



American  
Clinical Laboratory  
Association

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VIA E-MAIL ([www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments))  
(Original Sent By Regular Mail)

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

**RE: Docket No. 2006D-0347 – Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on *In Vitro* Diagnostic Multivariate Index Assays**

Dear Sir or Madam:

The American Clinical Laboratory Association (ACLA) is pleased to submit the following comments regarding the Food and Drug Administration's (FDA's) *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* ("the Draft Guidance.") ACLA is an association representing clinical laboratories throughout the United States, including local, regional, and national laboratories. ACLA helps promote public awareness about the value of laboratory services in preventing illness, diagnosing disease, assisting in the selection of appropriate medical treatment, and monitoring medical treatment. Many ACLA members create and perform laboratory-developed tests, some of which could be affected by the Draft Guidance.

ACLA recognizes that FDA, through the Draft Guidance, is attempting to resolve the existing confusion and lack of clarity regarding the FDA's regulatory approach toward laboratory-developed tests, some of which have been the subject of cautionary FDA letters to ACLA members. However, the Draft Guidance falls short of achieving that goal. ACLA would like to work with the 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.

ACLA therefore offers three key recommendations to achieve the goal of the Draft Guidance: (1) that FDA withdraw the Draft Guidance and issue a proposed rule to address this important subject matter through the formal notice-and-comment rulemaking process rather than through guidance; (2) that FDA consider proposals to narrow and clarify its definition of IVDMIAs to avoid unintended consequences; and (3) that through the Secretary of the Department of Health and Human Services (HHS), FDA collaborate with the Centers for Medicare and Medicaid Services (CMS) to consider how FDA's concerns could be met through

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enhancement and better enforcement of the regulations promulgated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

We recognize that FDA takes seriously its responsibilities to safeguard the public health and ensure the safety of *in vitro* diagnostic devices used to diagnose and help treat patients. ACLA therefore urges FDA to take the action recommended within these comments and continue to meet with interested stakeholders, including ACLA, in an ongoing dialogue to achieve our shared goals of providing access to safe, effective, and innovative clinical laboratory services for patient care.

## **I. FDA Should Issue A Proposed Rule To Address This Important Subject Matter Rather Than Issue Guidance**

### **A. Substantive Rules Require Notice-and-Comment Rulemaking**

Guidance, as consistently noted by FDA, is intended to represent the agency's current thinking on a particular topic without creating or conferring any rights on any person and without binding FDA or the public. Because the Draft Guidance announces that devices deemed IVDMIAs are Class II or Class III devices requiring, among other things, clearance or premarket approval from FDA, the Draft Guidance would effect a change in the agency's historical practice regarding laboratory use of laboratory-developed tests. As such, the Draft Guidance constitutes a legislative rule issued without the requisite notice-and-comment procedures under 5 USC § 553. *Community Nutrition Institute v. Young*, 818 F.2d 943 (D.C. Cir. 1987).

While FDA has suggested that the Draft Guidance is merely a statement of agency policy, the document has a present, binding effect. Specifically, FDA notes that it considers laboratories to be manufacturers subject to the Federal Food, Drug, and Cosmetic Act and that it is necessary for laboratories, as IVDMIA manufacturers, to secure FDA clearance or approval of certain tests before laboratories can offer them in the normal course of business.<sup>1</sup> Because the

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<sup>1</sup> While clinical laboratory services are typically performed using FDA cleared or approved test products purchased from device vendors, laboratories also frequently create and perform their own clinical diagnostic services on-site. The components of the testing process developed by the laboratory are not marketed as a kit or test system, and the components are not physically distributed or delivered outside the laboratory. Once a given test has been performed, the laboratory provides written reports of the results to the ordering physicians. Thus, clinical laboratories that develop and perform laboratory-developed tests are merely selling *services* to outside entities as opposed to any identifiable medical device.

Even if laboratory-developed testing services were somehow considered a medical device, FDA's legal mandate under the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) is to regulate products intended for introduction into interstate commerce. *See, e.g., U.S. v. Prigmore*, 243 F.3d 1, 4 (1<sup>ST</sup> Cir. 2001). The U.S. Constitution empowers Congress to regulate interstate commerce, and Congress, via the FDCA, has delegated powers to approve for interstate commercial distribution new medical devices that satisfy safety and efficacy conditions.

