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AdvaMed
Advanced Medical Technology Association

May 10, 2006

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

Re: Docket No. 2006D-0012: Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers

Dear Sir or Madam:

AdvaMed, the Advanced Medical Technology Association, is providing this response to the Food and Drug Administration's (FDA's) request for comments to the draft guidance entitled, "Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers" (draft guidance). AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. AdvaMed member companies have assumed a key role in developing many novel diagnostic tests for use in the clinical laboratory. Our companies, thus, have a significant interest in FDA's regulation of genetic tests.

GENERAL COMMENTS

AdvaMed commends FDA for replacing the February 27, 2003 draft guidance "Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers." We note that the draft guidance reflects much of FDA's recent, successful experience with the regulation of pharmacogenetic and genetic tests. With the need to improve cycle time for introducing novel products that contribute to better patient management through personalized medicine, we believe that several of the recommendations contained in the draft guidance would present significant hurdles to manufacturers attempting to bring new pharmacogenetic and genetic tests to market. Some of these hurdles could be more burdensome than necessary for safe and effective products.

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Specifics in the draft guidance presenting a burdensome approach to preparing and reviewing PMAs and 510(k)s for pharmacogenetic and other genetic tests follow:

- The draft guidance discourages enrichment for tests that evaluate rare events.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 may require 80,000 patient specimens to obtain 10 positive specimens. Such a requirement is not only counter to the concept of "orphan" product evolution, but is also counter to FDA's already established policy of encouraging research into the testing and treatment for rare disorders.

- Emphasis on demonstrating the clinical validity of a test for a genetic marker in addition to analytical performance, significantly increasing the scope of the evaluation studies.

- Requirement that the published studies focus on the same study population and utilize a test method of the same technology of the device.

We encourage the agency to provide additional guidance in regards 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. In these populations, effective use of such literature is essential to deliver useful care in the shortest time frame. As you know, the 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 guidance would greatly reduce the usefulness of this option.

The draft guidance also imposes certain commonly required IVD requirements that are not necessarily relevant for genetic or biomarker-based testing resulting in requirements that may be overly proscriptive. For example, the draft guidance provides performance specifications that have been commonly applied to IVD devices (including precision, cut-off, analytical specificity, carryover, sensitivity and specificity) and citation to the STARD publication as a reference for reporting diagnostic accuracy. We recommend FDA include concepts for assay evaluation that are specific to genetic tests, which may include assay evaluation procedures described by the Center for Disease Control-sponsored ACCE project (http://www.cdc.gov/genomics/gtesting/ACCE.htm#References). In other words, greater flexibility in line with the targeted product lines would be appropriate.

SPECIFIC COMMENTS

Section I. ***Purpose***

Page 1, paragraph 1 – states that the "recommendations within this draft guidance for elements of a genetic test submission apply to pharmacogenetic . . . and other types of genetic tests. Tests of gene expression and tests for non-heritable (somatic) mutations are not specifically addressed, although many of the same principles may apply."

We note that the guidance states that many of the principles outlined in the draft guidance may apply to gene expression tests and tests for non-heritable (somatic) mutations. It is unclear whether that includes comparative genomic hybridization tests (CGH) such as large deletions, large gains, large rearrangements, and polynucleotide expansions, or other tests for genetic disorders that are not amenable to sequencing. Many, but not all, of the principles outlined in the draft guidance would apply to CGH, as an "other type of genetic test."

Recommendation: To resolve the above issues we recommend that FDA either specifically address these CGH within the scope of the document and clarify when specific recommendations are not appropriate or address CGH in a separate guidance document. Our preference is that this be an all-inclusive document.

Section III. *Recommendations for the Preparation of the Pharmacogenetic or Genetic Test Application*

A. Intended Use of a Device

Page 4, paragraph 1 – Encourages manufacturers to file separate applications for each intended use that has unique and separate supporting studies.

Depending on its expected use in a laboratory setting, a single device may be designed and configured to target more than one marker. Such a product could not be marketed without clearance or approval of all of the target markers. In addition, such a device may have a single package insert and software configured to only report results for multiple markers. The requirement for filing separate applications for such a device would create unnecessary redundancies and further complicate the review process. Additionally, this could also create a cost burden for multiple applications when a "bundled" approach would be sufficient.

