Medical Products Group

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

RE: *Pharmacogenetic Tests and Genetic Tests for Heritable Markers; [Docket 2006D-0012]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document *"Pharmacogenetic Tests and Genetic Tests for Heritable Markers; Draft Guidance for Industry and FDA Staff,"* published in the Federal Register on February 9, 2006 at 71 FR 6779. Thank you for the opportunity to provide these comments.

GENERAL COMMENTS

The applicability of this guidance document to comparative genomic hybridization tests, such as large deletions, large gains, large rearrangements, and polynucleotide expansions, or other tests for genetic disorders that are not amenable to sequencing requires clarification. In many instances these tests appear to be within the scope of the guidance document. However, specific recommendations are not applicable to such tests. For example, the use of bidirectional sequencing as a reference or gold standard would not be appropriate for large deletions, large gains, large arrangements, and polynucleotide expansions. Similarly, demonstrating that a comparative genomic hybridization assay can distinguish between hetero- and homozygotes would not be appropriate.

To resolve the above issues we recommend either specifically addressing these tests within the scope of the document and clarifying when specific recommendations are not appropriate or addressing comparative genomic hybridization tests in a separate guidance document.

In regards to rare mutations, we are concerned that the guidance document does not provide an approach that meets the agency's least burdensome approach. The guidance document discourages enrichment, even in the context of rare mutations. Yet without enrichment or the use of synthetic samples, studies of tests for rare disorders will

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be burdensome. 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 the agency to provide additional guidance in regards to a least burdensome approach to studies for rare disorders.

SPECIFIC COMMENTS

III. A. Intended Use of a Device

Page 4 ¶2. It is stated, *"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."*

Comment:
We recommend defining screening as "an intended use is considered to be an indication to test patients regardless of symptomology," which is more consistent with the CLSI definition of screening test in "Molecular Diagnostic Methods for Genetic Diseases;" Approved Guideline MM1-A. This CLSI approved guideline defines screening test as "generally used to evaluate the genetic status of an asymptomatic individual who is not at increased risk due to a positive family history."

Page 4, ¶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." The second bullet states: "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:
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.

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 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 require large amounts of extra work to ascertain sufficient samples containing rare alleles, and collecting these data will not substantially influence the test sensitivity or specificity. A solution to this is to allow evaluation based on a molecular phenotype shared by multiple alleles. Alternatively, the use of synthetic samples may be used.

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

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

Lastly, in accordance with the least burdensome principle, we recommend the agency discuss how enrichment, synthetic specimens, and phenotypic data may be used to address tests for rare mutations, such as those occurring 1 in 5,000.

III. B. Device Design

Page 5, Fourth bullet. It is stated, "*Sequence or identity of oligonucleotides, primers, probes, or other capture elements.*"

Comment:
Please clarify what it is meant by *"identity"* in the following phrase, especially in regards to large probes (e.g., 500 KB).

Page 5, Twelfth bullet. It is stated, "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."

Comment:
QC functional testing of larger genome microarrays is inconsistent with FDA's least burdensome approach. Cross-hybridization is addressed by design, rather than through QC testing.

III. C. Analytical Studies

Item 1. General analytical performance considerations

Page 6 ¶2. It is stated, *"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."*

Comment:
The above demonstration may be important in some cases, such as 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 or completely dominant sequences. Unless comparative genomic hybridization tests are exempted from the scope of the guidance document, we recommend FDA clarify that the above demonstration is not expected for such tests by inserting "If appropriate" at the beginning of the sentence.

Item 2. Sample characterization and specifications

Page 6 ¶2. It is stated, *"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."*

Comment:
At the end of the sentence insert ", if contaminating genomic DNA interferes with the assay." Consideration of assay design is important. Such procedures are unnecessary and burdensome for assays designed not to be affected by genomic DNA. Additionally, for common platforms extracting DNA and RNA one would not want to introduce enzymes that would degrade the other.

Item 3. Effect of excess sample and limited sample

Page 7 ¶1, it is stated, *"You should investigate the range of nucleic acid sample concentrations that reproducibly yield acceptable results."*

Comment:
At the beginning of the sentence insert, "If extracting nucleic acid." The recommendations in this section are appropriate for assays that require extraction, but not all assays require extraction, *in situ* for example, and other assays, such as those using whole blood that do not require precise extraction.

Item 5. Controls and calibrators

Page 8 ¶1. It is stated, *"Controls should contain nucleic acid levels that span the input concentrations recommended in product labeling in order to adequately stress the system."*

Comment:
We recommend deletion of this sentence or qualifying language as to the types of assays that would benefit from such controls. For microarray assays, for example, external controls play a role in lot validation. However, it is internal controls that are more appropriate for enabling users to determine, if critical reactions have proceeded properly. Furthermore, assaying input controls per batch or daily is redundant because other quality assurance controls are assayed daily.