Under the FDCA's implementing regulations, commercial distribution means "any distribution of a device intended for human use which is held or offered for sale..." 21 CFR § 807.3(a). Therefore, a clinical laboratory would be subject to FDA regulation as a device establishment only if it produced an *in vitro* diagnostic product (device) for sale. When laboratories engage in testing using laboratory-developed assays, however, they are engaged in a process that does not involve any sale or distribution of a device to a third party. Thus, the

absence of any agency clearance or approval for these services would constitute a violation of law on the part of a clinical laboratory, the Draft Guidance is a substantive rule, which is only permissible when the appropriate notice and comment procedures have occurred. *Id.*; *see also Ball Memorial Hospital v. Leavitt*, 2006 WL 2714920 (D.D.C. 2006).

Under FDA's Good Guidance Practice rules, guidance documents "do not legally bind the public or FDA" and entities "may choose to use an approach other than the one set forth in a guidance document." 21 CFR § 10.11(d). However, it does not appear that other options are available to laboratories in this case. If the Draft Guidance, when finalized, would not be legally binding, then clinical laboratories offering test services that FDA would consider to be IVDMIAs would not be required to undergo pre-market review before offering these assays in clinical practice and would not be required to follow FDA post-market requirements, such as Quality System Regulations, once the test services are offered commercially. However, what approach other than pre-market review and compliance with post-market requirements is open for a laboratory to pursue? Given the lack of other options, and the risk of FDA enforcement action for non-compliance, it is difficult to see how the current document can reasonably be considered "guidance." As such, the subject matter of the Draft Guidance should be vetted through the formal, on-the-record notice and comment rulemaking procedures of the Administrative Procedure Act.<sup>2</sup>

#### ***B. Changing An Advisory Opinion Also Requires Notice and Comment***

FDA's prior history with regard to ASRs and laboratory developed tests also supports the need for a formal notice-and-comment rulemaking. Should FDA decide not to engage in a rulemaking process for IVDMIAs, its change in policy regarding laboratory-developed tests still requires a procedural action other than the issuance of the Draft Guidance. Specifically, several years ago, FDA adopted the approach of regulating most analyte specific reagents (ASRs) using general controls and exempting them from premarket notification requirements as the least burdensome approach (the ASR Rule). This approach relies primarily on current Good Manufacturing Practices (cGMPs), medical device reporting, and labeling requirements, along with the CLIA, to adequately control the risks associated with these devices. 62 Fed Reg. 62243, 62252 (Nov. 21, 1997). *See also* FDA, Draft Guidance for Industry and FDA Staff:

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jurisdictional prerequisite to FDA regulation is absent when clinical laboratories develop and use laboratory-developed assays.

<sup>2</sup> The broad impact, and the binding nature of this document, distinguish it from the types of Guidance documents, which were the subject of a recent memorandum from the Office of Management and Budget (OMB). *See* OMB, Final Bulletin for Agency Good Guidance Practices (Bulletin No. 0702) (Jan. 18, 2007). As noted there, agency actions, such as FDA's in this case, "which do not merely interpret existing law or announce tentative policy positions, but which establish new policy positions that the agency treats as binding, must comply with the APA's notice and correct requirements, regardless of how they initially are labeled." *Id.* at 3.

Moreover, despite the new procedures that are laid out in OMB's memorandum for Guidances, a regulation is still subject to greater procedural and substantive safeguards than exist for Guidances. These include justification and analysis, such as required under the Regulatory Flexibility Act, review by OMB, congressional oversight, access to judicial review, and publication in the Code of Federal Regulations. As a result, ACLA believes a formal rulemaking is still the required approach.

*Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions* (Sept. 2006), available at: <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>.

In the preamble to that rule, FDA stated that the ASR Rule does not extend to tests developed in-house by clinical laboratories, whether or not using commercially available ASRs. FDA also stated that the ASR Rule does not extend to ASRs created in-house and used exclusively by that laboratory for laboratory-developed testing. 62 Fed. Reg. at 62249. In promulgating the ASR Rule, the FDA declined to classify laboratory-developed tests as Class II or III medical devices because, as the agency stated, “FDA recognizes that the use of in-house developed tests has 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.” *Id.* However, in the Draft Guidance, the FDA is seeking for the first time to regulate certain laboratory-developed tests as Class II or III medical devices based on its assertion that without such significant regulatory changes, public health could be placed at risk—an opinion and policy position quite different than that expressed in the ASR Rule.

