August 20, 2018

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Senator Michael Bennet
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RE: Comments on FDA Technical Assistance on the Diagnostic Accuracy and Innovation Act

Dear Representatives Bucshon and DeGette and Senators Hatch and Bennet:

The American Clinical Laboratory Association (ACLA) is pleased to provide these initial comments on FDA's August 6, 2018 Technical Assistance (TA) on the Discussion Draft "Diagnostic Accuracy and Innovation Act" (hereinafter, DAIA Discussion Draft, DAIA, or Discussion Draft).

For the reasons set forth in these comments, the March 21, 2017 DAIA Discussion Draft, not the FDA TA, should remain the starting point from which Congressional and stakeholder discussions occur as we move forward to develop an appropriate regulatory framework for *in vitro* clinical tests (IVCTs). The DAIA Discussion Draft resulted from intensive discussion and consideration and represents a consensus approach that balances the need for appropriate regulatory oversight with the flexibility for developers to make innovative tests available to patients.

Nevertheless, below we set forth ACLA's comments on the FDA TA. As always, ACLA stands ready to answer any questions on our comments or otherwise collaborate with your staff on constructing a workable framework for the regulation of diagnostic tests. ACLA appreciates your efforts in addressing this important topic and considering these comments.

I. EXECUTIVE SUMMARY

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 perform laboratory developed test services (LDTs), in addition to purchasing and performing tests 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 increasing 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.

As ACLA expressed in our comments on the DAIA Discussion Draft (Attachment 1), it is appropriate for Congress to design a new oversight framework for diagnostic tests. We therefore support the pursuit of comprehensive statutory reform for the oversight of LDTs and IVDs through a transparent process with Congress, the Administration, and other stakeholders.

On August 6, 2018, Congress released for comment the TA prepared by FDA on the DAIA Discussion Draft. ACLA recognizes that the detailed TA provided by the Agency represents a critical milestone towards enacting comprehensive reform. It is clear that FDA has given serious consideration to the regulation of IVCTs. ACLA particularly recognizes FDA's inclusion of a comprehensive test information system and proposed precertification program in the TA. ACLA believes that, if properly designed and originally rolled out through a pilot program, precertification could become a potentially valuable pathway to provide streamlined and efficient regulatory oversight of IVCTs in a manner that drives patient access to cutting-edge, high quality, and accurate diagnostics.

As stated above, however, ACLA maintains that the DAIA Discussion Draft, not the FDA TA, should remain the starting point from which Congressional and stakeholder discussions occur. We note that rather than providing technical amendments to DAIA, FDA has drafted a distinctly different framework. ACLA recognizes that the FDA TA offers valuable insight into the priorities of FDA and certain concepts that could be incorporated into the Discussion Draft. However, given the many questions and concerns raised by the TA, ACLA believes that the framework set forth in the DAIA Discussion Draft should remain the starting point.

Furthermore, the FDA TA inappropriately suggests that FDA currently has authority to regulate LDTs as devices. The TA states, for example, that FDA "retains" jurisdiction over LDTs. ACLA has repeatedly asserted, and continues to assert now, that laboratory developed tests are *not* devices, and therefore FDA has no authority with respect to LDTs under current law that would be "retained" under any new framework.

As stated in our previous comments on the Discussion Draft, any new framework for regulating IVCTs must ensure continued innovation and patient access to reliable clinical laboratory diagnostic services. Core principles that will accomplish these paired goals include: 1) reform that recognizes diagnostics as distinct services rather than being incorporated into existing regulatory frameworks designed for other products; 2) "grandfathering" and transition policies that will not disrupt patient access to currently-available clinical laboratory services; and 3) an appropriate balance between innovation and assurances of accuracy and reliability through smart notice-and-comment regulation, rather than through guidance documents.

II. COMMENTS

The following comments are the result of a preliminary review by ACLA and our member laboratories and do not encompass all policy issues within the FDA TA. As we continue to consider the FDA TA, ACLA would be pleased to also provide specific legislative language concerning our comments.

A. Boundaries of Jurisdiction

Any new framework for regulating IVCTs must recognize diagnostics as presenting unique opportunities and challenges for regulation. Therefore, the regulatory approach should be tailored specifically for these tests, and should not simply attempt to fit them into regulatory frameworks for other products or services. Similarly, the framework must clearly delineate the lines of jurisdiction for regulating authorities that will be involved in diagnostic oversight and set clear limits on the scopes of such authorities. ACLA appreciates that the DAIA Discussion Draft establishes a new diagnostic-specific framework under a separate center at FDA, creates clear lines of jurisdiction between FDA and CMS, and carefully avoids limiting or interfering with the practice of medicine. ACLA continues to believe that this is the correct approach for the regulation of diagnostics.