Item 7. Analytical specificity (interference and cross-reactivity studies)

Page 8¶3.
Comment:
Within this section, the CLSI guideline, "Interference Testing in Clinical Chemistry," Approved Guideline, CLSI, EP-7A is referenced. We note this guideline has limited applicability to nucleic acid testing. Additional guidance from the agency as to the types of interfering substances that are reasonable for nucleic acid testing is requested.

Page 9, First bullet. The last bullet point states, *"results demonstrating that your test rejects sequences similar to the target sequence, at nucleic acid levels that span the input concentrations recommended in product labeling"*

Comment:
We recommend limiting the applicability of this sentence to those assays where mismatch has an outcome on assay results and those assays requiring a precise sequence site. When assessing a large genome span, for example, such testing is not pertinent.

III. D. Software and Instrumentation

Item 2. Validation of instrumentation

Page 10 ¶1.
Comment:
Please clarify the term "generic instrument," and that, as used in this section, it is not intended to include items such as centrifuges and pipetters. Rather, the focus of this section is instrumentation that is integral to running the assay to measure output and produce patient results, such as hybridization chambers. Alternatively, we recommend using the term analyzer and adopting the definition of analyzer in "Laboratory Automation: Electromechanical Interfaces; Approved Standard, CLSI, Auto5-A. In the standard, analyzer is defined as, "an instrument and/or specimen processor and handling device that performs measurement on patient specimens of quantitative, clinically relevant analytes; Note: A portion of a patient's specimen is consumed in the analytic process."

III. E. Comparison studies using clinical specimens

Item 2. Comparison to another device

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

Comment:
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 <u>instead of</u> comparison with the reference method." The use of bidirectional sequencing as a reference or gold standard would not

be appropriate for large deletions, large gains, large arrangements, and polynucleotide expansions. Unless such tests are exempted from the scope of the guidance document, we recommend FDA clarify that sponsors would not be expected to use bidirectional sequencing as a reference method for such tests.

Item 3. Resolution of Comparison Discrepancies

Page 11, ¶3.
Comment:
Because the referenced guidance, *"Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests"* is draft guidance, we recommend FDA provide examples of acceptable unbiased statistical techniques.

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

Page12.
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 doing relative to expectations.

Page 12, Bullet b.
Comment:
In defining the populations used for clinical evaluation, there should be an effort made 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.

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.

Pages 12-13, Bullet d. It is stated, *"You should identify clinical cut-off points in a training set and validate these in a separate test data set."*

Comment:
We recommend addressing the use of data subsets to validate clinical cut-off points. To the end of the sentence insert, "or through the use of other statistically significant methods, such as bootstrapping."

IV. Labeling

Directions for Use

Page 14 ¶2. It is stated, *"Devices incorporating nucleic acid amplification should provide work-flow recommendations in labeling."*

Comment:
As written, the statement is overly prescriptive, especially since a manufacturer cannot provide work-flow recommendations for all laboratories that would use the assay. We recommend inserting "sample" prior to "work-flow" and adding ", as appropriate" to the end of the sentence.

Interpretations and Precautions

Page 14 ¶4. 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 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."*

Comment:
It is not necessarily appropriate for commercial organizations to dictate to clinicians how to interpret and report results. This is better left to professional organizations. It would be more appropriate for sponsors to reference accepted standards or guidance documents. We recommend modifying this section to read, "we recommend that you reference accepted standards or guidance documents that provide for interpretations of results and the language to be used in reporting results."

Additionally, because manufacturer's do not have control over changes to standard nomenclature systems established by third party organizations, should the agency continue to recommend manufacturer's provide such a key, we recommend a provision that recommends manufacturer's identify the source and edition of the nomenclature standard used and inclusion of a statement that "future editions of the referenced standard should be consulted and followed."

Stability

Page 15 ¶1. It is stated, *"We recommend that you provide stability data to support the reagent shelf life that you state in your labeling."*

Comment:
Based on experience, summary stability data is generally acceptable to the agency for 510(k)s. We recommend inserting "summary" prior to "stability data" in the first sentence.

Page 15 ¶1. It is stated, *"You should provide recommendations for assessing the stability of input samples."*

Comment:
Clarification of the agency's expectations in regards to stability versus sample acceptability and/or integrity is requested. Examples of the types of information expected would be helpful.

Performance

Page 15 ¶2. It is stated, *"Failed assays (e.g., inability to sequence the sample) should be considered disagreements for the purpose of reporting performance characteristics."*

Comment:
Please clarify why no result is equivalent to discordance. No result does not necessarily mean disagreement. We recommend replacing this sentence with *"A report of incidence of failure should be provided."*

Appendix I

Page 17, ¶4
Comment:
Due to the complexity of recommendation number ten, we recommend providing additional examples for greater clarity.

Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 935-0766.

Sincerely,

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