Under 21 CFR § 10.85(d)(1), a statement of policy made in a preamble of a Federal Register notice constitutes an advisory opinion, which obligates FDA to follow the stated policy until it is amended or revoked. While an advisory opinion may be amended or revoked at any time after it has been issued, FDA is required to give notice of the amendment or revocation. *Id.* § 10.85(g). Notably, the notice of amendment must be given in the same manner as the notice of the original advisory opinion. *Id.* Because FDA set forth its policy regarding laboratory-developed testing in the Federal Register, pursuant to notice-and-comment procedures, if the agency is going to change its policy, then it must follow that same notice-and-comment procedure. *See also Yale-New Haven Hospital v. Leavitt*, \_\_\_ F.3d. \_\_\_, No. 05-1224-CV (2<sup>nd</sup> Cir. 2006); *Motor Vehicle Manufacturers Association of the U.S. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29 (1983); *Ball Memorial Hospital v. Leavitt*, 2006 WL 2714920 (D.D.C. 2006).

## **II. FDA Should Consider Proposals To Narrow and Clarify Its Definition of IVDMIAs To Avoid Unintended Consequences**

As currently written, the Draft Guidance states that IVDMIAs, even if produced as laboratory-developed tests, will be considered Class II or III devices that require premarket approval or clearance. 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, employment of an algorithm, and a result that cannot be interpreted by a health care provider without the help of the test developer. ACLA believes that this definition could be interpreted to apply to many well-established tests using algorithms, such as:

- Prothrombin Time INR
- 24-hour urinary analytes calculated when creatinine is ordered in addition to the analyte to normalize the result

- Creatinine Clearance
- Ionized Calcium (derived)
- Anion GAP
- Globulin
- Estimated Glomerular Filtration Rate (eGFR), a calculated result mandated by certain states
- Maternal biochemical prenatal screening
- HIV or Hepatitis genotyping

The ambiguity of the proposed definition in the Draft Guidance is highlighted by the fact that FDA officials have recently indicated that they did not intend to include well-established tests, including some of those noted immediately above, within the definition of IVDMIAs, and only intended to apply the Draft Guidance to a narrow subcategory of new, emerging, single-source laboratory-developed tests using proprietary algorithms with which physicians are unfamiliar and which the FDA believes they do not understand. However, because it is not possible to identify what is intended to be covered under the IVDMIA definition, more time and energy should be put into crafting an unambiguous and understandable definition, which should be re-issued for comment by the public. For these reasons, if FDA intends to pursue the regulation of IVDMIAs in some way, then its definition should be narrowed and clarified 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 as an acknowledgement that FDA has the authority to regulate these test 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 more narrow definition of IVDMIAs:

- A new, single-source test system,
- That uses clinical data derived from one or more *in vitro* diagnostic assays together with a proprietary, non-published algorithm, and
- Generates 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, and
- Presents significant safety and effectiveness risks not present in test systems that have become part of the standard of care.

Moreover, certain factors, if present, should indicate that FDA regulation is not warranted, because the test would not meet the criteria listed above. Therefore, test systems which meet one or more of the following guidelines should not be deemed IVDMIAs:

1. *Low-risk Consequences of Invalid or Inaccurate Test Result.*

- a. The test is not intended to be used alone to make a diagnosis or to guide a treatment decision, but rather is intended to be an additional assessment tool to be used with other accepted diagnostic tests or medical procedures prior to (i) establishing a definitive diagnosis of a disease/condition or (ii) using the test result in the cure, mitigation, treatment or prevention of disease; or
- b. The test is not the only available diagnostic, prognostic, or predictive tool for the condition being evaluated; or, if the test offers information that cannot be obtained through the use of any other test, the result can be confirmed through a combination of other accepted diagnostic tests or medical procedures; or
- c. The test result does not specifically direct the use or non-use of another FDA-approved product or therapy.

2. *Independent verification.* Claims made about the test and the test results themselves are independently verifiable; or the test is validated and a test for the same condition is offered at multiple clinical laboratories, permitting inter-laboratory proficiency assessment.

3. *Support of Clinical Validity in Peer-reviewed Literature.* The clinical validity of the test is supported in independent studies published in recognized, peer-reviewed, scientific journals, including either retrospective or prospective studies that examine and define performance across different populations or study groups.

4. *Transparent Algorithms.* The test uses one or more algorithms that have been described in detail in at least one article published in a recognized, peer-reviewed, scientific journal.

5. *Interpretation Support for Clinicians.* The test result is accompanied by performance characteristics or other guidance to assist the ordering clinician in understanding and interpreting the test result.

6. *Support in Clinical Guidelines.* Use of the test is supported in clinical guidelines published by recognized professional organizations.

