June 19, 2015

Chairman Fred Upton
Committee on Energy & Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

DELIVERED ELECTRONICALLY

RE: Response to June 2, 2015 Discussion Draft Bill proposing "to establish a regulatory framework for *In Vitro* clinical tests"

Dear Chairman Upton:

Following are the comments of the American Clinical Laboratory Association ("ACLA") on the Discussion Draft Bill on regulatory reform for in vitro clinical tests ("IVCTs") provided to ACLA by staff from the House Energy & Commerce Committee ("the E&C Committee"). ACLA is an association representing the nation's leading providers of clinical laboratory services, including local, 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 are actively engaged in the development and performance of countless laboratory-developed tests ("LDTs") that have helped transform the standard of clinical care in this country and provide vital information to physicians caring for patients, and they are committed to providing accurate, reliable, and clinically meaningful diagnostic testing services for the benefit of patients.

Recently, the United States Food & Drug Administration ("FDA") published two draft guidance documents asserting that the Agency has the authority under the medical device provisions of the Federal Food, Drug, & Cosmetic Act ("FFDCA") to regulate LDTs.[1] In fact, FDA lacks the authority to regulate LDTs as medical devices under the FFDCA, because they are not "medical devices," as defined therein.[2] Even if, for sake of argument, the FFDCA medical devices provisions did apply to LDTs, the standards of safety and effectiveness that serve as the lynchpin for regulation under that statute are both inappropriate and impractical for the provision of laboratory services. ACLA is pleased to see that the Discussion Draft Bill recognizes that the approach proposed by the FDA to regulate LDTs as medical devices under the FFDCA medical device provisions is not the right path for regulating LDTs.

[1] Framework for Regulatory Oversight of Laboratory Developed Tests: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; see also 79 Fed. Reg. 59776 (Oct. 3, 2014); 79 Fed. Reg. 59779 (Oct. 3, 2014).

ACLA has long advocated for legislative enhancements to the regulation of laboratory operations through modernization of the Clinical Laboratory Improvement Amendments ("CLIA"), to include many of the areas of regulation FDA seeks to address in the Draft Guidance (*e.g.*, clinical validity, adverse event reporting). However, as Congress is considering an alternative to the FDA Draft LDT Guidance, ACLA adopted a set of regulatory reform principles to guide our consideration of legislation to change the LDT regulatory framework. Many of the provisions of the Discussion Draft Bill align with ACLA's Key Principles on Diagnostic Reform, and we view the approach taken in the Discussion Draft Bill to be consistent with our principles.

Below, we highlight some important areas where the ACLA's Key Principles on Diagnostic Reform coincide with the Discussion Draft Bill, and some substantive comments on other portions of the document. Provided in the table at the end of the comments are some technical input on the wording of the document. We appreciate the opportunity to provide these comments on the Discussion Draft Bill, and look forward to continuing to work with the E&C Committee staff to inform your efforts on this legislation.

1) Comments on Particular Provisions of the Draft Discussion Bill as Aligned with the ACLA Principles

    a) LDTs Are Not Medical Devices

As noted above, ACLA strongly supports the exclusion of IVCTs from the definition of a medical device under the FFDCA. It is equally important to ensure that laboratory operations are not regulated as medical devices. As the Scope of Authority section on page 66 lines 7-12 (relating to CLIA) is currently drafted, we are concerned it would: 1) exempt labs from regulation by FDA under the new FDA IVCT regulations (subchapter J of chapter V of the FFDCA), in conflict with other provisions of the Discussion Draft Bill, and 2) fail to exempt laboratory operations from device regulations under sections of chapter V of the FFDCA outside of the new subchapter J. This section should be revised to clarify that laboratories, clinical laboratories, and laboratory operations shall be regulated by the Secretary under this section, and that laboratory operations shall not be subject to regulation under chapter V of the FFDCA (including but not limited to subchapter J thereof).

With regard to the application or exclusion of certain other provisions of the FFDCA to IVCTs, ACLA believes that a careful review should be performed to ensure no requirements are placed on IVCT development unintentionally. For instance, Section 510(j), governing listing of devices, should not apply to IVCTs. Instead, a new provision on listing should be drafted that is specific to IVCTs.

    b) Grandfathering

ACLA strongly supports the grandfathering of LDTs currently offered at the time of enactment of the statute from the pre-market review process. Throughout the FDA's recent assertion of authority over LDTs, the Agency has repeatedly failed to provide evidence that a serious and systemic problem exists under the current regulation scheme that threatens patient health. Wholesale application of any new legislative regulatory scheme to existing LDTs risks too much

disruption to patient access, in the absence of compelling evidence to suggest a systemic threat to patients. ACLA agrees that a legislative solution that includes agency authority to address any issues with analytical and clinical validity impacting patient safety that arise from test services already on the market is adequate to protect patients.

