



Better health through
laboratory medicine.

January 5, 2015

Representative Fred Upton
Chair, Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton:

The American Association for Clinical Chemistry (AACCC) welcomes the opportunity to provide input regarding the Energy and Commerce Committee's 21st Century Cures initiative, particularly in response to your questions regarding laboratory developed tests (LDTs). In general, we have serious concerns about the Food and Drug Administration's (FDA's) plans to expand its oversight to all LDTs.

Traditionally, the Center for Medicare and Medicaid Services (CMS) and various states and private sector accrediting organizations have provided effective oversight of LDTs. Without documented evidence of a problem we are concerned that the proposed level of FDA involvement, if implemented, may stifle laboratory test innovation and hinder improvements in patient care.

It's important to note that LDTs of the 21st century benefit patients of all ages, from babies still in their mother's womb who undergo fetal lung maturity testing to newborns who are screened for myriad genetic diseases or conditions. LDTs also aid children who must undergo follow-up testing if indicated by the results of newborn screening tests, as well as subsequent monitoring if a genetic disorder is detected. Bacterial speciation to determine appropriate antimicrobial drug therapy, as well as therapeutic drug monitoring, may help both children and adults who have bacterial infections. These are but a few of the many LDTs that have become critical components of modern patient care. Our specific comments follow.

Stakeholder Access

Testing of patient samples falls within the practice of laboratory medicine. Health care providers within this discipline include pathologists, doctoral level clinical scientists, clinical laboratory technologists and technicians. The positions, roles and responsibilities for these individuals are clearly defined in the regulations implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88). Their responsibilities include conducting the analytical aspects of a test as well as providing guidance on appropriate test utilization and interpretation of laboratory test results.

Laboratories typically develop LDTs to address special needs associated with unique patient populations and in cooperation with physicians to assist in the diagnosis and treatment of their patients. More recently LDTs have evolved as part of many multidisciplinary translational research efforts. Once a new method or test is developed, the laboratory frequently shares its data with other laboratories by publishing its findings in a peer-reviewed scientific journal and/or by presenting a paper and seminar at a scientific meeting. This process allows other testing facilities to critically evaluate and verify the performance and claims of such test methods or to identify issues and make improvements. To limit physician and patient access to these ‘personalized’ tests could result in misdiagnosis, worse patient outcomes and higher health care costs. We suggest that any regulatory changes in this arena be carefully researched and evaluated before adoption.

Current FDA Model and Adoption of Risk-based Model

The FDA regulatory structure for IVD medical devices is not appropriate for the vast majority of LDTs performed by clinical laboratories. The FDA clears and approves IVD medical devices that are marketed to be used in a variety of medical settings by a diverse group of health care personnel. LDTs, on the other hand, can only be performed by high complexity CLIA laboratories under the direction of highly trained and experienced personnel. Although each is invaluable to patient care, LDTs and IVD medical devices are distinctly different tools in the health care process and as such they need to be regulated separately and differently.

AACC supports the use of a risk-based classification approach to differentiate those medical laboratory tests that should be subject to FDA oversight. This classification scheme should identify three risk categories: high, moderate, and low. Only high risk laboratory tests (we expect this to be a small subset of LDTs) should be subject to joint FDA and CMS oversight. We recommend that professional laboratory associations, such as AACC, medical societies, medical device manufacturers and other stakeholders work collaboratively with the FDA to identify criteria and categorize LDTs prior to finalizing the guidance. Two candidates for inclusion in the high risk category are: In Vitro Diagnostic Multivariate Assays (IVDMIA) (IVDMIA are LDTs developed and performed by a single laboratory that cannot be independently validated) and direct-to-consumer genetic tests (predictive tests that may have unsubstantiated test claims and no mechanism for professional interpretation/involvement).

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 LDTs have internal laboratory controls associated with the analysis that will detect many analytical and pre-analytical errors and prevent wrong results from being reported. Those high risk LDTs that experience failures and ultimately impact a patient should be investigated by the laboratory – to change processes and help to prevent recurrences. We also

agree that such occurrences should be publicly reported as part of post-market monitoring 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.

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 the specific clinical management pathway designated for the target population of patients and are often incorporated into an algorithm that includes clinical and other diagnostic information to make the best treatment decisions. These tests are being utilized in conjunction with best practice algorithms 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, the College of American Pathologists 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.

Public Health Testing

The current regulatory structure has permitted clinical laboratories to respond quickly to public health emergencies, such as HIV, SARS & Ebola, develop LDTs for individuals with rare conditions for which it may never be cost-effective for an IVD medical device manufacturer to develop a test, and modify existing commercial IVD kits to meet specific clinician/patient needs. AACC is concerned that additional, duplicative regulatory requirements could obstruct efforts to meet public health emergencies and hinder the innovative abilities of clinical laboratories.

Grandfathering of LDTs and Maintaining Innovative LDTs

Grandfathering existing LDTs is a disincentive for labs to introduce new LDTs. There needs to be a fair and comprehensive system that focuses on high risk laboratory tests, while continuing to allow moderate and low risk tests to be performed under current CMS regulatory oversight.

The development of LDTs plays a critical role in providing new innovative technologies that offer hope and assistance to many patients. The clinical laboratory community has historically been quick to respond to changing clinical and service needs, such as meeting the need for more sensitive and specific therapeutic drug monitoring tests, and filling the gaps when FDA-cleared or approved commercial tests are unavailable. The best means of maintaining this innovative process is to keep the current regulatory structure in place with only minor modifications.

By way of background, 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. 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,



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President, AACC