7. *Established Use.* The test has been performed regularly as a laboratory developed test for a period of at least one year without any MDR reportable events (as described under 21 CFR § 803.3) that would be reportable if the test had been subject to FDA pre-market clearance or approval.

8. *CPT Code Assignment.* A Category I CPT code to report the test service has been approved for release by the AMA's CPT Editorial Panel.
9. *Payer Recognition.* The test is covered for reimbursement by both public and private third party payers.

### **III. FDA Should Collaborate With CMS to Address Its Concerns Through Enhancement and Better Enforcement of CLIA Regulations**

ACLA firmly believes that the most appropriate regulatory scheme for clinical laboratories continues to be the one that Congress specifically designed to regulate laboratories – CLIA. CLIA is a comprehensive set of rules that CMS implemented through extensive regulations, which ensure the accuracy and reliability of all laboratory tests. ACLA believes that many of FDA's concerns could be addressed through CLIA's regulatory scheme. Therefore, FDA should also consider working with CMS, 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. As a regulatory framework specifically designed for clinical laboratories and the services they provide, a CLIA approach could avoid the difficulties associated with regulating services under a regulatory framework designed for commercially manufactured and distributed products.

#### **A. CLIA Is a Viable Regulatory Scheme for Clinical Laboratory Services**

The clinical laboratory industry is one of the most highly regulated health care delivery sectors. Virtually all laboratories performing patient tests must be certified pursuant to CLIA. Congress clearly intended for CLIA to be the controlling mechanism for regulating laboratory testing services, as it expressly noted when enacting CLIA that "the current system offers a patchwork of inconsistent and overlapping standards that leaves some laboratories trying to comply with multiple layers of regulation." S. REP. NO. 561, 100<sup>TH</sup> CONG., 2D SESS. 3-4 (1988); H.R. REP. NO. 899, 100<sup>TH</sup> CONG., 2D SESS. 11 (1988).

CLIA constitutes a comprehensive regulatory scheme that governs nearly every aspect of a laboratory's performance of testing. All laboratories certified under CLIA must meet specified standards in the areas of proficiency testing, quality assurance, patient test management, and personnel. In addition, laboratories certified to perform either moderate or high complexity testing are inspected very two years by state agencies acting under agreement with CMS or by CMS-approved accreditation organizations. Furthermore, the CLIA regulations specifically address and establish requirements for those test systems, assays, and examinations that are not commercially available and not subject to FDA review. Consequently, there is no need for additional, concurrent oversight of these processes.

Based on various public statements, it appears that the FDA has three essential concerns that have prompted it to issue the Draft Guidance. The first is the FDA's observation that the CLIA validation process only requires that laboratories validate the analytic performance characteristics of tests and its conclusion that no regulatory agency determines the clinical validity of laboratory-developed tests in general, or laboratory-developed IVDMIAs in

particular. Second, the FDA has expressed concern about the use of “algorithms” incorporated in some laboratory-developed tests that are not transparent to the end user, who therefore cannot interpret the algorithm’s role in the final test result. Third, FDA is concerned when other laboratories cannot replicate the end point of the test due, at times, to the proprietary nature of the underlying data.

The FDA’s conclusion that CLIA itself does not have an impact on clinical validity is unwarranted. The laboratory director of a high complexity laboratory—the only type of laboratory that could create and perform an IVDMA—is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures, record and report test results promptly, accurately and proficiently, and for assuring compliance with the applicable regulations. 42 CFR § 493.1445. More specifically, CLIA regulations under 42 CFR § 493.1445(e) explicitly require the laboratory director to ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this responsibility is the clear regulatory imperative to choose medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies could not be said to be “required for patient care.”

Regarding FDA’s concern about laboratory use of “algorithms” in some laboratory-developed tests to arrive at an “index” or “score” type of result that is not transparent to the end user (the ordering physician) and which cannot be replicated by other laboratories due to the proprietary nature of the underlying data, we note that the CLIA regulations sufficiently address these concerns. Specifically, the mandate that a laboratory validate the performance characteristics of laboratory-developed tests includes a requirement to validate the performance of any algorithm or formula that the laboratory relies upon to issue a result. *Id.* § 493.1253(b)(2). This is made clear by the requirement that the laboratory establish “any other performance characteristic required for test performance.” Notably, the College of American Pathologists (CAP) requires that laboratories provide information on each of the algorithms used by the laboratory as part of its inspection program for accreditation. In addition to the CAP requirement, some state programs, such as the New York program, further require specific information about algorithms and their validation data before any tests can be performed for residents of those states.<sup>3</sup>

In addition, CLIA makes the laboratory director responsible for ensuring that the laboratory engages qualified personnel to develop and perform tests. That, along with the other requirements, is designed to ensure on-going quality in the performance of testing. CLIA also requires the laboratory to have a clinical consultant, who “must be qualified to consult with and render opinions to the laboratory’s clients concerning the diagnosis, treatment and management of patient care.” *Id.* § 493.1455. The responsibilities of the clinical consultant are to provide information about the “appropriateness” and “interpretation” of the test results. *Id.* This clinically focused responsibility is essentially the determination that the FDA would make about a product’s clinical validity.