The Discussion Draft Bill provides that modifications to grandfathered tests will subject them to FDA review if they meet the "meaningful clinical impact" standard. We are concerned that FDA may construe virtually any modification of a high risk IVCT to meet this standard. We propose that language be included that makes clear that modifications that fall into the categories of changes in specimen type and optimization of protocols and reagents for use in a particular lab do not meet the "meaningful clinical impact" standard if they are documented and validated by the laboratory to have the same or substantially similar analytical validity.

c) Modifications

Modifications to IVCTs are a critical part of how testing is performed for the benefit of patients today. ACLA believes that the Discussion Draft Bill takes the correct approach in requiring review only where it would change the IVCTs intended use or result in a meaningful clinical impact to the patient. However, we believe it is critical the meaningful clinical impact standard be applied post-verification and post-validation of the modification. Similarly, as discussed above regarding modifications to grandfathered tests, the statutory language should make clear that "meaningful clinical impact" is a narrow standard that does not include changes in specimen type, and optimization of protocols and reagents for use in a particular laboratory.

i) Labeling

The provisions on labeling in the Discussion Draft Bill are largely consistent with ACLA's view on labeling for IVCTs. However, we suggest specifically stating that the laboratory test result is not labeling, as result reporting is part of laboratory operations governed exclusively by the Centers for Medicare & Medicaid Services ("CMS") under CLIA under the proposed framework.

d) Preemption

ACLA supports the proposal in the Discussion Draft Bill to preempt state requirements addressing the same subject matter, and to reserve the regulation of the practice of medicine to the States. We recommend that the preemption provisions be broadened to explicitly state that both "design" and "validation" are protected by Federal preemption. For reference, the preemption provisions in the Discussion Draft Bill are on page 60, lines 18-24.

e) Fees

ACLA supports an approach that provides the FDA with adequate resources in order to carry out its mandate under the new framework. Accordingly, we support a user fee approach to enable the FDA to review submissions in a timely and accurate manner. We recommend that when the

section regarding FDA fees is added to the Discussion Draft Bill, it should specifically reference the CLIA fee credit created by section 5(f).

f) Duplication in Regulatory Requirements

ACLA appreciates the demarcation in the Discussion Draft Bill regarding the jurisdiction for FDA and CMS relating to test development and laboratory operations. ACLA is concerned that, during the process of promulgating regulations based on these provisions, there is a potential for inconsistencies or duplicative requirements. We would suggest including language in the bill instructing both agencies to ensure that implementing regulations do not result in any inconsistencies or unnecessary overlap for any activities.

g) Incentivizing Innovation

ACLA appreciates that the Discussion Draft Bill contains provisions intended to foster continued innovation in the development of IVCTs. The provisions regarding unmet need and rare diseases are important carve outs to ensure patient access to test services that may otherwise not be made available. With regard to the proposal for priority review vouchers for tests intended for use in areas of unmet need, we are uncertain how effective these provisions would be to incentivize development of new laboratory testing services. Although priority review vouchers have proven valuable in the context of drugs and biologics, the differences in life cycle and return on investment for novel in vitro clinical tests and the relatively small (*i.e.*, 30 days) benefit provided by the priority review voucher present a much different incentive than the in the drug/biologic context. We would encourage the E&C Committee to continue to explore other methods which might increase innovation for new and innovative in vitro clinical tests.

2) Additional Issues in the Discussion Draft Bill

a) Requests for Advisory Panel Review

The Discussion Draft Bill contains two provisions that afford a stakeholder the opportunity to "request review" by an advisory panel on appeals of classification and reclassification decisions by the FDA. ACLA is concerned that FDA could interpret this provision as granting FDA the ability to deny the request for review by an advisory committee. Accordingly, we would suggest changing the language referring to an appellant requesting review by an advisory panel to clarify that the appellant shall be entitled to review by an advisory panel. These references occur on page 12 lines 21-23, and again on page 60 lines 13-14.

b) IVCTs with Multiple Intended Uses

The Discussion Draft Bill provides that an IVCT with multiple intended uses will be placed into the risk class associated with the highest risk intended use. Language should be added to state that the Discussion Draft Bill would allow the same IVCT to be used for each intended use, but that each intended use of the IVCT would fall into its own associated risk category. In this way, the lower-risk uses have their own classification and approval. We note that FDA takes a similar approach now for in vitro diagnostic tests (some uses are only subject to 510(k) clearance, but

others require a PMA). The reference in the Discussion Draft Bill is on page 12 lines 24-25 and page 13 lines 1-2.