Recommendation: We recommend FDA not require separate applications for a device that is specifically designed to target multiple markers.

Page 4, paragraph 2 – states that "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."

The definition of "screening" is inconsistent with the Clinical and Laboratory Standards Institute (CLSI) definition of a screening test. MMI-A, Molecular Diagnostic Methods for Genetic Diseases; Approved Guideline defines a screening test as a test "generally used to evaluate the genetic status of an asymptomatic individual who is not at increased risk due to a positive family history."

Recommendation: We recommend FDA revise the wording as follows: "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. This approach would also be consistent with the application of screening tests outside the genetic venue.

Page 4, paragraph 2 – addresses issues that apply to screening tests for common alleles and to any test that evaluates rare events.

Lumping screening applications and tests for rare variants together is very confusing. Additionally, the few bulleted items that follow are not exhaustive enough to provide a useful list of issues that need to be considered when designing studies for the evaluation of tests intended to detect rare events.

Recommendation: We recommend separating, within the guidance document, the recommendations pertaining to screening for common alleles from the recommendations pertaining to tests for rare variants, especially commenting on special considerations given to products potentially in the "orphan" category. Consider rewording this portion of the "intended use" section (paragraph 3 and associated bullets) to convey a high-level message regarding difficulties of testing for rare events. Reference could also be made to literature or other sources where a comprehensive treatment of the topic has been made.

Page 4, paragraph 2, bullet 1 – states that the ethnic makeup of the study population should be based on the frequency of the alleles, genotypes, or mutations.

Individual determination of ethnic identity can be problematic, including those based on self-reporting. If banked samples are used to determine genotype detection rates, knowledge of national origin or ethnicity can create significant hurdles in procuring samples. More flexibility is required to deliver new and valuable products in a timely fashion.

Recommendation: We recommend that the frequency of a genetic marker in various populations be described based on published literature and that stratification of test specimens by ethnicity not be a requirement of the performance studies.

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 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. This statement does not consider the various scenarios where 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.

FDA should also consider that 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.

Also, 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 simulated samples may be used.

Recommendation: We recommend FDA separate the recommendations pertaining to screening for common alleles from the recommendations pertaining to tests for rare variants. We also recommend FDA address how enrichment and simulated specimens may be used to address test for rare mutations, such as those occurring 1 in 5,000. Time to market considerations need fuller evaluation by the draft's authors and should also be considered in conjunction with the potential of post-approval requirements under Section 522 of the Act.

> Page 4, paragraph 2, bullet 2 – 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."

Nucleic acid screening tests are no different from other screening tests. When samples are tested for rare events, careful discussion in the labeling is warranted to address the test's ability to detect true positives in low prevalence conditions.

> Page 4, paragraph 2, bullet 3 – states that long-term follow-up studies may be needed to demonstrate the validity of predictive screening tests.

Long-term, longitudinal studies may be useful to support test reimbursement, but should be beyond the scope of the initial regulatory application.

Recommendation: We recommend FDA delete the requirement for long-term, longitudinal studies and focus on safety and effectiveness of the product applications. Studies of academic interest have been and will be conducted by academics.

B. Device Design

> Page 5, paragraph 1, bullet 5 – recommends that the sequence or identity of oligonucleotides, primer, probes or other capture elements be described.

We ask that FDA clarify what is meant by "identity" especially in regards to large probes (e.g., 500 KB). Further, we ask why FDA would need such highly sensitive and confidential information to evaluate the safety and effectiveness of a product or the reproduciblity of the manufacturing processes.

Page 5, paragraph 1, bullets 8 and 12 – makes reference to the need for a description of the methods used in attaching the probe material to a solid surface and for functional testing to address the potential for probe cross-contamination during manufacturing.

Since this section begins by stating that whether the submission is a PMA or 510(k) it must include information on the design of the device. However, the need to provide details of manufacturing methods and in-process testing and QC testing are beyond the scope of 510(k) applications. The August 12, 2005 CDRH guidance "Format for Traditional and Abbreviated 510(k)s" recommends that manufacturers include a brief description of the device design that may include diagrams, dimensions, tolerances, and/or schematics.