1. Diagnostic-Specific Regulation Under a Separate FDA Center

ACLA maintains that IVCTs should be governed by their own regulatory framework, developed with the understanding that IVCTs include LDTs that are distinct from medical devices. ACLA objects to the TA's approach that inappropriately sets forth a framework where device regulations are the starting point for IVCT oversight. For example, under the FDA TA, the device quality system regulations (QSRs) apply to IVCTs until the Secretary amends the applicable regulations. There is no deadline by which such regulations must be amended.[1] The TA appears to take the same or a similar approach with regard to labels and labeling, adverse event reporting, corrections and removals, and investigational use IVCTs.[2] It could be years or even decades before FDA amends these regulations to specifically apply to diagnostics, effectively subjecting IVCTs to device regulation for the foreseeable future. Diagnostics present unique challenges for regulation given that many IVCTs are developed and performed in laboratories. As such, we believe it is inappropriate to shoe-horn oversight of IVCTs into a device framework until such point that FDA establishes IVCT-specific regulations.

Additionally, the FDA TA sets forth transition provisions under which IVCTs are required to "comply with the applicable device provisions" at least until the effective date of the Act.[3] Here,

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[1] *See* FDA TA, page 38 ("As necessary, the Secretary shall amend part 820 of title 21 of the Code of Federal Regulations, or successor regulations, to implement the provisions of this [section]. . . . Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests and developers.").

[2] *See id*. at 40, 41, 43, 44, and 49.

[3] *Id*. at 56 (requiring non-grandfathered and non-transitional IVCTs available prior to enactment to "continue to comply with the applicable device provisions of the [FDCA] and the [PHSA] until the effective date of this Act" and requiring IVCTs made available after enactment but prior to the effective

existing IVCTs are expressly regulated as devices at least until the Act becomes effective. For the same reasons stated above, ACLA considers this to be the incorrect approach. We believe the transition provisions in the DAIA Discussion Draft are preferable. We address the transition provisions at length later in this document.

Finally, unlike the DAIA Discussion Draft, the FDA TA does not contemplate a separate diagnostic-specific center at FDA to fully differentiate diagnostics from devices. A diagnostic-specific center at FDA is a critical component of any framework to regulate IVCTs. Relegating IVCTs to an authority otherwise charged with medical device regulation or medical product regulation is inappropriate as IVCTs are distinct from such products. Additionally, FDA should have the appropriate resources to carry out its mandate under this regulatory framework, including specifically personnel who have training and experience related to clinical laboratory activities.

2. Regulation of Laboratory Operations

Unlike the DAIA Discussion Draft, the FDA TA does not account for the distinct role CMS plays in the regulation of laboratory operations. Instead, the TA appears to contemplate an overlapping system, where labs would be subject to redundant regulation by both FDA and CMS. For example, the DAIA Discussion Draft clearly states that FDA's authority to regulate IVCTs "shall not apply to laboratory operations, as defined in section 353 of the Public Health Service Act, or any regulations promulgated thereunder."[4] Meanwhile, the FDA TA caveats that, under the new regulatory scheme, "the Secretary shall, *to the greatest extent possible*, unless necessary to protect public health, avoid undertaking *programmatic* regulatory functions separately being undertaken by the Secretary under section 353 of the Public Health Service Act."[5] While the TA makes modest mention of not subsuming *programmatic* functions otherwise dealt with in CLIA, it does not set clear boundaries for FDA and CMS in non-programmatic areas. And even in programmatic areas, the TA grants FDA virtually unfettered discretion to regulate when FDA believes it "necessary to protect the public health." The TA thus leaves significant discretion to FDA to regulate laboratory operations already regulated by CMS under CLIA.

Furthermore, as stated above, the TA wholesale applies certain FDA device requirements to all IVCTs, including laboratory-based IVCTs, until FDA revises the applicable regulations, and no deadline is specified for revising such regulations.[6] Besides such device regulations being potentially duplicative and sometimes conflicting with existing CMS requirements, it would be unnecessarily costly and burdensome for laboratories to create and implement compliance

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date to "comply with applicable device provisions of the [FDCA] and the [PHSA]," unless it is subject to the grandfathering or transitional IVCT provisions) and 57 (permitting the Secretary to "enforce the device provisions of the [FDCA] and the [PHSA] . . . as the Secretary determines necessary to protect the public from a serious risk to health" for grandfathered and transitional IVCTs until the effective date of the Act).

[4] DAIA Discussion Draft, page 5.

[5] FDA TA, page 8 (emphasis added).

[6] *See supra* notes 1 & 2.

programs consistent with device regulations and *then* to create and implement new compliance programs consistent with published IVCT regulations.

Finally, ACLA is concerned that the TA regulates collection articles "for taking or deriving specimens from the human body" as separate IVCTs.[7] Activities associated with the collection of specimens are already regulated under CLIA[8] and collection devices are already regulated under FDA's medical device authority.[9] By including such collection articles in the IVCT definition, the TA would create further redundancy. Moreover, it is inappropriate to assign regulatory responsibility for collection devices to IVCT developers in situations where the collection devices are used in conformity with their FDA cleared or approved uses.

