April 7, 2017

American Clinical Laboratory Association

Representative Larry Bucshon, M.D.
Committee on Energy & Commerce
U.S. House of Representatives
1005 Longworth HOB
Washington, D.C. 20515

Representative Diana DeGette
Committee on Energy & Commerce
U.S. House of Representatives
2111 Rayburn HOB
Washington, D.C. 20515

DELIVERED ELECTRONICALLY

RE: Comments on March 21, 2017 Discussion Draft of the Diagnostic Accuracy and Innovation Act

Dear Representatives Bucshon and DeGette:

The American Clinical Laboratory Association (ACLA) is pleased to provide these initial comments on the March 20, 2017 Discussion Draft "Diagnostic Accuracy and Innovation Act" (hereinafter, DAIA Discussion Draft, DAIA, or Discussion Draft).

ACLA is a trade association representing the nation's leading providers of clinical laboratory services, including regional and national laboratories. Its diverse membership includes a broad array of clinical laboratories: large national independent labs, reference labs, esoteric labs, hospital labs, and nursing home labs. ACLA members both develop and furnish laboratory developed test services (LDTs), in addition to purchasing and performing test services with *in Vitro* Diagnostic test kits (IVDs).

Over the past thirty years, the clinical laboratory industry has been at the forefront of significant advances in molecular and genetic diagnostics. These powerful tools have advanced medical knowledge through levels of accuracy and precision in both screening and diagnostic tests never before contemplated or achievable, and, thereby, better guide diagnosis, and prevention or treatment decisions. Through this innovation, clinical laboratories have played a critical role in reducing medical costs and increasing the quality of patient care.

The current oversight framework has worked well to promote this innovation and advance patient care. In order to continue these advancements into the twenty-first century, however, ACLA believes the appropriate time has arrived to design a new, logical framework that contemplates the future of clinical laboratory diagnostics. We, therefore, support the pursuit of comprehensive statutory reform for the oversight of both LDTs and IVDs through a transparent process with Congress, the Administration, and other stakeholders. ACLA welcomes the DAIA Discussion Draft as an important, transparent step in this process towards enacting reform.

In pursuing reform, ACLA strongly asserts that any new framework must ensure continued innovation and robust patient access to accurate and reliable clinical laboratory diagnostic services. Core principles that will accomplish these paired goals include: 1) reform that recognizes diagnostics as distinct and not inappropriately incorporated into regulatory frameworks designed for other products or services; 2) "grandfathering" and transition policies that will not disrupt patient access to currently-available clinical laboratory services; and 3) an appropriate balance between both innovation, and assurances for accuracy and reliability through smart regulation.

In beginning our comments, we positively note that the DAIA Discussion Draft creates a distinct regulatory framework for *in Vitro* Clinical Tests (IVCTs, as named by the Discussion Draft), as a reasonable alternative to past proposals, some of which have inappropriately suggested regulation of LDTs as "medical devices" under the Federal Food, Drug, and Cosmetic Act (FDCA).

The following body of our comments will primarily focus on both smart regulation and avoiding disruption to patient access. These comments are the result of a preliminary review by ACLA and our member laboratories during the comment period and do not encompass all policy issues within the Discussion Draft. As we continue to review these and other issues, ACLA would be pleased to also provide specific legislative language concerning our comments. We offer these comments in a spirit of collaboration and look forward to continuing discussions with you, the House Committee on Energy & Commerce, your Congressional colleagues, the Administration, and other stakeholders.

Grandfathered Tests (pp. 81-86)

Over the past several years, numerous stakeholders have emphasized the importance of strong grandfathering and transition policies for any new diagnostic oversight framework. Absent these policies, patients would lose access to valuable diagnostic, monitoring, and screening LDTs, some of which may be the gold standard in clinical practice.

ACLA's position is that any new regulatory framework affecting LDTs should be a *prospective* framework that does not *retroactively* increase regulatory burden and harm patient access. Accordingly, we are pleased to see that pre-DAIA IVCTs would be considered legally marketed and would not be subject to premarket review (pp. 81-82).