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<sup>3</sup> Because New York imposes its regulatory authority on laboratories testing specimens received from New York, any laboratory that offers a test on a nationwide basis, must comply with New York’s pre-market requirements.

Furthermore, CLIA makes the laboratory director responsible for ensuring that the ordering physician can properly interpret results by requiring the laboratory to include pertinent interpretive information in the reports and make consultation available to its clients regarding the quality of the test results and their interpretation. The CLIA regulations thus clearly require that a test have both clinical validity and transparency by requiring the laboratory director to select clinically relevant tests and provide clinical interpretation for those tests.

***B. Where Warranted, CMS Clarification of CLIA Regulations Should Adequately Address FDA Concerns***

Where FDA has identified certain areas of concern, the CMS laboratory regulations can be clarified to deal more specifically with those concerns. FDA has consistently stressed the importance of “smart regulation” and following the “least burdensome” approach. Thus, where possible, the existing CLIA regulatory process should be used, and enhanced where necessary, to address the concerns of the FDA and to avoid imposing additional burdensome regulatory requirements that are ill-suited to laboratories and would be incredibly resource-intensive for the FDA to enforce.

Specifically, we believe that CMS could amend the Interpretive Guidelines for Laboratories—which provide insight to laboratories and inspectors regarding CMS’ interpretation of the CLIA regulations—to give the laboratory director guidance on how to select clinically relevant testing. Changes to the Interpretive Guidelines could include some or all of the following clarifications:

- The Laboratory Director of the clinical laboratory would be responsible for ensuring that all tests offered by the laboratory are clinically relevant and based upon sound science.
- A test would be deemed to be clinically relevant if its use is well established in clinical practice, described in medical textbooks, or supported by peer-reviewed literature. Unless such references are readily available to the ordering physician, then, upon the ordering physician’s request, the laboratory would be required to make available to the ordering physician full reprints of the supporting literature upon which the Laboratory Director relied in determining the clinical relevance of the test, including, where applicable, studies representing differing views of clinical relevance.
- If the use of the test is not supported by peer-reviewed literature (e.g., a test for a rare condition for which no clinical studies have been reported), the laboratory offering the test would be required to make available to the ordering physician upon his or her request:
  - the data upon which the laboratory relied in determining the analytic performance characteristics of the test, and
  - if available, any additional data or studies upon which the Laboratory Director relied in determining the clinical relevance of the test, including studies reporting conflicting findings in terms of clinical relevance.

- As part of its validation process, the laboratory is already required to validate any algorithm used to determine any calculated result (e.g., score, index, classification, etc.). However, in addition, the laboratory also could be required to make available to the ordering physician, upon his or her request, a general description or explanation of the scientific basis and rationale for the algorithm, as well as examples of the algorithm's application using representative patient result data.
- The laboratory would make available to CMS or to representatives of its accrediting agency, upon request:
  - its analytic validation studies, including the analytic validation studies for algorithms and the underlying data upon which the laboratory relied in determining the analytic performance characteristics of the test, and
  - the references to textbooks, peer-reviewed literature, and other data or studies, if any, upon which the Laboratory Director relied in determining the clinical relevance of the test.

Thus, existing laws and regulations—which may be easily clarified through modifications to the Interpretative Guidelines—serve to adequately provide the proper assurances that laboratory developed tests are medically valid, useful, and properly validated. Further, CMS has broad enforcement authority under CLIA. Not only can it revoke or suspend a laboratory's license, where the laboratory has not complied with CLIA requirements, but it also can impose civil monetary penalties and require on-site monitoring. Finally, it can also seek an injunction in federal court where there is a significant hazard to public health. 42 USC § 263a(h)-(j).

Not only is CLIA sufficient to deal with these issues, but also adopting a CLIA solution avoids the difficult regulatory problem of how to concurrently and consistently apply both FDA's Quality System Regulations (QSRs) and the CLIA requirements to the laboratory and laboratory services. In addition, FDA requirements for medical device labeling and promotion would create additional problems when IVDMIAs are used in a clinical laboratory setting. In Appendix A to these comments, we have provided a more detailed explanation of the differences – and inconsistencies – between the two regulatory frameworks.