3. Practice of Medicine

The FDA TA also provides insufficient protections related to the practice of medicine. The DAIA Discussion Draft protected the practice of medicine by, among other things, prohibiting the "limit[ation] or interfere[nce] with the authority of a health care practitioner [(HCP)] to prescribe, order, or use the results of an [IVCT] with respect to a patient . . .."[10] The Discussion Draft also carefully excluded from the definition of "modification" "any activity that constitutes the practice of medicine"[11] and amended CLIA such that "[t]he Secretary shall not regulate the practice of medicine under this section," but rather "[t]he authority to so regulate shall be reserved to the individual States."[12]

In contrast, the FDA TA is much more narrow. The TA states only that nothing in the TA shall limit or interfere with the authority of an HCP to "prescribe or administer any legally marketed [IVCT]...."[13] Unlike the Discussion Draft, the TA does not include language protecting the ability of an HCP to "use the results of an [IVCT] with respect to a patient." In addition, the TA states that FDA may establish and enforce restrictions on the sale or distribution of IVCTs, thereby allowing FDA to limit which health care practitioners could access IVCTs.[14]

B. Ambiguity and Discretion

ACLA supports an oversight framework that avoids both unnecessary ambiguity and the granting of unfettered discretion to regulatory agencies. Instead, the framework should clearly outline the standards and structure of the regulatory scheme. Unfortunately, the FDA TA introduces ambiguity into the standards and structure of the regulatory scheme and grants FDA overly-wide discretion with regard to IVCT regulation.

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[7] *See* FDA TA, page 17.

[8] *See* 42 CFR § 493.1242 (Standard: Specimen submission, handling, and referral).

[9] *See e.g.*, 21 CFR § 864.3250 (Specimen transport and storage container).

[10] DAIA Discussion Draft, page 6.

[11] *Id.* at 9.

[12] *Id.* at 161.

[13] FDA TA, page 8.

[14] *Id.*

1. Ambiguous Standards and Lack of Deadlines

The TA caveats many standard-setting provisions in such a way that negates any standard purportedly set by the proposed legislation. For example, although FDA defines the types of information that must be submitted in a premarket application, the TA states that an application also shall include "[s]uch other information as the Secretary may require through guidance."[15] Additionally, the TA includes a claw-back provision requiring a premarket submission for any exempted IVCT "[i]f the Secretary has reason to believe," that the test meets one of the listed conditions.[16] These caveats and vague provisions introduce serious ambiguity into the standards set under the TA and grant FDA overly-wide discretion such that laboratories may not be certain of the Agency's expectations under the proposed framework.

Furthermore, although the TA states that FDA shall promulgate regulations or guidance to implement many provisions of the TA, there are *no* deadlines by which FDA would be expected to introduce or finalize such regulations or guidance. Thus, developers may be left with no guidance on the implementation of the TA for years, decades, or longer. Furthermore, for those provisions that apply device regulations until such time as IVCT-specific regulations are implemented, IVCTs may remain subject to device regulations for an indefinite period of time. Having *no* IVCT standard may be the *most* ambiguous standard.

Similarly, FDA sets no timelines for making approval decisions on premarket applications. Whereas the DAIA Discussion Draft made clear that FDA would make approval decisions for high-risk tests within 120 calendar days[17] of application submission and for moderate-risk tests within 75 calendar days of application submission,[18] the FDA TA currently leaves an "X" in the place where a firm deadline should be for action on premarket submissions.[19] These types of ambiguity are repeated throughout the FDA TA; thus, again, ACLA believes the DAIA discussion draft remains a better starting point for further discussions on the appropriate framework for IVCT regulation.

2. Rulemaking rather than Guidance

The TA also grants the Agency authority to implement many provisions through guidance,[20] whereas the DAIA Discussion Draft required implementation by rulemaking. Implementation

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[15] *Id*. at 18.

[16] *Id*. at 8–9.

[17] DAIA Discussion Draft, page 42.

[18] *Id*. at 48.

[19] FDA TA, page 18.

[20] *See, e.g.*, *id*. at 34 (permitting the Secretary to "establish[] by guidance a date [of implementation for registration requirements] later than [the date of implementation] for all or a category of . . . establishments"), 35 (permitting the Secretary to "specify in guidance" the form and manner for IVCT notifications), 36 (permitting the Secretary to "establish[] through guidance" the process for assigning test notification numbers, and permitting the Secretary to "specif[y] . . . in guidance" additional information required to be submitted in a notification by a person who is not a developer but is otherwise required to

by guidance is unacceptable because, as ACLA explained in comments on FDA's Draft Guidances on LDTs, it bypasses the Administrative Procedure Act's well-established notice-and-comment procedures, and it fails to account for an economic impact analysis.

First, the use of notice-and-comment rulemaking creates critical opportunities for transparency and public accountability that is not present when guidance is used. Although FDA's guidance policy affords interested parties the opportunity to submit public comments to guidance documents, FDA is not required to respond to significant comments. Rather, FDA merely is expected to review the comments and incorporate suggested changes "when appropriate,"[21] with all discretion regarding what is "appropriate" left up to the Agency. This is especially problematic when provisions of the FDA TA permit the Agency to promulgate guidance with little constraint as to the content of the guidance, such as the example in section II.B.1. above, regarding inclusion in a premarket submission "[s]uch other information as the Secretary may require through guidance."

Second, implementation by guidance means that FDA will not have to conduct an economic impact analysis for its proposed implementation schemes. Given the wide array of topics that FDA is permitted to implement by guidance under the TA, such economic impact analysis is essential.