Recommendation: We recommend that the requirements for Device Design and Device Descriptions for 510(k) submissions and for PMA applications be treated separately, since the former do not require detailed descriptions of manufacturing procedures and test methods. Further, we ask that FDA be very careful to avoid product line requirements that are already dealt with in 21 CFR part 820, and especially the design control portion of the Quality System Regulation.

C. Analytical Studies

Page 6, item 1, sentence 1 – requires manufacturers to demonstrate the device's ability to differentiate genotypes, alleles, or mutations using nucleic acid levels that span the input concentrations recommended in the product labeling.

This requirement would greatly expand the scope of the studies and is not consistent with least burdensome principles. Requirements for input concentrations should be established in dedicated studies and need not be demonstrated in multiple analytical studies.

Recommendation: We recommend this FDA delete the proposed requirement.

Page 6, item 1, sentence 5 – states, "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."

There are some situations where demonstrating that the assay can distinguish between hetero- and homozygotes may be important, 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, for completely dominant sequences.

Recommendation: We recommend FDA note that there may be situations that this requirement is not appropriate by inserting "If appropriate" at the beginning of the sentence.

Page 6, item 2, sentence 1 – states that if the manufacturer intends to provide reagents he must demonstrate "that the chosen sample preparation method consistently provides quality nucleic acid samples that yield reproducible results. . ."

Requirements for sample preparation should be consistent with sample preparation recommendations in other guidance documents e.g., FDA's Class II Special Controls Guidance Document: RNA Preanalytical Systems (RNA Collection, Stabilization and Purification Systems for RT-PCR used in Molecular Diagnostic Testing).

Recommendation: We recommend FDA revise the statement as follows: "that the chosen sample preparation method consistently provides nucleic acid samples appropriate for analysis that yield reproducible results. . ."

> Page 6, item 2, sentence 2 – states, "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."

Consideration of assay design is important. Such procedures are unnecessary and burdensome when assays are 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.

Recommendation: We recommend adding to the end of the sentence ",if contaminating genomic DNA interferes with the assay."

> Page 7, item 3, sentence 2 – states, "You should investigate the range of nucleic acid sample concentrations that reproducibly yield acceptable results."

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.

Recommendation: We recommend adding to the beginning of the sentence insert, "If extracting nucleic acid." ."

> Page 7, item 4, sentence 5 – states, "Precision panel samples should contain nucleic acid levels that span the input concentrations recommended in the product labeling."

Depending on the required diversity in the reproducibility test panel, the addition of multiple input concentrations would add unnecessary complexity to these studies.

Recommendation: We recommend the reproducibility test panel include specimens near the analytical sensitivity of the assay as would be appropriate for any other test.

> Page 7, item 4, sentence 8 – states, "You should also perform testing . . . at different times of the day to maximize detection of potential sources of variability."

The benefit of performing precision testing at different times of the day is unclear, particularly for nucleic acid-based tests. What variability is being addressed by this

approach? On board stability studies are more effective for determining reproducibility of test results within the recommended daily testing periods.

Recommendation: We recommend FDA delete the requirement to perform testing at different times of the day.

> Page 8, item 5, paragraph 2, sentence 4 – requires that controls span the recommended sample input concentrations.

For some assays, for example microarray assays, external controls play a role in lot validation. However, internal controls 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 of other quality assurance controls are assayed daily. Single level system controls should be sufficient for qualitative tests.

Recommendation: We recommend FDA delete the sentence or add qualifying language as to the types of assays that would benefit from such controls.

> Page 8, item 7, sentences 1 and 2 – states, "Potential inhibitors present in patient specimens may not be efficiently removed by sample preparation procedures and may even interfere with sample preparation itself. We recommend that you examine potential interfering substances . . . for their effects on sample preparation and performance."

The need to test for interfering substances in patient specimens should be based in part on the demonstrated efficiency of the specimen preparation method.

Recommendation: We recommend that studies of possible interfering substances not be required if a highly efficient specimen preparation method is provided as part of the test system. Some methods, such as magnetic target capture, are well known to neutralize this concern.

