



American Clinical Laboratory Association  
Public Comment  
In Vitro Diagnostic Multivariate Index Assays

Docket # 2006D-0347

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I am Alan Mertz, President of the American Clinical Laboratory Association. ACLA is an association that represents local, regional and national hospital and independent clinical laboratories. ACLA thanks FDA for scheduling this public meeting and for the opportunity to speak on these issues, since many ACLA members perform laboratory-developed tests that could be affected by the FDA's Draft Guidance on IVDMIA's.

ACLA strongly supports the goal of the Draft Guidance – namely, to dispel the existing confusion and lack of clarity regarding FDA's regulatory approach toward certain laboratory-developed tests. Although the concerns identified by FDA in its Draft Guidance are clear, the Guidance Document falls short of achieving the goal. ACLA would like to work constructively with FDA toward resolving those concerns in a responsible manner to promote the promise of personalized medicine and encourage the continued investment in these rapidly advancing areas of laboratory medicine.

Today, we would like to focus our remarks on three key recommendations to achieve the goal of the Draft Guidance;

- First, ACLA recommends that FDA issue a proposed rule to address this important subject matter through the formal notice and comment rulemaking process rather than through sub-regulatory guidance.
- Second, ACLA recommends that FDA consider proposals to narrow and clarify its definition of IVDMIA's to avoid confusion and unintended consequences.
- Third, ACLA recommends that FDA work with CMS and through HHS to address its concerns through enhancement and better enforcement of the regulations promulgated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

The procedural recommendation in favor of notice and comment rulemaking is important for several reasons. Since the Draft Guidance announces that laboratory-developed tests deemed IVDMIA's are Class II or Class III devices requiring FDA premarket clearance or approval, it represents a significant change from the agency's historical practice regarding laboratory-developed tests and has a present, binding effect. Rather than merely stating the agency's

current thinking on the topic without creating or conferring any rights or binding FDA or the public, the Draft Guidance operates as a substantive rule; as such, its subject matter should be vetted through the formal, on-the-record, notice and comment rulemaking procedures of the Administrative Procedure Act.

Similarly, while FDA declined to classify laboratory-developed tests as Class II or Class III medical devices in the ASR Rule on the policy grounds that laboratory developed tests have contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health, the Draft Guidance seeks to regulate certain laboratory-developed tests on the ground that the public health requires it. Since the FDA's advisory opinion in the ASR Rule was published in the Federal Register as part of a formal notice and comment rulemaking, the modification of that policy which the Draft Guidance represents must be treated in the same manner procedurally. The best substantive result for all stakeholders is most likely to be achieved only when all stakeholders are afforded the full procedural protections of notice and comment rulemaking.

While FDA has noted that IVDMIAs are intended to describe a narrow niche of "devices", the Draft Guidance defines IVDMIAs so broadly, and so vaguely, that the scope of the Draft Guidance's application could easily be interpreted to extend far beyond its intended reach. Specifically, the Draft Guidance defines IVDMIAs as "test systems that employ data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease." The Draft Guidance further describes three interlocking criteria of IVDMIAs – use of clinical data, an algorithm, and a result that cannot be interpreted by a health care provider without the help of the test developer.

As written, the Draft Guidance could be interpreted to apply to many well-established tests that are part of the standard of care. Upon citing examples of such tests to FDA, ACLA was informed by FDA officials that it was not their intent to include such well-established tests within the scope of the Draft Guidance, and FDA requested our assistance in clarifying and narrowing the definition of IVDMIAs to conform to its intended application.

While the following recommendations for clarifying and narrowing the definition of IVDMIAs should not be construed as an endorsement by ACLA of FDA regulation of any laboratory-developed tests (nor an acknowledgement that FDA has the authority to regulate these tests services), and while ACLA and its members reserve the right to offer modified recommendations at a future date, we offer the following recommendations in a good faith effort to make progress toward the achievement of our shared goals.

FDA should consider the following linked factors in formulating a definition of IVDMIAs:

- A new, single-source test system
- Uses patient and/or clinical data derived from one or more in vitro diagnostic assays together with a proprietary, non-published algorithm

- Generate a patient-specific, binary result that is intended definitively to diagnose a condition or to direct behavior for the cure, mitigation, treatment, or prevention of disease
- Presents significant safety and effectiveness risks not present in test systems which have become part of the standard of care.

Moreover, certain factors, if present, would indicate that FDA regulation is not warranted. Specifically, test systems which meet one or more of the following criteria should not be deemed IVDMIAAs:

- Low –risk consequences of invalid or inaccurate test results;
- Independent verification by one or more laboratories;
- Support of clinical relevance in peer reviewed literature;
- Transparent algorithms;
- Interpretation support for clinicians;
- Support in clinical guidelines;
- Established use;
- CPT code assignment;
- and Payer recognition.

We will provide further elaboration on these points in our formal written comments on the Draft Guidance.

Nevertheless, ACLA firmly believes that FDA should also consider working with CMS and through HHS to enhance the CLIA regulations and provide means for their systematic and rigorous enforcement. This approach has the potential to address the concerns that prompted FDA to issue the Draft Guidance in the context of the regulatory framework specifically designed for clinical laboratories and the services they provide --CLIA, and could avoid the difficulties associated with regulating services under a regulatory framework designed for commercially manufactured and distributed products.

CLIA regulations explicitly require the laboratory director to ensure that selected test methodologies are capable of providing the quality of results required for effective patient care, which implicitly requires the selection of medically relevant tests that have an effective clinical purpose. Likewise, CLIA regulations require the laboratory to have a clinical consultant, who is responsible for providing information about the appropriateness of a test in the clinical context. Systematic and rigorous enforcement of these requirements by CMS could approximate the

independent validation of clinical relevance that FDA seeks to achieve for IVDMIA through the IVDMIA Draft Guidance.

CLIA regulations also require the laboratory to validate the performance characteristics of laboratory-developed tests, including any algorithm or formula that the laboratory relies upon to issue a result, and further require the laboratory director to ensure that the ordering clinician can properly interpret results by including pertinent interpretive information in the reports and making consultation available. Thus, the foundations for algorithm transparency and interpretive guidance for clinicians already exist within the CLIA regulations.

Amendments to the CLIA Interpretive Guidelines or to the CLIA regulations themselves if deemed necessary, coupled with systematic and rigorous enforcement by CMS, would be consistent with the FDA's emphasis on "smart regulation" and following the "least burdensome" approach to address the issues which prompted FDA to issue the Draft Guidance. Thus, we encourage FDA to consider working with CMS in this manner.

In conclusion, ACLA looks forward to working with FDA in an ongoing dialogue to achieve our shared goals of providing continued access to safe, effective and innovative clinical laboratory services for patient care.

Thank you for the opportunity to present.