3. Class Exemptions

ACLA objects to the TA's provision that permits the Secretary to "exempt a class of persons from any section under this subchapter upon a finding that such exemption is appropriate in light of public health and other relevant considerations."[22] Consistent with ACLA's objections above, "other relevant considerations" is not a meaningful standard to discern when FDA may apply this exemption authority. More importantly, this provision undermines FDA's stated concern that "inadequate and inconsistent oversight in which different test developers are treated differently can also discourage innovation by making it difficult for high-quality test developers to compete with poorer performing counterparts."[23] Rather, the exemption provision would do exactly what FDA says it wants to avoid, have "different test developers [be] treated differently."

C. Transition Provisions

ACLA strongly objects to the transition provisions set forth in the FDA TA.

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register), 42 (permitting the Secretary to "issue guidance on standardized, general content and format for [IVCT] labeling"), and 46 (requiring the Secretary to "issue guidance on the factors that the Secretary will use in determining whether a test group or a scope of precertification is eligible for review by an accredited person").

[21] 21 CFR §§ 10.115(g)(1)(iv)(A), 10.115(g)(3)(ii), 10.115(g)(4)(ii), & 10.115(g)(5).

[22] FDA TA, page 16.

[23] *Id.* at 1.

The FDA TA transition provisions subject IVCTs to regulation under "applicable device provisions of the [FDCA] and the [PHSA]" *immediately* after enactment.[24] Thus, IVCT developers will need to comply immediately with device regulation—regulations which are completely unfamiliar to most laboratories—with no transition provision. Moreover, the FDA TA would then apply the IVCT framework *immediately* after the TA becomes effective. Thus, in addition to immediately implementing a compliance program for a device regulatory framework, those same laboratories are expected to immediately implement a different compliance program for an IVCT regulatory framework (in addition to maintaining compliance with CLIA) upon the effective date of the TA.[25] This lack of transition period imposes a huge burden on laboratories without providing space and time for a learning curve. In contrast, the DAIA Discussion Draft included a three-to-five-year transition period for developers to come into compliance with the IVCT regulatory framework.[26]

Furthermore, under the IVCT framework in the FDA TA, many of the device regulations continue to apply until FDA revises the applicable regulations—i.e., indefinitely. IVCT developers should not have to go through *two* regulatory frameworks to make the transition to the IVCT framework. Rather, developers should be permitted to continue operating under CLIA until a new framework is effective.

Finally, the transition provisions inappropriately state that IVCTs shall "continue" to comply with applicable device provisions under authority that the Secretary "retains", thereby retroactively asserting that such tests, including LDTs, have been subject to device regulation under the FDCA. As stated previously, FDA has no authority with respect to LDTs under current law that would be "retained" under any new framework.[27]

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[24] *Id*. at 56. There is an exception for grandfathered and transitional IVCTs, but even these IVCTs are subject to "enforce[ment of] the device provisions of the [FDCA] and the [PHSA] . . . as the Secretary determines necessary to protect the public from a serious risk to health." *Id*. at 57. Thus, all IVCTs are, at a minimum, subject to potential enforcement under the device provisions of the FDCA and the PHSA immediately upon enactment. Transition provisions for grandfathered tests are discussed *infra* at section II.D.4.

[25] Moreover, the TA fails to specify an effective date, therefore the length of the transition period between enactment and the effective date is unknown. *See* FDA TA, page 56.

[26] *See* DAIA Discussion Draft, pages 151–52, 206–13 (posturing application of the transition provisions around the "date of promulgation of final regulations," which are to be promulgated not later than three years after enactment, and the "effective date of [final] regulations," which shall take effect two years after the date of promulgation).

[27] *See* ACLA, *Comments on March 21, 2017 Discussion Draft of the Diagnostic Accuracy and Innovation Act* (April 7, 2017); ACLA, *Comments to the Framework for Regulatory Oversight of Laboratory Developed Tests; Draft Guidance for Industry (Docket No. FDA-2011-D0360) and Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests (Docket No. FDA-2011-D0357)* (Feb. 2, 2015); ACLA, *Citizen Petition re: Laboratory Developed Tests* (June 4, 2013).

D. Grandfathered Tests

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 tests, some of which may be the gold standard in clinical practice. As stated in our earlier comments on the Discussion Draft, ACLA's position is that any new regulatory framework affecting IVCTs should be a *prospective* framework that does not *retroactively* increase regulatory burden and harm patient access. ACLA still views the Discussion Draft grandfathering approach as the appropriate starting point so that pre-DAIA IVCTs would be considered legally marketed and would not be subject to premarket review.[28]

ACLA has many issues with the revised grandfathering provisions in the FDA TA. First, we have concerns about the meaningfulness of the grandfathering provisions given the wide range of modifications that may trigger a premarket submission requirement, causing such a test to lose its grandfathered status. ACLA also believes that many of the additional conditions set by the FDA TA for grandfathered tests are unnecessary; that the TA permits FDA to "claw back" grandfathered tests at its discretion without basis in meaningful standards; that grandfathered tests may be inappropriately subjected to device regulation in the transition period between enactment and the effective date; and that additional notification requirements for grandfathered tests are unnecessarily burdensome.