> Page 8, item 7, sentence 4 – references CLSI guideline, "Interference Testing in Clinical Chemistry," Approved Guideline, CLSI, EP-7A.

We note that this guideline has limited applicability to nucleic acid testing. We believe that additional guidance is needed as to the types of interfering substances that are reasonable for nucleic acid testing.

Recommendation: We recommend FDA and industry work together to develop a relevant list of the interfering substances for nucleic acid testing.

> Page 9, item 7, bullet 6 – 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."

This testing is not always applicable. For example such testing is not pertinent when assessing a large genome span. Further, the concept is part of the normal sensitivity/specificity determination.

Recommendation: We recommend limiting the applicability of this sentence to those assays where a mismatch has an impact on assay results and those assays requiring a precise sequence site. Alternatively, delete the requirement all together as it's a normal consideration for any test.

D. Software and Instrumentation

Page 9, item 2, sentence 1 – refers to "generic instruments."

It is unclear whether the term "generic instrument," as used in this section, is not intended to include items such as centrifuges and pipetters. We believe that it is intended to refer to instrumentation that is integral to running the assay, including measuring output and producing patient results, such as hybridization chambers.

Recommendation: To add clarification, 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." If the intent was to use the term general laboratory equipment, clarification is needed.

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We also recommend that FDA clarify that any analyzer that allows the operator to set cut-offs is still considered generic even if proprietary reagents are used.

Page 10, item 2 – recommends that instrument descriptions and test data be provided for value assignment, feature location, size, concentration, volume, drying of small samples, effect of small volume reactions and its impact on test results. It also recommends that instrument calibration and procedures and potential instrument sources of uncertainty be described.

Details regarding the design and performance of a 510(k)-cleared IVD instrument need not be provided in a reagent submission. Standard laboratory equipment used for sample preparation (spectrophotometer for absorbance measurement, fluorometer for DNA quantification or gel analysis of amplifiable DNA) should not need separate validation.

Recommendation: We recommend that if a previously 510(k)-cleared instrument is included in the test system, instrument design and performance information need not be repeated in the reagent submission. Standard laboratory equipment should be validated as part of the test system.

E. Comparison studies using clinical specimens

Page 10, paragraph 1, sentence 2 – states "You should include in your evaluation all matrix types with which your device is intended to be used."

Recommendation: We recommend FDA add a description of methods that may be employed to expand the types of specimens that may be tested (e.g., blood, buccal cells, saliva), including the use of bridging studies, that would allow manufacturers to avoid repeating all performance studies with each specimen type.

Page 11, item 2, sentence 1 – states, "You may choose to describe comparison studies with another well characterized or predicate device, in addition to comparison with the reference method."

Recommendation: We recommend the following wording revision: "Unless specifically required that a comparison be made to a gold or reference standard method, you may choose to describe comparison studies with another well-characterized or predicate device, instead of comparison with the reference method."

Page 11, item 2, sentence 3 – states, ". .FDA believes that the best measure of test performance will come from comparison to bidirectional sequencing."

Use of bidirectional sequencing as a reference or gold standard is not appropriate for large deletions, large gains, large rearrangements, and polynucleotide expansions. While bidirectional sequencing has been the standard in the past, the real gold standard is the quality of the sequence data, not the bidirectional sequencing.

Recommendation: Unless such tests are specifically exempted from the scope of the guidance document, there is a need to explicitly state that sponsors are not expected to use bi-directional sequencing, as a reference method, for such tests. If sequence is critical, we recommend that the results be compared to "industry accepted high quality sequence data" which could be more specifically defined in the future as methods change.

Page 11, item 3 – references FDA's draft guidance "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests."

Recommendation: We recommend FDA provide examples of acceptable unbiased statistical techniques.

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

Page 12, item a – uses the term "clinical truth" and defines it as the "best clinical evidence for a specific diagnosis or allele assignment."

The need to determine clinical status should be based on the intended use of the test. Genotype identity may be determined by sequencing methods.

We also remind FDA that some genetic results do not show clinical manifestations at the time of the test result, e.g., ALS. New terms for sensitivity and specificity should not be invented for particular product types.

Page 12, item b – recommends that geneotype/phenotype correlations be validated, if necessary.