ACLA's strong view is that the DAIA grandfathering provisions should be further strengthened by exempting IVCTs introduced prior to enactment from any premarket review, design control, registration, notification, and listing requirements. Even the Food and Drug Administration (FDA) recently proposed this approach, stating: "previously marketed LDTs would not be expected to comply with most or all FDA regulatory requirements, including premarket review, quality systems, and registration and listing, unless necessary to protect the public health."[1] ACLA notes that the Discussion Draft creates clear authority for the FDA to protect public health with provisions to review tests (including grandfathered tests) that the agency feels potentially pose a public health threat (p. 83, ln. 11-17).

[1]FDA, "Discussion Paper on Laboratory Developed Tests (LDTs)" (Jan. 13, 2017) at 4, *available at* https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf (hereinafter "Discussion Paper").

Finally, ACLA urges caution in considering any new regulatory requirements for "grandfathered" tests, such as requirements to list or submit data to the FDA. ACLA recognizes the need to monitor the public health broadly, but we also emphasize the need to balance the burden and cost of compliance that may quickly escalate from the addition of new regulations. If the new requirements are too costly, laboratories may cease offering particular tests, such as for rare diseases. Simultaneously, provisions retroactively applied to grandfathered tests would place a substantial burden on FDA and strain FDA resources and staff to implement. This strain could reduce resources to review new IVCT submissions, creating backlogs and barriers to patient access.

Quality System Requirements (QSRs) (pp. 126-128)

ACLA agrees that quality requirements should account for the differences between IVCTs that are finished products and IVCTs that are laboratory test protocols. Laboratory operation of laboratory test services are subject to, and should remain being regulated under, the Clinical Laboratory Improvements Amendment (CLIA). It is important to avoid imposing unduly duplicative regulation under two statutory frameworks. As such, there should be clear boundaries and transparent coordination between FDA regulation of IVCT developer activities and the Centers for Medicare and Medicaid Services (CMS) regulation of laboratory operations.

To account for the differences between a laboratory test protocol and a finished product, ACLA urges several changes to the proposed DAIA, as discussed below. First, only three FDA-regulated QSRs should apply to IVCTs that are laboratory test protocols: 1) design controls; 2) acceptance activities; and 3) procedures for corrective and preventive actions (CAPA).[2] This approach was previously proposed by FDA.[3]

ACLA recommends amending the legislative language (p. 127, ln. 7-9, and any other pages requiring necessary conforming edits) concerning QSRs for laboratory test protocols. These types of IVCTs should only need to meet the three quality requirements outlined above and should also be exempt from the 13 other requirements listed in the legislation (p. 126, ln. 9-25). Potentially requiring laboratory test protocols to meet all 16 quality requirements could result in duplicative, inapplicable, unnecessary, and burdensome regulation. IVCT laboratory protocols already meet overlapping CLIA certification requirements. ACLA contends that changes to suppliers or equipment should continue to be regulated only under CLIA, except to the extent such a change has a meaningful clinical impact or changes the intended use.

Modifications (pp. 49, 88-98)

ACLA has taken the position in prior comments that any review of modifications to an already marketed test (including grandfathered tests) should be limited to only those modifications which have a meaningful clinical impact or significantly modify the test's intended use after validation and verification.

[2] While the Discussion Draft lists labeling and package controls as a potential quality requirement, ACLA and FDA's Discussion Paper deal with labeling outside of the QSR context (discussed further, below, under "Labeling").

[3] *Id*. at 9. In its 2017 Discussion Paper, FDA proposed that a quality system for LDTs should "leverage certification to CLIA requirements" and that FDA concluded it should "narrowly focus its assessment on ***only three*** FDA QS requirements that address aspects of the test development process not covered by CLIA" (emphasis added).

In accordance with balancing clinical impact with premarket review, ACLA recommends that significant modifications to new or grandfathered IVCTs should be exempted from premarket review, QSRs, and registration and listing requirements (unless necessary to protect the public health) when the modified IVCT is classified in any of the following three categories: 1) low-risk IVCT (pp. 49, 88); 2) IVCT for rare disease (p. 49); or 3) traditional IVCT (discussed below). Such a policy was also proposed in FDA's 2017 Discussion Paper.[4]

In this context, the Draft should define "traditional IVCTs" as, "tests that use components that are legally marketed for clinical use and whose output is the result of manual interpretation by a qualified laboratory professional, without the use of automated instrumentation or software for intermediate or final interpretation"[5] (pp. 2-3).