1. Conditions for Grandfathered Tests

Many of the additional conditions set by the FDA TA for grandfathered tests are unnecessary. In particular, the condition that a test must have been developed by a high-complexity laboratory *for use only within that laboratory* is inappropriate.[29] ACLA appreciates FDA's thoughtful consideration that only tests developed within CLIA-certified high-complexity laboratories should be grandfathered under the resulting legislation. Indeed, this requirement is consistent with CLIA regulations.[30] Tests developed within high-complexity laboratories also should be grandfathered when they are performed in other high-complexity laboratories that are under common ownership or control with the developing laboratory. There is no reason to treat these tests differently simply because they are performed in a separate location. Failure to grandfather these tests would deprive patients of access to valuable tests on which they and their HCPs have relied for years. Furthermore, FDA recognizes in other parts of the TA that certain high-complexity laboratories *should* in fact garner the benefit of reduced regulatory burden that another high-complexity laboratory under common ownership receives.[31]

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[28] DAIA Discussion Draft, pages 81–82.

[29] *See* FDA TA, page 11.

[30] 42 CFR § 493.17(c)(4); *see also* CMS, "What is CMS' authority regarding Laboratory Developed Tests (LDTs) and how does it differ from FDA's authority?" at 4 ("LDTs are considered high complexity tests").

[31] *See, e.g.*, FDA TA, page 39 (describing abbreviated quality system requirements for certain laboratories distributing protocols to high-complexity laboratories under common ownership).

2. "Claw-Back" Provisions

ACLA also is concerned that the TA grandfathering provisions are significantly less likely to ensure continued patient access to grandfathered IVCTs because of vague "claw-back" provisions that would trigger premarket submissions for tests that have been available for decades. For example, the TA requires premarket submission for otherwise grandfathered tests when the Secretary has "reason to believe" that "there is insufficient valid scientific evidence to support the analytical validity or the clinical validity of such in vitro clinical test."[32] This provision provides FDA extremely wide discretion to require a premarket submission for grandfathered tests, leaving laboratories no transparent, objective standard to rely upon in determining whether any test will truly be grandfathered.

3. Modification Provisions Severely Limit the Meaningfulness of the Grandfathering Provisions

Even assuming a test would meet the conditions for grandfathering (and is not subject to one of the many claw-back provisions), under the TA, a test would lose its grandfathered status if it is modified in key ways. As described further below, the FDA TA greatly expands the conditions under which a modification triggers a premarket submission as compared to the Discussion Draft—thereby nullifying the grandfathered status of a test under a much broader set of conditions than under the Discussion Draft. For the reasons described in the modifications section below, ACLA disagrees with these expanded conditions for requiring premarket submissions for modifications to IVCTs, and ACLA especially disagrees with applying such expanded conditions to terminate the exempt status of grandfathered IVCTs. In effect, these requirements significantly undermine the meaningfulness of the grandfathering provisions.

4. Grandfathered Tests Potentially Subject to Device Regulation During Transition Period

The FDA TA transition provision for grandfathered tests inappropriately subjects such tests to possible regulation under the device provisions. Under the TA, a grandfathered test "may continue to be offered for clinical use until the effective date of this Act, except that the Secretary of Health and Human Services retains authority to enforce the device provisions of the [FDCA] and the [PHSA] for any specific product or test or any type of product or test as the Secretary determines necessary to protect the public from a serious risk to health."[33] This provision inappropriately grants FDA the authority to apply device regulations to supposedly grandfathered tests.

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[32] *Id*. at 8–9.

[33] *Id*. at 57. Transitional IVCTs are subject to the same transition provision as grandfathered IVCTs, i.e., that they are subject to enforcement under the device provisions of the FDCA and the PHSA "as the Secretary determines necessary to protect the public from a serious risk to health." Transitional IVCTs are those IVCTs that (1) were introduced within 90 days of enactment and up to the effective date of the FDA TA, (2) were developed by a CLIA-certified laboratory that meets the requirements for performing high-complexity testing, (3) were developed for use only within the laboratories in which they were developed, and (4) are not cleared or approved under FDA's device authority or under the PHSA. After the effective date, a transitional IVCT must be the subject of an application for premarket review or precertification to continue being marketed. *Id*.

Furthermore, under this transition provision, the Secretary has authority to enforce either FDCA or PHSA provisions or both "as the Secretary determines necessary," which provides no guidance to developers regarding with which regulatory framework they are expected to comply during the transition. The purpose of transition provisions is to make clear how IVCTs will be regulated until the IVCT framework is effective. The FDA TA transition provisions fail to do this for grandfathered tests.

Finally, use of the word "retains" inappropriately retroactively asserts that FDA has had authority to regulate IVCTs, including LDTs, under its device authorities. As stated above, ACLA strongly disagrees with this assertion.

5. Notification Requirements

Finally, as stated in our previous comments on the Discussion Draft, ACLA urges caution in considering any new regulatory requirements for grandfathered tests, such as requirements to submit data in a notification to FDA. ACLA continues to recognize the need to monitor the public health broadly, but we also emphasize the importance of balancing the burden and cost of compliance that may quickly escalate from the addition of new regulations. If 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 Agency resources and staff to implement. This strain could reduce resources to review new IVCT submissions, creating backlogs and barriers to patient access.