Recommendation: We ask that FDA specifically state that in cases where genotype/phenotype correlations are well understood, additional studies to demonstrate penetrance are not required and normal sensitivity and specificity measures, whether analytical or clinical, be applied as appropriate.

Page 12, item b – also specifies the information required when defining the population(s) used to validate genotype/phenotype correlations. It recommends the information include statistically determined performance data from studies of demographically stratified normal populations and demographically stratified performance data for each disease, condition, or genotype.

The requirements for testing specimens from a normal population, and for demographic stratification of test results, should be dictated by the intended use and indication(s) for use of the test. A general requirement for statistically determined numbers of specimens from multiple categories of patients is not a least burdensome approach to test validation. AdvaMed understands the academic interest in this area, but a statistical basis for this information in a submission is often not necessary to deliver a safe and effective product in a timely fashion.

Recommendation: The requirements for testing specimens from a normal population, and for demographic stratification of test results, should be dictated by the intended use and indication(s) for use of the test. We recommend FDA not apply this requirement to tests for which the target population for a test is narrowly defined or for when demographic information is not required for genotype determinations. Also, in defining the populations, 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 one ethnic group and the cases from another.

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

Recommendation: We recommend FDA also address the use of data subsets to validate clinical cut-off points by adding "or through the use of other statistically significant methods, such as bootstrapping" to the end of the sentence.

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."

Data from published studies, utilizing a test of different technology with similar genotype coverage, should be usable to support the clinical performance of a new test, providing that the analytical performance (genotype detection) of the two methods is comparable. 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, not in every case. Also, 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 its relationship to the disease or condition for which it is intended to describe rather than the method for which it was determined. While sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test (all performance descriptors) *may* be affected by technology and/or patient populations studied, the link between the biomarker and health condition is not.

Recommendation: We recommend FDA delete the requirement that the same technology be used.

G. Clinical Effective of the Device

Page 13, paragraph 1, sentence 1 – appears to recommend that clinical data be submitted for PMAs and for *de novo* submissions.

It is unclear whether it is FDA's intent to require clinical data for *de novo* applications. If so, the need for such studies should be dictated by the intended use of the test and the current level of knowledge regarding the clinical usefulness of the test result.

Recommendation: We recommend FDA clarify whether clinical studies are required for *de novo* applications.

Page 13, item 2, sentence 3 – states, "You should establish comparability between the new device and the device used in the published literature in order to ensure that the data can be confidently extrapolated."

The relevance of published data for determining the link between analytical and clinical performance is dictated more by the performance characteristics of the two methods in genotype determination, irrespective of the technologies used. As stated previously, data from published studies, utilizing a test of different technology, may be usable to support the clinical performance of a new test, providing that the analytical performance (genotype detection) of the two methods is comparable.

If one were to use published data to support genotype—phenotype linkages it should not be required to separately establish the equivalent analytical performance of the published method and the new device. For example, the CYP2D6 allele table (http://www.imm.ki.se/CYPalleles/cyp2d6.htm) contains 50 references linking genotype to phenotype. Demonstrating analytical equivalence to the methods used for genotype determination in each of these references would be a heroic task.

Recommendation: AdvaMed recommends that this restriction be eliminated. Other innovative products have been accelerated to the market with heavy use of prior publication on the same, different or modified technologies. It is inconsistent with our mutual goals of innovation and least burdensome to overly restrict the use of valuable publications to speed new products to market. This is another area where FDA should consider post-approval requirements to help manufacturers launch new products and would be a good application of FDA's "total product life cycle" approach.

Section IV. *Labeling*

Directions for Use

Page 14, sentence 1 – requires that the labeling include instructions that delineate "how the device is to be used on patients."

This reference does not apply to IVD devices since they are not used directly on patients, but rather for *in vitro* examination of patient specimens.

Recommendation: We recommend the statement be rephrased to narrow the scope to *in vitro* use and remain consistent with existing IVD rules and processes.

Page 14, sentence 3 – states, "Devices incorporating nucleic acid amplification should provide work-flow recommendations in labeling."

As written, the statement may be overly proscriptive. Manufacturers cannot provide workflow recommendations to every laboratory that might use the assay, however, AdvaMed recognizes the intent of this statement and our recommendation addresses it.