ACLA recognizes that there may be some concern regarding whether CMS, and the various inspection agencies that it uses to inspect and enforce CLIA, have the necessary resources to carry out such increased obligations. To the extent this is a concern, then steps can be taken to ensure that the various agencies have the resources they need to fulfill their responsibilities. ACLA would be happy to work with HHS to discuss what steps should be taken to reach that goal.

### **C. Other Mechanisms Also Exist for Ensuring the Validity of Testing**

To the extent that some outlier laboratories or other providers offer testing that may be of questionable clinical validity, there are other mechanisms in place to protect consumers. First, in most instances, a patient's physician, who acts as an intermediary between the laboratory and the patient, orders testing. It is the physician's professional obligation to ensure the appropriateness of laboratory testing, just as they do for all other services they order for their patient. If a physician has concerns about a laboratory test or the testing procedure, then he or she can review the literature from the laboratory, contact the clinical consultant, or review the studies relied upon by the laboratory.

Physicians, particularly those specialized in a given area who are the most likely to order tests that fit the Draft Guidance's IVDMA designation, routinely inform themselves about the nature of the testing they order on behalf of their patients. Moreover, in the laboratory context, the laboratory test is almost always one of several diagnostic and predictive tools used by the physician. It is unusual for a laboratory test to be the sole basis on which the physician decides to act.

Finally, to the extent that laboratories or other providers are offering testing that is clearly without medical value, the Federal Trade Commission and other federal agencies routinely constrain various forms of medical "quackery," as do state attorneys general. Thus, existing mechanisms can deal with those providers who offer a medical test that is without medical value, without the need for instituting additional corrective mechanisms through the FDA.

### **IV. FDA's Draft Guidance and Regulations Will Stifle Innovation**

Because the Draft Guidance requires FDA preclearance or approval of IVDMA's before a laboratory may commercially offer the test, the ability to innovate quickly will be precluded. This could have a profound impact on healthcare delivery and the practice of medicine. Currently, laboratory tests may arise either in response to an unmet clinical need (as identified by the physician) or arise from a scientific development or discovery (as identified by the scientist). As such, laboratory tests are the natural outgrowth of the ongoing advancements taking place in medical science.

Thus, new laboratory tests are essentially an ongoing service to the underlying customer. While thousands of such tests are created in academia every year, only a handful of these tests are promoted to broad commercial markets. As such, the ability and flexibility that various laboratories (including those in academic institutions) have to respond to emergent medical needs enables those laboratories to offer services that would never generate the financial and operational parameters necessary to allow broad commercial introduction of an *in vitro* diagnostic test kit.

In many cases, no *in vitro* diagnostic device manufacturer will ever manufacture a kit for such tests. If all laboratories were required to preclear their tests with FDA, then many tests would simply not be made available by laboratories, just as they are not offered by any kit manufacturer. The volume of certain tests and the number of people who need these tests often

are relatively small. Yet, laboratories perform these tests because they are ordered by physicians—i.e., laboratories are providing critical diagnostic tests as a service to physician clients who specialize in certain diseases and disorders.

Because of the small volume for some of these tests, it is not feasible for any laboratory to commit to the time and expense of submitting a 510(k) or PMA to the FDA before being able to offer a test. Additional road blocks placed in this process would subsequently have an adverse impact on patient care for many diseases and disorders that currently have adequate diagnostic services.

## V. Conclusion

In conclusion, because compliance with the Draft Guidance would require laboratories to adhere to new requirements that were not appropriately promulgated, ACLA respectfully requests that FDA promulgate a proposed rule and invite stakeholder comments. In addition, because the Draft Guidance could be interpreted to apply to many well-established tests that are part of the standard of care, ACLA requests that FDA consider proposals to narrow and clarify the IVDMA definition in order to avoid unintended consequences. Finally, Congress enacted CLIA and CMS wrote regulations to implement CLIA for the purpose of comprehensively regulating laboratories and ensuring the quality of laboratory services. To meet the FDA's concerns, the CLIA regulations can be clarified through changes to the Inspection Guidelines for Laboratories. 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, ACLA encourages FDA to consider working with CMS (through HHS) in this manner.

We appreciate the opportunity to comment on FDA's Draft Guidance regarding IVDMIAs. We also look forward to working with the agency to ensure that the purposes of the Draft Guidance are achieved in an expeditious and practical manner.