Although ACLA maintains that it is unnecessary to include *any* notification requirements for grandfathered tests, it is our position that when compared to the Discussion Draft, the FDA TA requires an onerous amount of information.[34] Such a requirement would divert resources and not otherwise advance the public health.

E. Test Classification

1. Risk Classifications

In order for laboratories to operate in compliance with a new regulatory oversight framework, laboratories should have certainty concerning when and how they will be regulated by FDA. There also should be clear Agency expectations for the tests that are developed and used in such laboratories. As such, any classification scheme for IVCTs must be clear, and regulatory oversight of tests with different risk profiles should be meaningfully different.

ACLA believes the TA's risk classification is confusing and unclear. Importantly, we disagree with FDA's approach that would eliminate the moderate-risk category for IVCTs. ACLA is concerned that without clear categories of high-, moderate-, and low-risk, FDA is granted overly-wide discretion regarding when tests should be classified as high- or low-risk. Under this scheme, a test with a moderate-risk profile could be regulated as a high-risk test or a low-risk test, at FDA's discretion. ACLA believes that for a risk-based classification scheme to be meaningful, the risk levels must be adequately defined and consistently applied. To ensure that

[34] *See id.* at 34–37.

such risk levels are consistently applied, the IVCT regulation framework should facilitate the classification of every test as high-, moderate-, or low-risk.

Additionally, as a practical matter, there is concern that omission of a moderate-risk level may encourage FDA to apply its discretion to classify *more* tests as high risk. This also is problematic for a number of reasons, among them that high-risk tests are not eligible for the proposed precertification program. This is discussed further below in section II.H. on precertification.

ACLA urges Congress to focus instead on the proposed test classification system for IVCTs under the Discussion Draft, which ensures that decreasing risk levels are associated with decreased regulatory burden.

2. Additional Categories of Tests

ACLA commends FDA for identifying categories of tests that should be exempt from certain requirements under the new oversight framework. These proposed categories include: manual tests, rare tests, public health surveillance tests, tests for law enforcement, custom tests, low-volume tests, and investigational tests. ACLA agrees that there are important public policy reasons for exempting these categories of tests from regulation under the new framework. But certain of the provisions related to these categories of tests are unnecessary and/or otherwise problematic.

a) Nonclinical Tests

The DAIA Discussion Draft would create an exemption from FDA regulation for "any test intended by its developer solely for nonclinical use."[35] Rather than adopt this straightforward and logical approach, the FDA TA creates only a narrow exemption for "law enforcement" tests. This proposed exemption would be inappropriately narrow. For example, a forensic test result reported back to an individual or a healthcare provider, even if intended for law enforcement purposes, would not be exempt from oversight under the TA.[36] Nor would this exemption include tests for other nonclinical uses, such as tests for use in the employment setting, ancestry tests, and other nonclinical tests. Accordingly, ACLA strongly prefers a broad-based nonclinical exemption, like the one in the DAIA Discussion Draft.

b) Rare Disease Tests

ACLA is concerned that the TA definition for a "rare disease" test creates an unclear and operationally infeasible evidentiary bar. Under the FDA TA, a rare disease test is one for which "fewer than 8,000 individuals per year in the United States would be subject to testing using such in vitro clinical test," and that is not cross-referenced or for a communicable disease.[37] We believe that there should be further discussion of what evidence is needed to demonstrate that fewer than 8,000 individuals per year in the United States would be subject to testing with the IVCT. Instead, ACLA continues to recommend using the DAIA definition for a rare disease

[35] DAIA Discussion Draft, page 3.

[36] FDA TA, page 15.

[37] *Id*. at 14.

IVCT. This definition is an IVCT used "for a *disease or condition with an incidence of* 8,000 or fewer per year or a prevalence of 50,000 or fewer in the United States," excluding IVCTs "intended solely for the screening of asymptomatic patients or predicting the occurrence of a future disease or condition in asymptomatic patients."[38]

c) Cross-referenced and First-of-a-Kind Tests

ACLA disagrees with the FDA TA's regulation of cross-referenced and first-of-a-kind tests. Under the FDA TA, these tests essentially are regulated as high-risk tests, but it is fully possible that cross-referenced and first-of-a-kind tests may be low-risk, and otherwise would be exempt from premarket review requirements. Instead, under the FDA TA, such tests are subject to additional requirements, such as requiring raw data in the premarket submission "unless the Secretary determines otherwise."[39]

ACLA is especially troubled by the FDA TA definition for "cross-referenced test," which does not account for authorization of a developer to have its test cross-referenced in the labeling of another medical product.[40] As defined, an IVCT could become a cross-referenced test, and therefore subject to regulation as a high-risk test, without any intent by the developer to have its test referenced in the labeling of another medical product. ACLA strongly objects to any definition of a cross-referenced test that does not include a requirement that the IVCT developer *authorize* use of its IVCT in the labeling of another medical product. ACLA also recommends that a cross-reference to a specific IVCT does not render other IVCTs of the same type cross-referenced because this also would have the effect of rendering such IVCTs cross-referenced without authorization by the developer.