Recommendation: We recommend the following revision: "Devices incorporating nucleic acid amplification should provide <u>sample</u> work-flow recommendations in labeling."

Interpretation and Precautions

Page 14, sentence 1 – recommends the use of a standard nomenclature to describe alleles, genotypes, and mutations, and requires that source of the nomenclature system be provided. If a standard nomenclature is not used, a translation to standard nomenclature should be provided.

It is not necessarily appropriate for commercial organizations to dictate to clinicians how to interpret and report results. This is the responsibility of professional organizations. It would be more appropriate for sponsors to reference accepted standards, guidance documents or practice guidelines.

Recommendation: 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."

Manufacturers do not have control over changes to standard nomenclature systems established by third party organizations. Should the FDA continue to recommend manufacturers provide such a key, we recommend a provision that directs manufacturers to identify the source and edition of the nomenclature standard used and to include a statement that "future editions of the referenced standard should be consulted and followed." An option to provide a web reference to such standards should also be explicitly permitted so that changes will be reflected in the standard setting organization's site.

Stability

Page 15 – recommends stability data be provided to support the reagent shelf life.

FDA's Guidance document "Format for Traditional and Abbreviated 510(k)s August 12, 2005" states that "For a submission that identifies a shelf life for the device, your shelf life should be supported by appropriate bench tests and/or sterilization (packaging) validation." It does not suggest that stability data be provided in the application. The need to include stability data in a 510(k) application represents a burdensome requirement and is not in keeping with current FDA guidance.

Additionally, requiring stability data in 510(k) submission would lead to an expectation for manufacturer's to submit a new 510(k), traditional or special, for extensions to reagent shelf life. Generally, based on experience, summary stability data is acceptable to the agency for 510(k)s. AdvaMed strongly objects to this new requirement for one type of diagnostic product and there has been no basis for this requirement documented.

Recommendation: We recommend this requirement be deleted and that this product line not be handled differently in this area than any other diagnostic product. There is no scientific or regulatory basis for such special treatment.

Page 15, sentence 2 – states, "You should provide recommendations for <u>assessing the stability of input samples</u>."

FDA's expectations with regard to stability versus sample acceptability and/or integrity is unclear.

Recommendation: We recommend FDA provide examples of the types of information expected.

Performance

Page 15 – states, "Failed assays (e.g., inability to sequence the sample) should be considered disagreements for the purpose of reporting performance characteristics."

It is unclear why FDA considers no result to be equivalent to discordance. No result does not necessarily mean disagreement. In any evaluation there may be some samples that cannot be evaluated for a variety of reasons, including mishandling. Data exclusion and the reasons should be requested for clarification rather than naming all such samples as "disagreements."

Recommendation: We recommend replacing this sentence with a report of incidence of failure along with potential reasons for failure and data exclusion should be provided.

Appendix I: General considerations for planning and evaluating clinical studies

> Page 17, item 7 – states "For genetic tests, you should include samples from individuals with diseases or conditions that may cause false positive or false negative results with the device (i.e., within the differential diagnosis), if appropriate."

Because of their specificity for human DNA or RNA targets, the likelihood of false results being associated with patient clinical status is far less likely for genetic tests than for clinical chemistry tests and tests for microbial pathogens. Finding such patients as likely individuals to test would be a significant challenge that has the potential to delay access to important new products.

Recommendation: Unless indicated by risk assessment, the regulatory submissions for genetic tests should not be required to assess the impact of disease condition on test accuracy.

> Page 17, item 10 – addresses diagnostic devices that assay the presence of a particular pattern.

Recommendation: Due to the complexity of recommendation number ten, we recommend providing additional examples for greater clarity.

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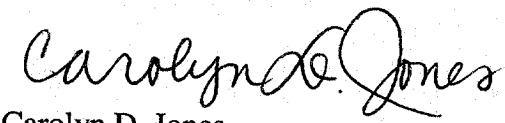
AdvaMed appreciates the opportunity to provide these comments. We look forward to working with FDA to complete this important guidance. Please feel free to contact me to discuss any of the issues raised in these comments.

Respectfully submitted,



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