



1992 7 21 10

February 13, 2007

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

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to comment on the September 7, 2006 draft guidance, "In Vitro Diagnostic Multivariate Index Assays," which asserts that IVDMIAs are subject to FDA regulation as class II or class III medical devices. These assays, according to the FDA, are more complex than traditional in-house developed tests.

In general, AACC agrees with the FDA's approach, as outlined in this document, to expand federal oversight to assays that: use clinical data from one or more assays; employ algorithms that often cannot be independently derived and confirmed by another laboratory without access to proprietary information; and report results that cannot be interpreted without information from the test developer regarding its clinical performance and effectiveness. We believe this document must be modified, however, to eliminate its ambiguity, particularly in regards to the scope of the guidance.

**Definition and Regulatory Status of IVDMIAs**

The FDA states that "IVDMIAs reflect the following characteristics..." AACC believes this language is too ambiguous. The agency implies that all three characteristics, as described on page three, are necessary for an assay to be categorized as an IVDMIA. We suggest that the agency modify the sentence to read "To be classified as an IVDMIA, an assay must have all of the following characteristics." This change more clearly states the FDA's intent.

Also, under characteristic two, the agency states that "this result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test." The FDA seems to view the proprietary nature of the information as a critical aspect of what constitutes an IVDMIA. We urge the FDA to more clearly spell this out in the guidance.

2006D-0347

C5

We also recommend that the agency include examples of tests, which employ algorithms, but would not be subject to this guidance. For example, we expect that a test employing simple calculations to obtain a result, such as a creatinine clearance, would not be considered an IVDMA, nor would an assay utilizing publicly available algorithms or clinical guidelines, such as prenatal screening for open neural tube defects. AACC believes these, and other examples, would more clearly demarcate the limits of the document.

#### **Regulation of In-House Developed Tests**

In the Background section, the agency states that “IVDMAs do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion.” This seems to imply that in-house developed tests, which do not meet the three criteria for an IVDMA, remain under CMS CLIA oversight. AACC supports that decision. However, we think the FDA needs to more clearly articulate and expound this distinction to eliminate some of the confusion pertaining to document.

#### **Post Market Requirements**

The agency further states that “IVDMAs are subject to the Quality System Regulation (QSR)” and that it “intends to issue guidance to assist laboratories that manufacture IVDMA” comply with the QSR.” AACC recommends that FDA more clearly define this recommendation to ensure that clinical laboratories fully understand the intent and scope of this initiative. For example, will registration and listing be required? Will there be routine FDA inspections in addition to the CLIA inspections?

#### **Policy Considerations**

Although AACC agrees the agency needs to take action in this area, we are concerned that the agency has not fully examined the unintended consequences that could arise from this policy nor identified mechanisms to address them. At a minimum, we think the FDA should fully consider and address the following questions before implementing this policy:

- What impact will this policy have on incremental advances to existing technologies, as well as the development of first-of-a-kind assays?
- Will certain tests no longer be offered as a result of this policy? If so, which tests? Would the loss of these tests hinder the delivery of patient care?
- Will the agency allow laboratories to continue to utilize existing, unapproved algorithms, until it, or a similar algorithm, is approved by the FDA?
- How will FDA inspect laboratories under the promised QSR guidance?

FDA  
February 13, 2007  
Page Three

Also, we are requesting that the agency clarify whether IVDMIA's can serve as a predicate device, particularly if the IVDMIA is not available for clinical comparison or precision comparison studies. Typically, devices approved or cleared under the PMA or 510(k) processes serve as a predicate for future submissions to the FDA. In this instance, however, a manufacturer or laboratory would not have access to the reagents, since they are not in commercial distribution. These issues need to be clearly addressed before FDA moves forward in this area.

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 worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and its application to health care. If you have any questions, please call me at (504) 568-4281, or Vince Stine, PhD, Director, Government Affairs, at (202) 835-8721.

Sincerely,

A handwritten signature in black ink, appearing to read "Larry Broussard". The signature is written in a cursive, flowing style.

Larry Broussard, PhD  
President-Elect, AACC