d) Manual Tests

ACLA has concerns regarding the FDA TA exemption of "manual tests."[41] Although ACLA agrees that such tests should be exempt from regulation, we are concerned that by exempting manual tests, FDA is indirectly asserting jurisdiction over such tests. ACLA also is concerned that the FDA TA definition of "manual test" may scope out other tests or activities resembling the practice of medicine. Such tests or activities may therefore then be regulated as IVCTs, even though they also should be exempt.

e) Investigational Use Tests

The FDA TA significantly changes the investigational use provisions compared to the DAIA Discussion Draft. The provisions in the DAIA Discussion Draft were extensively negotiated with FDA prior to circulation of the Discussion Draft, and it is unclear why FDA has so significantly departed from what stakeholders considered a reasonable compromise. In particular, FDA has

[38] DAIA Discussion Draft, page 10 (emphasis added).

[39] FDA TA, page 17.

[40] *See id.* at 4.

[41] *See id.* at 13.

significantly redefined the term "significant risk" such that many more applications would need to be submitted for an investigational use IVCT than anticipated in the Discussion Draft.[42]

F. Modifications

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. ACLA believes the DAIA Discussion Draft, compared to the FDA TA, provides a better standard for determining when modifications to IVCTs require a new submission.

ACLA strongly disagrees with FDA's approach to require a premarket submission for a wider set of conditions than anticipated by DAIA. Some of these conditions are considerably vague. For example, under the TA, it is completely up to the discretion of FDA whether performance has been "adversely affect[ed]" for the condition or that the modification "adversely affects performance."[43] Other conditions would not have a meaningful clinical impact or significantly modify the test's intended use. For example, making a specimen modification for the purpose of extending specimen stability could be a modification that changes an element of a "test group," thereby requiring a submission.[44] Such a change is unlikely to have a meaningful clinical impact or significantly modify the test's intended use, as recognized by the DAIA Discussion Draft, which exempted such modifications from requiring a premarket submission or listing.[45] The DAIA Discussion Draft also exempted specimen-related modifications "made pursuant to methods or criteria approved or included in a premarket submission [for the IVCT] being modified or methods, standards, or criteria otherwise approved or recognized by the Secretary," or "otherwise subject to an exception from, or not described in" other provisions of the Discussion Draft.[46] ACLA believes such exemptions are appropriate for specimen-related modifications, which should continue to be regulated under CLIA.

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[42] *Compare* DAIA Discussion Draft, pages 104 & 124 (requiring an investigational use application when the investigational use "poses a significant risk to the public health" and "significant risk" means an investigational use that is "of substantial importance . . . [regarding] a serious or life-threatening disease or condition without confirmation of the diagnosis . . .; requires an invasive sampling procedure; or otherwise presents a reasonably foreseeable serious risk to the health of a human subject") *and* FDA TA, page 49 (requiring an investigational use application when the investigational use "poses a significant risk," where "significant risk" means that the investigational use "is for a use of substantial importance in performing the activities described in section (ss)(1)(A) [i.e., intended use of an IVCT] or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of an [IVCT] subject; or otherwise presents a potential for serious risk to the health, safety or welfare of a human subject of the [IVCT]").

[43] FDA TA, page 16.

[44] *See id.* at 6, 15–16.

[45] DAIA Discussion Draft, pages 92–93.

[46] *Id.*

Finally, ACLA objects to the TA requirement that any IVCT developed on a test platform five years after enactment must be developed on a platform that FDA has cleared, authorized, or approved.[47] Such a requirement inappropriately crosses FDA-CMS jurisdictional lines and regulates laboratory operations. Additionally, the requirement imposes on laboratories costly burdens to update test platforms before such updates may otherwise be required to ensure continued analytical validity.

G. Approval Standards and Premarket Submission Requirements

ACLA agrees with both the DAIA Discussion Draft and the FDA TA determination that, generally, "reasonable assurance of analytical and clinical validity" is an appropriate standard of approval for IVCTs. Such a standard should instill confidence in HCPs and patients relying on the results of IVCTs. ACLA would welcome further description of the IVCT approval standards, including the process for standards development, implementation, and application. We have serious concerns, however, regarding the definitions and terminology used to describe the approval standards, as well as the premarket submission requirements set by the FDA TA.

1. Approval Standards

ACLA strongly opposes the FDA TA revised definitions of "analytical validity" and "clinical validity" as well as the use of the term "safety" in the approval standards.[48] Under the TA, "analytical validity" and "clinical validity" contain a new subjective and vague "adequacy" requirement in lieu of the clear and objective definition of "reasonable assurance" in the DAIA Discussion Draft. The "adequacy" requirement grants FDA unprecedented discretion to determine whether an IVCT is analytically and clinically valid.

ACLA also objects to the omission of "calculat[ing]" and "analyz[ing]" in the "analytical validity" definition in the FDA TA. Under the DAIA Discussion Draft, an IVCT may be analytically valid if it is able to "calculate[] or analyze one or more analytes, biomarkers, substances, or other targets . . .."[49] Omission of these terms severely limits the ways in which a developer may establish that an IVCT is analytically valid, and it is not clear why FDA omitted these terms.