Sincerely,

Handwritten signature of Alan Mertz in cursive, with the initials "SDB" written at the end of the signature.

Alan Mertz  
President

**APPENDIX A**  
**Docket No. 2006D-0347**

**IT IS DIFFICULT FOR CLINICAL LABORATORIES TO COMPLY WITH BOTH  
CLIA AND FDA REGULATIONS BECAUSE THESE REGULATIONS ARE OFTEN  
INCONSISTENT OR INCOMPATIBLE**

Fundamental differences between the regulatory approaches of the FDA and of CMS, built into their respective regulatory schemes, make simultaneous compliance with both sets of regulations difficult and impractical for most laboratories. FDA's quality assurance system requirements, the Quality Systems Regulations (QSRs), do not mesh well with CMS' quality assurance requirements under the CLIA. In addition, FDA requirements for medical device labeling and promotion create possible problems when IVDMIAs are used in a clinical laboratory setting.

**A. *FDA's QSRs vs. CLIA Regulations***

FDA's QSRs are intended to produce essentially identical products—from the first lot to the last. The regulatory focus of the QSRs is to ensure that device manufacturers follow the required design and manufacturing controls with full traceability to investigate and recall products that do not meet performance claims. In addition, FDA's premarket review process is designed to produce the appropriate level of oversight relative to risk before commercialization of the products.

CMS oversight under CLIA, by contrast, covers thousands of laboratories, each performing a given test its own way, including tests using FDA cleared or approved products, but perhaps modified in some way by a laboratory. Rather than focusing on trying to standardize the manner in which each laboratory performs its own testing, the CLIA regulations focus on the standards that each laboratory must meet to produce accurate and reproducible test results. Under these regulations, laboratories must have the necessary facilities and equipment, must have and follow their specific standard operating procedures, must meet standards for shipping and handling and timely reporting systems, must engage in quality control and utilize proficiency testing, and must have skilled employees and professional oversight.

In contrast to the QSR approach ensuring the production of standardized products, the CLIA approach focuses on requiring all laboratories to build and follow systems that will ensure they achieve accuracy and reproducibility of their testing despite the variability in how different laboratories perform similar testing. Checks such as pre-implementation test validation, quality control with each run, trending of results, and proficiency testing to compare test results with other laboratories, are all part of the built-in quality process. The quality and oversight built into CLIA standards should not be undervalued.

Moreover, it would be difficult to determine exactly how to concurrently and consistently apply both the QSR and the CLIA requirements to the laboratory and laboratory services. Laboratories are concerned that treating laboratories as IVD manufacturers for purposes of compliance with FDA laws and regulations will create confusing and conflicting sets of

standards that will be problematic for a single entity to follow. For example, QSR requirements include highly prescriptive design controls that may be appropriate for a manufacturer that makes standardized products used by many laboratories, but which are not necessarily appropriate for a single laboratory performing its own laboratory-developed test. Similarly, it would be difficult to know where the "manufacturer" part of the entity ends and the laboratory begins; that is, what personnel and physical part of the entity would be subject to FDA regulation and inspection, and which would not.

***B. It is Unclear How Labeling Requirements Would Apply***

The Draft Guidance is silent on how labeling requirements applicable to medical devices would apply to IVDMIAs. Specifically, under 21 CFR § 809.10(a), a medical device label must include the proprietary name and established name of the product, the intended use, warnings or precautions, the statement "For In Vitro Diagnostic Use," name and place of business of the manufacturer, and lot or control number. Where FDA deems that certain laboratory-developed tests are IVDMIAs, it is not clear where this label is to be affixed, or what would constitute a lot or control number. For example, would each run constitute a lot? If so, would the label need to be updated for each run?

In addition, 21 CFR § 809.10(b) requires a package insert to accompany each medical device. Among other things, the package insert must bear the proprietary name and established name of the product; the intended use of the product, summary and explanation of the test, including a balanced statement of the special merits and limitations of the method or product; a step-by-step outline of the recommended procedures from receipt of the specimen to obtaining results; and specific performance characteristics, including accuracy, precision, specificity, and sensitivity.

Where FDA deems that certain laboratory-developed tests are IVDMIAs and the laboratory would therefore be required to adhere to the package insert requirements, to whom is this package insert to be shipped (i.e., who is the end user)? Because the laboratory is not only developing the test, but is also making use of it, FDA's typical regulatory scheme does not really apply here. If this information is to be provided to the ordering physician, then many of the elements required to be included in the package labeling are irrelevant. In addition, it is not clear how the package insert is to be provided to the referring physician (e.g., included with each test report?).

