2006D-0012, 71 *Federal Register,* 6779 – 6781, 9 February, 2006.]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit its comments on the Food and Drug Administration's (FDA's) Draft Guidance, as above. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than $40 billion in 2006 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

Please find PhRMA's comments in the appended document.

Thank you for your consideration.

Best regards,

Marie A. Vodicka, PhD

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Pharmaceutical Research and Manufacturers of America

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PhRMA appreciates and shares FDA's intent to encourage progress in the field of pharmacogenomics and genetics by striking a balance between facilitating product development and ensuring high quality products. Although not a new field, pharmacogenomics is evolving and is still in an early stage of development. FDA and industry will need to work together in establishing complementary processes and evaluations to ensure the scientific progress of this field and the delivery of its full value, both in drug development and in the clinic. PhRMA is pleased to note that many of our comments on the first (2003) version of this guidance seem to have been taken into account in writing the current draft. We find the Draft Guidance to be well written and organized and to provide a seemingly appropriate "least burdensome approach" to developing a pharmacogenomic test or genetic test for heritable markers and preparing a premarket notification (510(k)) submission.

General Comments:

We agree with FDA's decision to narrow the focus of the guideline to DNA-based genetic and pharmacogenetic markers, as expression pattern based tests involve issues distinct from DNA-based genetic tests. However, it may also be appropriate to incorporate the tests for somatic mutations into this guidance, as nearly all of the issues discussed in this draft document should apply to such tests.

The Draft Guidance appropriately states, *"The recommendations within this draft guidance for elements of a genetic test submission apply to pharmacogenetic and other types of genetic tests."* While PhRMA agrees with this view, it should also be recognized that pharmacogenetic tests raise issues distinct from those of genetic tests for heritable diseases, which will require additional regulatory consideration. A pharmacogenetic

test's clinical benefit and its potential risk can greatly vary depending on the drug with which it is combined, and this should have an implication on the labeling of both the pharmacogenetic test and the therapeutic. The current Draft Guidance only describes the labeling considerations for the diagnostics, but does not provide any guidance for the labeling requirement of the pharmaceuticals that will be used together with the pharmacogenetic test. We recommend that the Agency gives comprehensive guidance that addresses the labeling of both the diagnostic and the therapeutic products, and address any relationship that this guidance may have to others issued by the Agency.

Specific Comments:

I. The Least Burdensome Approach

Comment
The Draft Guidance focuses heavily on requirements for demonstrating the clinical performance validity of a test for a genetic marker, and less on analytical performance. As a result, data requirements for a submission are expanded to reflect prevalence of the disease or condition, geographic distribution of markers and predictive value. Requirements for statistically significant data to demonstrate clinical validity become particularly burdensome as they are applied to markers associated with rare diseases.

Specific examples in this Draft Guidance where the least burdensome approach to establishing device effectiveness has not been applied include:

- Requirement for separate submissions for each genetic marker, even if the kit configuration provides test results for multiple markers
- Need for a significant number of test results with specimens containing rare alleles.
- Need to test specimens from patients in defined ethnic groups to ensure that data are representative of geographic distribution of alleles.
- Need for long term, longitudinal studies to demonstrate the predictive value of a genetic marker.
- Emphasis on need to demonstrate clinical validity empirically *versus* use of literature bridges to link genotype and phenotype.

II. Pharmacogenetic Testing versus Genetic Testing.

First line: *"Genetic mutations"* should be changed to "germline genetic mutations" for clarification.

The Draft Guidance states (page 3, para. 2): *"We consider pharmacogenetic tests for clinical use to be mostly those that are intended to provide information that may aid in selection of certain therapeutics".*

Comment

The use of "selection" is quite restrictive. A test could be used to provide information about when not to use a therapeutic (even if there is no alternative). Alternatively, there may be a situation in which a test is available but is not mandatory (as patients are not at risk if they take the drug). The use of "selection" may suggest that the drug should not be used in the case in which a patient receives negative test results.

III. A. Intended Use of A Device

Page 4, para. 2, it is stated: *"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)."* Furthermore, the first bullet –4th sentence 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."*

Comments

We find the recommendations referring to screening applications and tests for rare variants confusing. Further, as applied to tests for rare variants, we find the recommendations inconsistent with the "Least Burdensome Approach." It is unclear that detection of rare events (such as would be the intention of screening in the general population) should be within the scope of this guidance. The statements made in this section bring up a few different concepts, but only in a superficial way, including the fact that observed associations can be confounded by population admixture and the fact that predictive value is dependent upon the prevalence rate of the event within the population. *In lieu* of a more detailed discussion here, it may be better to state that detection of rare events is problematic and would be expected to require additional attention to experimental and statistical design.

First, the statement pertaining to enrichment implies that enrichment for *rare* alleles can be undesirable. We agree that an enriched design is not necessarily appropriate to determine the positive and negative predictive values of an assay. However, this does not appear to be the subject of this guidance document. 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.

Second, there are applications in which both common and rare alleles share a common phenotype that has been demonstrated *in vitro*. CYP2D6 is a good example of this - the *4 allele (frequency ~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, a CYP2D6 multiplex test, for example, might have the ability to detect up to 40 poor metabolizer alleles as demonstrated using positive controls (e.g., plasmids). However, during clinical trials, it is likely that most of those alleles will not be detected or only rarely. Thus, it would be very burdensome to collect sufficient samples containing rare alleles, and collecting these data will not substantially influence the test sensitivity or specificity. A solution to this would be to allow evaluation based on a molecular phenotype shared by multiple alleles.

In addition, while it is correct that CYP2D6 affects the metabolism of many drugs, the clinical utility of a CYP2D6 genotype test can greatly vary depending on the drug. If a drug is only partially metabolized by CYP2D6 and has alternative pathways for metabolism, the clinical utility of the CYP2D6 genotype test may not be clear, as the poor metabolizer genotype does not necessarily indicate that the person is a poor metabolizer of that drug in such a case.

