



Better health through  
laboratory medicine.

January 29, 2015

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for Clinical Chemistry (AACC) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) draft guidance "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)," which outlines the agency's proposal for regulating LDTs. Although we share the FDA's goal to improve the safety and effectiveness of LDTs, AACC does not believe this proposal accomplishes that goal. We recommend that the agency limit its oversight to a narrow group of high risk tests.

AACC is the principal scientific association of professional laboratorians—including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and practice 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 medicine and its applications to health care.

### **Current Regulatory Structure**

There appears to be a misconception that because the FDA is using its "enforcement discretion" in regards to LDTs that these tests are unregulated. This belief is inaccurate. LDTs are currently subject to a variety of oversight mechanisms at the federal and state levels and by professional accreditation organizations. Expanding oversight to include another federal agency will, in many instances, add to the regulatory burden and costs of performing LDTs, possibly resulting in many laboratories discontinuing these tests.

Currently, all laboratories performing LDTs are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). These testing facilities are categorized as high complexity laboratories, subject to stringent personnel, quality control and proficiency testing requirements as well as regular inspections. Many of these same high complexity facilities participate in the New York, Joint Commission, College of American Pathologists or other oversight programs. Under the existing structure, clinical laboratories continuously evaluate the analytical and clinical performance of all tests performed by their staff. It is through the use of robust quality practices and tools that laboratories identify shortcomings, allowing them to take steps to avoid failure and errors – regardless of the source of a test.

AACC believes it is important to remember that the FDA regulatory structure is designed for medical device manufacturers, not clinical laboratories. Manufacturers provide invaluable test kits and instrumentation that assist laboratories in providing accurate test results. Laboratories that occasionally modify FDA cleared or approved tests do so to meet specific clinical needs. The laboratory providing this service is not a medical device manufacturer, but a group of health care professionals engaging in the practice of laboratory medicine with the intent to provide safe and effective testing. The results from these tests are used by other health care providers in the care of their patients. To apply FDA regulatory requirements to all hospitals and independent laboratories utilizing LDTs would be misguided and counterproductive to excellent patient care.

### **Clinical Validity**

AACC agrees that clinical laboratories using LDTs should demonstrate the analytical and clinical validity of the test prior to its use. Laboratories should continue to use multiple approaches to establishing the predictive value of a test, including reviews of the scientific literature, independent assessments of patient outcomes, and use of guidelines and clinical protocols. Those laboratories subject to New York, CAP or Joint Commission oversight already meet this objective.

### **Categories for Continued Enforcement Discretion**

There are many medical conditions for which it is not cost-effective for an IVD manufacturer to develop a commercial assay. Clinical laboratories have traditionally filled this void through LDTs. A comprehensive list of such laboratory tests would be quite lengthy and include categories such as testing for rare diseases, newborn screening, emergency testing, modified test kits and testing involving world health issues, such as the recent Ebola virus outbreak. Rather than focusing on those categories for enforcement discretion, we suggest the FDA direct its attention towards identifying the narrow group of high risk tests that should be subject to joint FDA and CMS oversight.

In the draft guidance, the agency identified a number of testing categories that it plans to exempt from pre-market review, such as rare diseases and tests with unmet needs, if they meet certain criteria. We have concerns regarding the FDA's proposals for these categories. The agency suggests that a disease that involves less than 4,000 tests annually would be exempt. AACC asserts that defining the limit based on this small number of tests, rather than on number of disease incidents, would have the unintended consequence of restricting access to certain critical tests. For example, under the FDA's proposed criteria, nearly every newborn screening test on the Health Resources and Services Administration recommended list would be subject to pre-market review. We recommend that FDA work with the health care community to determine the appropriate level of incidents that must occur annually to qualify for this exemption.

Similarly, the FDA is proposing to remove the unmet needs exception for LDTs once a test is approved or cleared by the agency for that condition. We are concerned that this approach would stifle innovation and potentially diminish the quality of care. As was mentioned at the

FDA public workshop, agency approval or clearance does not mean a test is the best—just that it met a threshold established by the agency. In many instances, the LDT may be the better test. Forcing clinical laboratories to submit these LDTs for pre-market review would most likely result in their discontinuation for that condition. This would stifle laboratory medicine and negatively impact patient care.

### **Public Process for Classification and Prioritization**

AACC agrees with the proposed risk-based classification approach for determining the level of oversight for LDTs. This regulatory scheme should include three categories: high, moderate, and low. We recommend that professional laboratory associations, such as AACC, medical societies, medical device manufacturers and other stakeholders work in collaboration with the FDA to identify criteria and categorize LDTs prior to implementation.

AACC recommends the following as possible criteria for designating tests as high risk:

- the accuracy of the test cannot be independently verified;
- there is a lack of transparency regarding the underlying data to support claims made about the test; and
- the absence of professional consultation/interpretation could lead to serious patient harm.

Examples of high risk tests include In Vitro Diagnostic Multivariate Index Assays (IVDMIAs) and direct-to-consumer genetic tests.