Furthermore, under 21 CFR § 809.30(e), a laboratory that develops a laboratory-developed test using an analyte specific reagent (ASR) is required to append to the test report the statement: "This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration." This disclaimer is not required when test results are generated from tests cleared or approved in conjunction with review of a Class II or III ASR. Thus, if an IVDMIA were developed using a Class II or III ASR that the IVDMIA developer/laboratory purchased from an ASR manufacturer, would the exception to the required disclaimer apply?

Numerous other questions arise in trying to harmonize the QSR and CLIA requirements. Because the Draft Guidance generates such limitless questions affecting the manner in which clinical laboratories conduct their day-to-day activities, this document is essentially a rulemaking. Several of the most challenging questions are discussed below.

1. Would CLIA Requirements Constitute Labeling Under FDA Regulations?

The Draft Guidance makes it difficult for laboratories to harmonize CLIA requirements for test requisition forms and reporting with FDA labeling requirements and promotional restrictions. For example, CLIA requires that certified laboratories have a written or electronic request for patient testing which solicits, among other things, the name and address or identifier of the person requesting the test, patient name or identifier, patient sex and age, the test(s) to be performed, the source of the specimen, and any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results. 42 CFR § 493.1241.

Would FDA construe the test requisition form to be part of the FDA-cleared or approved labeling? If so, would modifications to the requisition form be subject to pre-market review procedures for supplemental medical device updates? Would the laboratory have to seek a supplemental clearance/approval for a modification to the requisition form if it needs to change the form to obtain additional information when necessary for a specific test, as required by CLIA? Where the answers to any of these questions are “yes,” then the binding nature of these requirements greatly impacts the typical activities of clinical laboratories. As such, FDA can only institute such changes through notice-and-comment rulemaking.

Similarly, 42 CFR § 493.1291 requires that certified laboratories provide a test report that must indicate, among other things, the patient’s name, name and address of the laboratory where the test was performed, the test performed, specimen source, the test result, and any information regarding the condition and disposition of specimens that do not meet the laboratory’s criteria for acceptability. Would FDA construe this test report to be part of the product labeling? If so, would modifications to the report form be subject to potential pre-market review? Again, where the answers to these questions are “yes,” then notice-and-comment rulemaking is required because of the effect upon daily laboratory activities.

CLIA also puts an affirmative obligation on the certified laboratory to update testing information whenever changes occur that affect the test results or the interpretation of results. For many tests, such changes are virtually constant—e.g., laboratories routinely update what they learn about the implications of test results. In genetic testing, the impact of observed mutations may be evolving constantly. For drug resistance assays, the import of results will change as new drugs are developed and new resistance patterns emerge. Would each such change require an updated filing with FDA? If so, the Draft Guidance is likely to significantly impede the development of new and worthwhile scientific discoveries. Moreover, a requirement to seek FDA approval before utilizing such information would conflict with the laboratory’s requirement under CLIA to keep referring physicians informed.

## 2. Additional Labeling Issues

CLIA regulations clearly contemplate that laboratories may modify FDA cleared/approved test systems and require that laboratories validate such modified test systems before patient use. Specifically, each laboratory that modifies an FDA cleared or approved test system, or introduces a test system not subject to FDA clearance or approval, must, before reporting patient test results, establish performance specifications for each test system (i.e., specifications regarding accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals [normal values], and any other performance characteristic required for test performance. 42 CFR § 493.1253(b)(2). Based on the Draft Guidance, it is not clear whether certified laboratories would be able to modify an IVDMA consistent with CLIA regulations, or whether such laboratories would be required to strictly follow FDA labeling requirements.

Finally, CLIA-certified laboratories may receive requests to test specimens shipped from outside the US for testing at the certified US laboratory, as long as the relevant requirements are met for import/export, international specimen shipping, and state laboratory operations. Given the Draft Guidance, would the performance of an IVDMA test on specimens shipped from outside the US be considered exportation of a medical device? Would the package insert need to be shipped to the referring physician outside the US? These questions are of the type that necessarily will arise as a result of blurring the line between medical device and laboratory service. We are therefore interested in working with FDA to alleviate the possible challenges that may occur in this area.

### **Conclusion**

For the reasons set out above, it will be difficult for laboratories to comply with both QSRs and CLIA, a concern that highlights the differences between the two regulatory schemes. As a result, as explained in the body of our comments, the Guidance should be withdrawn, and reissued as a rule so these issues can be addressed fully.