Lastly, we recommend separating, within the guidance document, the recommendations pertaining to screening for common alleles from the recommendations pertaining to tests for rare variants.

Finally, the document should also include a section on definition of terms, including the various definitions of the context of "device."

III. B. Device Design
Comment
The list of requirements in Section IIIB is too prescriptive. We suggest making it more general or at least use the phrase "may include, but is not limited to" the following elements. Alternatively, the list could be eliminated altogether. There should be some accommodation for "homebrew" tests.

Page 5, First bullet.
Comment:
Please clarify what it is meant by "Overall design of the test, including quality control of feature identity and placement, where applicable."

III.E. Comparison studies using clinical specimens

Comparison to a reference method

Comment

It is reasonable to designate bidirectional sequencing as the reference method. However, it should also be recognized that other types of reference methods could be needed for some of the genotyping assays, especially those that detect a deletion or an insertion. Bidirectional sequencing is a highly accurate standard for determining the sequence of a homogeneous DNA sample, but for heterogeneous, and particularly heterozygous, DNA samples, the methodology is less clearly defined. An intrinsic part of the sequence identification is the basecaller algorithm that converts the instrument read data to a four-letter code with quality scores. For homozygous stretches of DNA, many basecallers deliver hundreds of bases of sequence with accuracies above 99.9%, at high quality scores. The standard heterozygous base caller, Polyphred, is undergoing continuous modification to improve its ability to correctly call heterozygous bases. In addition, it only is successful at calling substitutions, and not insertion-deletion polymorphisms. An improved definition or guidance towards measurement of heterozygote base calls, and especially heterozygote insertion-deletion base calls would be beneficial.

Often identification of heterozygous SNPs in target genes involves sequencing multiple clones from amplification reactions. This generates multiple homogeneous samples from which a statistical argument would be made as to the initial heterozygosity. While this is likely a more reliable method for unknown SNP identification, it is not well established, and might require some argument to be accepted as a reference method. The Draft Guidance does not address using a mix of two different homozygous samples to create artificial heterozygote standards to validate heterozygous call efficiencies, nor using genetically identified heterozygotes from CEPH families. In short, the reference method may require more guidance to be easily interpreted, and may place a hurdle of comparing against an ill-defined analysis method.

Comparison to another device

Page 11, ¶2. It is stated, *"You may choose to describe comparison studies with another well characterized or predicate device, in addition to comparison with the reference method."*

Comment:

We recommend that this sentence should be changed to: "Unless specifically required that a comparison be made to a gold standard method, you may choose to describe comparison studies with another well characterized or predicate device, instead of, comparison with the reference method."

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

Comment
It would be helpful to address the situation in which the clinical endpoint is a continuous rather than categorical parameter. Particularly for efficacy pharmacogenetics, this will often be the situation. For example, the response rate for *H. pylori* eradication by amoxicillin + a proton pump inhibitor in peptic ulcer differs according to CYP2C19 phenotype. It is not the case that CYP2C19 extensive metabolizers are necessarily non-responders, or that poor metabolizers are necessarily responders. Similarly, the mean change of a depression rating scale in patients dosed with an SSRI might differ by a few points 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 reacting to treatment relative to expectations.

Page 12 bullet a, Clinical Truth.
FDA states in the Draft Guidance that an applicant should define "clinical truth" because it will be used in evaluating the clinical performance of the device. FDA defines clinical truth as *"the best clinical evidence for a specific diagnosis or allele assignment."*

Comment
Further clarification of the term clinical truth and how the applicant should apply the concept in comparing the pharmacogenomics test or genetics test to accepted diagnostic procedures is necessary. For example, does FDA intend the applicant to compare the performance of the test regarding the function that provides the best clinical evidence with the same function of the predicate diagnostic procedure? Furthermore, because genetic data are probabilistic, it is unclear how such data can represent "clinical truth". Finally, how can one achieve clinical evidence for an allele assignment? Additional elaboration in this section of the guidance, along with any expectations for specific statistical tests or "cut-offs"/confidence intervals would be useful for applicants.

Page 12, Bullet b.
Comment
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, and the cases from another. In addition, FDA should consider including a statement in this section regarding a recommendation to specify an appropriate duration for follow-up.

Page 13, Bullet d.
"You should identify clinical cut-off points in a training set and validate these in a separate test data set".

Comment
Additional information about choosing the training and test data set would be useful. For example, should they be data from two separate studies, or perhaps random samples from pooled data?

Pages 12-13. III.F. Clinical Evaluation and III.G. Clinical Effectiveness of the Device

Comment:
Further distinction between requirements for tests that have a clinical outcome (such as PathVysion®) and those that do not (such as the CYP AmpliChip®) would be helpful.

Page 13, G. 1. New Markers.
The Draft Guidance recommends that *"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 21CFR860.7."*

Comment:
This is an important aspect of test validation, but the section just refers the reader to the CFR. This guidance should at the least summarize the key points of the CFR section so that the reader will have a general idea of what is expected.

IV. Labeling

Comment:
Pharmacogenetic tests are intended to be used with certain therapeutic agents. Thus, it is desirable that FDA considers effects on labeling for such pharmaceuticals and includes language to that effect in the labeling. The current draft guidance only describes the labeling consideration of the *in vitro* diagnostic.

Interpretations and Precautions
It is stated, *"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 <u>standard nomenclature</u> 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 <u>to standard nomenclature</u>."*

Comment:
The "standard nomenclature"mentioned is undefined. The Agency should define in the final guidance what is considered to be "the standard nomenclature". We suggest adopting the Human Genome Organization nomenclature.