AACC
Advancing
Clinical Laboratory
Science Worldwide

July 15, 2003

Dockets Management Branch (HFA-305)
Center for Devices and Radiological Health
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20850

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) draft guidance entitled, "Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers," which starts to outline what information the agency would request from manufacturers when making multiplex test submissions. We commend the agency for taking this opportunity to work with the private sector in exploring how these new, emerging technologies should be regulated.

General Approach

The agency states that its "goal is to establish a set of recommendations that will both define the levels of data needed to establish a reasonable assurance of safety and effectiveness of a device, and suggest the least burdensome path to market for manufacturers of multiplex and array devices." AACC supports this approach. We believe it is important that the FDA take an incremental and flexible approach to regulating multiplex tests for heritable DNA markers, mutations and expression patterns, so as not to stifle the development and dissemination of this new and promising technology. In addition, the agency should be prepared to make periodic adjustments as it learns more about this technology and how it is, and can be, applied.

We understand FDA's desire to draft a single guidance document that covers all multiplex testing. Certainly, a single document would be more convenient for all parties involved. However, because different technologies are affected, and multiarray technology can be used for different purposes, the agency should consider drafting separate documents for the different types of multiplex testing (e.g., nucleic acid testing, proteomics, etc...). Alternatively, subsections within a single document could be included that address the unique characteristics of differing areas, such as: germline DNA genotyping; mixed sample genotyping (e.g., HIV and cancer); and mRNA expression analysis testing. In addition, we recommend that future versions address important pre-analytical issues, such as mRNA stabilization or tissue microdissection for cancer applications.

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Recommendations for the Preparation of The Multiplex Test Applications

The draft guidance mentions that "the FDA may request different types of data and statistical analyses in premarket applications for in vitro diagnostic tests." It then lists eight specific characteristics of the test that a manufacturer needs to provide data and statistical analyses. However, the document only describes the first of these characteristics, "intended use of a test or device," and neglects to provide addition guidance on the remaining seven. We recommend that explanatory language be included on the other characteristics.

II. Analytical Validation

Quality Control (QC) should not be limited to the array method alone; it should also include the efficiency of the extraction and Reverse Transcriptase (RT) (if necessary). This can be accomplished using outside standards that are spiked into the original sample prior to extraction and RT and subsequent amplification (if required by the method). Different size spike standards might permit the determination of the quality of the extraction and RT step. We are unaware of studies that demonstrate whether mRNA is degraded preferentially from the polyA site or the cap site. As a result if the location of gene specific probes/primer are located at the extreme ends of 5' or 3' portions of the strand it is possible that during sample processing that these may be lost periodically due to degradation.

Because the QC sections of CLIA have been revised this year, there is still some confusion over the manner in which the new regulations will be applied. This guidance document represents an opportunity for FDA to clarify expectations under the new regulations. For example, do the current CLIA requirements regarding the use of control suffice or do controls need to be provided in the kit? Also, what controls are appropriate for chip QC by the manufacturers vs. in the clinical laboratory as part of routine use?

IV. Clinical Evaluation Studies Comparing Test Performance to Accepted Diagnostic Procedure(s); (B.2.) Clinical Validation

The FDA mentions that "clinical truth" should be defined "as it will be used in evaluating the clinical performance of the device." We recommend that the FDA expand this section to address a number of issues that manufacturers and the agency may have to consider when evaluating the clinical performance of microarrays, such as:

- What to do when the array method provides more accurate sub-typing than established methods;
- What is expected from an independent validation; and
- How to demonstrate clinical validation when patient data may take years to obtain.

VI. Clinical Effectiveness of the Device (B)
The agency states that "if a sponsor wants to use peer-reviewed literature to support effectiveness, you should furnish copies of all relevant articles and provide a justification for the use of the literature in place of clinical studies." AACC agrees that there must be flexibility on the part of the agency in determining when a clinical study is required, especially with regard to many of the new technologies that are on the horizon. We suggest, however, that the FDA provide more explanatory details, including examples, of when literature alone is sufficient to demonstrate the clinical effectiveness of the device.

Appendix I: General Considerations for planning and evaluating clinical studies, Subpart (5)
The FDA makes a number of general recommendations for manufacturers to consider when they are planning and evaluating clinical studies. One of the areas the agency offers guidance about is the use of archived specimens. Specifically, the agency states that a manufacturer should "describe the sampling method used in the selection and exclusion of patients. If it is necessary to use archived specimens or a retrospective design, provide adequate justification for why the sampled population is relevant to your patient population." Given the confusion, and ongoing discussions in this area, AACC suggests that the agency describe how manufacturers should address the issue of using archived specimens that do not have informed consent.

By way of background, AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry nationwide. The AACC provides national leadership in advancing the practice and profession of clinical laboratory science and its application to health care. If you have any questions or we may be of any assistance, please call me at (408) 395-0807 or Vince Stine, Director, Government Affairs, at (202) 835-8721.

Sincerely,

Susan Evans, PhD
President