c) Mandatory Notification to Users and Mandatory Recall

The Discussion Draft Bill should limit the FDA's use of these authorities to instances where the IVCT developer refuses to take adequate remedial action voluntarily. This reference is on page 56 lines 6-19.

d) Adverse Event Reporting

The application of the adverse event reporting standard set forth in the Discussion Draft Bill intends to trigger reporting when there is a "reasonable probability…of causing death or serious injury." The phrase on page 53, line 12 "more than a remote possibility" should be removed. ACLA is concerned that this part of the parenthetical could cause "reasonable probability" to be interpreted as just a little more than "remote" instead of what the Discussion Draft Bill intends, which takes into account those factors to establish a "reasonable probability."

Sincerely,

Alan Mertz
President

ATTACHMENT: Table of Recommended Technical Revisions to the Discussion Draft Bill

Table of Recommended Technical Revisions to the Discussion Draft Bill

Reference in Discussion Draft Bill	Proposed Revision
Page 4, Line 3	Change “reagant” to “reagent”.
Page 7, Line 4	Change “us” to “use”.
Page 12, Line 17	Change “590E” to “590G” to correct the reference to the appeals section.
Page 15, Line 14	Change “590(b)” to “590(c)” to correct the reference to the section establishing the new Center.
Page 15, Line 23	Change “590E” to “590G” to correct the reference to the appeals section.
Page 17, Line 14	After “subsection (l)(3)(B)”, add “of Section 590B” to clarify the Section under which this subsection appears, since it is in a different Section.
Page 18, Line 7	Change “(1)(A)(i)” to “(2)” to correct the paragraph under which recommendations are published.
Page 18, Line 10	Change “(3)(B)” to “(4)(B)” to correct the paragraph under which the public comment period is established.
Page 18, Line 16	Change “(4)” to “(5)” to correct the paragraph under which the 180 day period for Secretary action is established.
Page 18, Line 22	Insert a period after “classification”.
Page 19, Line 6	Change “590E” to “590G” to correct the reference to the appeals section.
Page 26, Line 5	Change “590C” to “590E” to correct the reference to the section on quality requirements.
Page 27, Line 16	Change “(3)(A)” to “(2)(A)”.
Page 29, Line 12	Change “(3)(A)” to “(2)(A)”.
Page 32, Line 10	Change “590(b)” to “590(c)”.
Page 36, Line 3	Change “590C” to “590E” to correct the reference to the section on quality requirements.
Page 36, Lines 13-14	Clarify “manufacturer/developer” as “developer”.
Page 38, Line 18	Change “(3)” to “(2)”.
Page 39, Line 14	Change “590D(d)(2)” to “590D(e)(2)”.
Page 42, Line 9	Delete “Nonhuman”.
Page 42, Line 25	Delete “Nonhuman”.
Page 46, Line 12	Change “30-day” to “10-day” period.
Page 46, Line 16	Change “(b)” to “(c)”.
Page 46, Line 22	Change “(b)(2)” to “(c)(2) and (c)(3)”.

Reference in Discussion Draft Bill	Proposed Revision
Page 48, Lines 12-13	Section 590E(a) specifies the development of quality requirements for development and production of in vitro clinical tests "that are finished test products", but 590E(b)(2) indicates the requirements will apply regardless of whether the test is a protocol or a finished product. To reconcile, delete "that are finished test products" from Section 590E(a).
Page 53, Line 9	Delete "for".
Page 53, Lines 23-24	Change 'caused by an in vitro clinical test' to 'caused by an in vitro clinical test error'.
Page 55, Line 11	Change comma to period.
Page 61, Line 22	Change "subchatper" to "subchapter".
Page 63, Line 14	Change "7(d)(4)" to "6(d)(4)".
Page 70, line 25	Change "test" to "tests.
Page 71, Lines 6-10	On line 8, after "test", insert "is a modification of a laboratory test protocol that".
Page 71, Line 25	After modification, insert "to a laboratory test protocol".
Page 72, Line 5	Change "Dug" to "Drug".
Page 72, Line 15	Change "(3)" to "(2)".
Page 72, Line 17	Change "(4)" to "(3)".
Page 81, Line 1	Change "develop" to "developer".
Page 81, Line 16	Change "3(b)(2)(A)" to "3(c)(2)(A)".