On less clinically impactful modifications, ACLA appreciates the approach in the DAIA Discussion Draft that specimen-related modifications would not require a premarket application or FDA listing submission if the changes are made pursuant to methods or criteria included in a prior premarket submission for the IVCT, made pursuant to methods or criteria recognized by FDA, made solely for the purpose of extending specimen stability, or otherwise subject to an exception (pp. 92-93).

Labeling (pp. 102-104)

Any labeling requirements applicable to IVCTs developed by laboratories should be limited to reasonable requirements appropriate for laboratory protocols. For the sake of comparison, traditional FDA labeling predominantly encompasses labels that either physically accompany or are physically affixed directly on the packaging for a medical product (*e.g.*, a drug or device). Laboratories, however, are transmitting laboratory test results and interpretations as opposed to shipping a physically-packaged product. Requiring physical labeling delivered to the public would be inappropriate and impractical.

In the case of an LDT, "labeling" as part of the laboratory protocol still includes important clinical information (*e.g.*, the intended use of the test) that should be available for health care professionals and patients. ACLA supports such labeling being made available as appropriate through electronic formats, as the Discussion Draft currently allows (pp. 102-103).

Further, ACLA strongly agrees that patient-specific test results or interpretations of such results, as well as patient-specific scientific or clinical exchanges or discussions, should *not* constitute labeling (p. 103, ln. 12-17). Any adopted statutory language should clarify that laboratory operations documents -- including test request forms, sample collection instructions, mailing instructions, sample shipment packages, and patient-specific test report forms -- are *not* labeling. These documents are currently covered under CLIA and laboratory operations. It would, therefore, be duplicative and unnecessary to include such documents under FDA labeling regulation.

[4] *Id*. at 4.
[5] *Id*. Components would include general purpose reagents, immunohistochemical stains, and other components marketed in compliance with FDA regulatory requirements. *Id*. at 11.

Adverse Event Reporting (pp. 128-133)

Similar to QSRs and labeling, adverse event reporting (AER) will require clear delineation between and among FDA-regulated activities and CMS-regulated activities. For example, clinical laboratories currently qualify as "user facilities" under medical device regulation and, therefore, must report adverse events as "users" to FDA or the manufacturer; whereas, "medical device" manufacturers have separate and distinct AER reporting obligations. Similarly, laboratory operation errors are currently governed under CLIA and, therefore, should not be subjected to new or duplicative requirements. In designing the adverse event reporting process in the new framework, the obligations to report as a developer, a user, or in laboratory operations should be distinct, clearly delineated, and not duplicative.

Inspections (pp. 77, 150-151)

Under the present-day regulatory regime, clinical laboratories are subject to frequent and regular inspections by numerous national authorities including, but not limited to: CMS-CLIA, the College of American Pathologists (CAP), the Joint Commission, and the American Society for Histocompatability and Immunogenetics. On the state-level, a laboratory is subject to inspection by the laboratory's state department of health; in addition, if the laboratory provides services for *any* patient sample originating in New York (NY) state, the lab will also be inspected by the NY Department of Health, Wadsworth Center, regardless of whether the laboratory is physically located in NY or not.

While some of these authorities provide voluntary accreditations and inspections (as opposed to mandatory), laboratories will frequently attain and maintain these various accreditations depending on the laboratory's menu of services, specialties, and patient population served. ACLA has received one anecdotal report that a single member laboratory location received eleven routine inspections in one calendar year from nine different authorities (certain authorities issue multiple accreditations and each accreditation has distinct requirements and inspections).

Given the existing burden of inspections, ACLA urges careful consideration of any new inspection regime. In particular, we caution against additional *mandatory* inspections that would be triggered by routine administrative activities (*e.g.*, submissions or registrations), as opposed to mandatory inspections to investigate potential public health risks. ACLA agrees, for instance, that premarket inspections by FDA should *not* be required for the developers of IVCTs. This is provided in the current legislative language (p. 77, ln. 18-22), that the "Secretary may not condition the approval of an application … on the occurrence of a premarket inspection or manufacturing review related to the application."

ACLA also agrees that third parties should be accredited to conduct inspections of IVCT facilities and that each facility should be permitted to select an accredited entity to perform an inspection (pp. 150-151). For example, many third parties now accredited under CLIA have expertise and experience inspecting clinical laboratories. Any oversight framework should require that inspectors have specific experience and training concerning clinical laboratories, especially with regard to design control and acceptance activities within the laboratory (discussed further, below, under "FDA Resources").