### **Notification**

FDA wants to collect data regarding 14 elements for each LDT developed and performed by a laboratory. AACC is concerned that this process is redundant and costly and presents undue administrative burden to many clinical laboratories. Much of this information is already collected by the Centers for Medicare and Medicaid Services (CMS) CLIA'88 program and/or its deemed accrediting bodies. We recommend that FDA work with CMS, the College of American Pathologists and other CLIA-approved organizations to gather these data. AACC suggests that these data be gathered during routine CLIA inspections.

### **Post-Market Controls and Supplemental premarket submission**

Post-market controls require the evaluation of patient events (and near-events) as a consequence of LDT failures, malfunctions and use-errors. Which types of events should be reported is subject to debate, as most laboratories using LDTs have internal laboratory controls associated with the analysis to detect analytical and pre-analytical errors and prevent wrong results from being reported. These laboratories also have processes for investigating and reporting such events to CMS and/or relevant accrediting bodies. We support the establishment of a reporting mechanism for failures and significant errors for those LDTs to be classified as high risk to enable the identification of trends and weaknesses associated with particular tests or methodologies.

Regarding the issue of supplemental pre-market submissions for high risk LDTs that may be subject to regulation by FDA, only those modifications that change the intended use should be subject to supplemental premarket submissions. If a modification to a test improves analytical performance, but does not change the intended use or interpretation of the test, then no supplemental review should be required – to do otherwise would prevent laboratories from engaging in process improvement.

### **Product Labeling**

Most LDTs are created to meet a specific and highly specialized clinical need for particular patients under the care of medical institutions served by a given laboratory. The LDT results are applied in light of specific clinical management pathways designated for the target population of patients and are incorporated into specific treatment plans in consideration of clinical and other diagnostic information to make the best treatment decisions. These tests are being utilized in conjunction with best practices of care and through direct interactions with clinicians and other clinical information.

Although LDTs performed within a clinical laboratory are not currently subject to FDA labeling requirements, the laboratory must comply with disclosure obligations prescribed by CMS and its deemed accrediting bodies. These criteria stipulate that results from an LDT must be accompanied with a statement that the data were produced using a method that has not been reviewed by the FDA and was developed by the reporting laboratory. Similarly, CAP requires the use of a disclaimer when the laboratory is asked to perform a test/analysis that has not been validated by the FDA process. The statement often includes the caveat that the provider must interpret the results in the context of the total patient findings.

### **Relationship between FDA and CMS**

The FDA is responsible for regulating commercial IVD medical device test kits that have been cleared or approved for use in clinical laboratories. Commercial IVD medical device manufacturers must research and develop the test, acquire evidence to support its intended use and indications, meet various quality system controls and comply with marketing, labeling and post-market surveillance requirements. These companies are also subject to periodic inspections and pay user fees to the FDA.

Clinical laboratories utilizing LDTs under the existing CLIA '88 regulations must go through a similar process of research, development, performance evaluation, quality assurance and inspection, but are subject to different regulatory requirements. An IVD medical device is a product sold typically to a large number of unaffiliated and diverse clinical laboratory providers by a broad range of foreign and domestic commercial entities, whereas LDTs developed in clinical laboratories provide a service offered to well-known and affiliated physician partners.

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AACC believes the current CMS oversight process should remain in place for the vast majority of LDTs. CMS and FDA should work together, however, to streamline any overlap between the two agencies regarding oversight of high risk laboratory tests, particularly in regards to test validation (many laboratories performing high risk tests may already be participating in a private sector accreditation program that requires clinical validation prior to introducing a test), quality control and post-introduction test evaluation. This collaborative effort should also consider the important role that private sector accreditation bodies play in LDT oversight

#### **Administrative Procedures Act**

AACC is concerned that additional regulatory oversight by the FDA may significantly increase the costs of developing and performing these tests, possibly stifling innovation and forcing many facilities to stop offering these tests. Given the significant expansion in federal oversight proposed by the FDA, and the possible consequences of its actions, AACC believes that the agency should follow the rulemaking process outlined in Administrative Procedures Act. Following the APA would ensure greater transparency and accountability on the part of the agency by requiring it to respond to all public comments and explain the rationale for its policy decisions. The FDA would also be required to conduct an economic analysis of the regulatory changes and report the potential costs and burdens on affected parties, including consumers, thus informing policymakers and the affected community of the potential impact of the proposed changes.

In summary, AACC believes the current regulatory structure for LDTs is adequate. Joint FDA and CMS oversight should be limited to a narrow group of high risk tests determined by the government agencies and a broad cross-section of the stakeholder community. We are concerned that duplicative, costly federal oversight will stifle test innovation and hinder patient care.

We look forward to the FDA's continued engagement of the stakeholder communities in this process. If you have any questions, please call me at (404) 616-5489, or Vince Stine, PhD, AACC Director of Government Affairs, at (202) 835-8721.

Sincerely,



David D. Koch, PhD, DABCC  
President, AACC