Lastly, ACLA supports the legislative principles that regulations: 1) must account for differences between finished products and laboratory test protocols (p. 152, ln. 23-25), and 2) must be developed and implemented so as to allow a regulated entity to satisfy its statutory obligations "in the least onerous and most efficient manner possible" (p. 153, ln. 10-14).

FDA Resources (pp. 6-7)

FDA would need adequate resources to carry out its mandate under this new regulatory framework, including specifically personnel who have training and experience related to clinical laboratory activities.

The DAIA Discussion Draft recognizes this need by requiring the proposed Center for In Vitro Clinical Tests to include senior management with "management experience in clinical laboratory operations" (p. 7, ln. 6-8). ACLA believes, however, that senior management should include more than just one individual with such experience.

As outlined above, ACLA also urges the addition of legislative language requiring that the new Center's application reviewers, inspectors, and staff members have real-world clinical laboratory experience and training. The number of staff with such laboratory experience and the breadth of such experience should be substantial and adequately proportional to the number of clinical laboratories overseen by the new Center. Individuals with clinical laboratory expertise, including possible third-party reviewers, will be vital in the IVCT review and oversight process. This staff experience requirement should also be included as a performance goal for FDA tied to the payment of user fees.

User Fees (pp. 156-160)

Any fees associated with a new regulatory framework must reasonably take into account not only the resources necessary to implement the framework but also the impact on the entities from which the fees will be assessed. For this reason, a portion of user fees should be utilized to hire a certain percentage of reviewers and agency staff members with clinical laboratory experience, as previously discussed above in FDA Resources.

It is also important to recognize that many (if not most) developers of laboratory test protocols are small laboratories or academic research centers. User fees may be a financial burden that present a significant barrier to innovation by these entities. Any new federal framework should not prevent patient access to cutting-edge, high quality, and accurate diagnostics. As such, we support a user fee cap for the funding of the new regulatory structure that is currently proposed in the legislation (p. 160, ln. 7-14), as well as the availability of fee waivers for small laboratories or academic research centers. Similar fee waivers exist under the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee Act (MDUFA).

Risk Reducing Factors Relating to Moderate-Risk IVCTs (pp. 15-16)

The Discussion Draft designates a number of "risk reducing factors" whereby a test that may otherwise be classified as "high-risk" is, instead, designated as "moderate-risk" (pp. 15-16). In recognition that certain laboratories may develop specialized expertise in the operation of unique test protocols or methodologies, ACLA proposes adding an additional risk reducing factor,

whereby the Secretary could assess a laboratory's demonstrated experience and expertise with a particular protocol or methodology (that may not otherwise be well established), and deem the expertise adequate such that the submitted IVCT could be down-classified to moderate-risk. Further, ACLA recommends adding "labeling instructions and warnings" as an additional risk reducing factor.

Distinguish IVCTs Sold for the Purpose of Third-Party Use (pp. 39, 45)

As the Discussion Draft contemplates, an IVCT developer may intend to directly perform the IVCT, as in the case of a clinical laboratory, or sell an IVCT finished product for use by third parties, as currently done when an IVD manufacturer sells an IVD test kit to a laboratory or physician office. In the case of a high complexity laboratory, the laboratory is presently regulated through various employee safety protocols under both CLIA and the Occupational Safety and Health Administration (OSHA).[6] These same safety protocols may not exist in other third-party user environments, to which IVCTs are sold. ACLA recommends that, where the Discussion Draft requires "instructions that relate to the protection of the individual performing the test", any final legislation require that such instructions be mandated only when the IVCT is sold to "third-party users" (pp. 39, 45). These instructions should not be required in cases where other agencies (*e.g.*, CMS or OSHA) are regulating the activity within the respective laboratory.

Concluding Comments

Thank you for the opportunity to submit these comments. If you have any questions, please do not hesitate to contact Tom Sparkman at tsparkman@acla.com.

Sincerely yours,

Julie Khani
President

[6] *Id*. at 6 ("Controls and oversight mechanisms in place under CMS and [OSHA] generally address potential safety issues with LDTs that are unrelated to performance, including the potential for direct harm through transmission of infectious disease, or physical harms to users").