Similarly, ACLA prefers the DAIA Discussion Draft definition of "clinical validity" that excludes "clinical utility."[50] We are concerned that the TA's failure to specifically exclude clinical utility from this definition signals that the Agency intends to regulate IVCTs on the basis of their clinical utility, which would be inappropriate. Further, we recommend that the definition of "clinical validity" include the intent of the developer, as reflected in the DAIA Discussion Draft. Not including the intent of the developer suggests FDA plans to look beyond the claims of the developer with regard to intended use. Both concerns outlined here are only exacerbated in the context of the new proposed "adequacy" requirement, because data may be required to "adequately" establish clinical utility or intended uses not claimed by the developer.

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[47] *See* FDA TA, page 57.

[48] *See id.* at 3–4.

[49] DAIA Discussion Draft, page 7.

[50] *Id.* at 8.

Finally, ACLA believes that it is inappropriate for FDA to use the device term, "safety," in the approval standard for IVCTs that are articles for taking or deriving specimens from the human body.[51] Device terminology is inapplicable in the context of IVCTs, which are wholly distinct from devices.

2. Premarket Submission Requirements

ACLA also is concerned with the types and amount of data that FDA proposes to require in premarket submissions. Although the FDA TA has a definition of "valid scientific evidence" that contemplates multiple sources of evidence, the TA proposes that "valid scientific evidence from clinical investigations" must be submitted to support premarket applications for any IVCT that requires a demonstration of clinical validity.[52] By specifying that such evidence be "from clinical investigations," FDA severely limits the expanded definition of "valid scientific evidence."

ACLA also finds that it is inappropriate for FDA to require raw data for all tests "upon the Secretary's request," regardless of risk.[53] In conjunction with supplying data from clinical investigations, this particular requirement creates serious uncertainty for laboratories that will stifle innovation and development of novel tests, much to the detriment of patients in need. Furthermore, it significantly limits any meaningful distinction between risk classifications. As discussed above, risk classification should be meaningful.[54] Tests with moderate-risk profiles should correlate with a reduced burden in premarket submission requirements, as compared to tests with high-risk profiles. Requiring raw data for all tests "upon the Secretary's request," coupled with the TA's elimination of a defined moderate-risk category, could result in a requirement for raw data for moderate-risk tests being regulated as if they were high-risk tests. DAIA avoids these issues by clearly differentiating submission content requirements based on risk.

Finally, ACLA recommends that only a finite set of criteria be required to be included in annual reports. Laboratories may have thousands of tests, and submitting an annual report for each one has the potential to become excessively burdensome. DAIA's approach of requiring only summary reports of modifications to high-risk tests is appropriate and preferred.

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[51] *See, e.g.*, FDA TA, pages 6 (defining the relevant standard for articles for taking or deriving specimens from the human body as "reasonable assurance of analytical validity and, where applicable, safety"), 16 (stating that a modification renders an IVCT a new IVCT if the modification "as applicable, affects the safety of an article for taking or deriving specimens from the human body"), 17 (requiring a premarket submission to include "safety information, as applicable" for articles for taking or deriving specimens from the human body), and 21 (permitting a developer to make modifications to an IVCT without a supplement if the modification "do[es] not change, as applicable, safety of the [IVCT]" or is a "[l]abeling change[] . . . appropriate to address a safety concern").

[52] *Id.* at 17.

[53] *Id.*

[54] *See supra* section II.E.1.

H. Precertification

While ACLA supports the concept of voluntary precertification and its inclusion in any framework for IVCT regulation, the details of precertification will require further discussion in order to ensure that such a program results in a meaningful reduction in regulatory burden. Precertification should be workable for both laboratory developers and manufacturers, accounting for differences between laboratory developers and manufacturers where appropriate. In lieu of the TA precertification provision, ACLA encourages Congress to authorize in DAIA a voluntary pilot program with reasonable parameters to determine how a precertification program might be designed to provide streamlined and efficient regulatory oversight of IVCTs in a manner that drives patient access to cutting-edge, high quality, and accurate diagnostics.

ACLA disagrees with several aspects of the approach to precertification as proposed in the FDA TA. Under the TA, precertification would need to be renewed every two years and a renewal application would be required to include data for a different test than that included in the prior application.[55] Bi-annual renewal imposes a recurring regulatory burden on both industry and the Agency. Also, requiring data for a different test would prevent renewal if no new tests have been offered within two years. It is unclear what the rationales are for these requirements, which would cause precertification to expire for a number of laboratories.

Additionally, the program proposed in the TA greatly limits the utility of precertification by excluding a wide range of tests for which precertification would be useful. High-risk IVCTs, test systems for home use, and first-of-a-kind IVCTs all are ineligible for precertification under the FDA TA; cross-referenced and direct-to-consumer IVCTs are eligible for precertification only upon a determination by the Secretary that eligibility is appropriate; and low-risk tests already are exempt from premarket review requirements.[56] This leaves a very narrow band of non-high-risk and non-low-risk tests that can benefit from precertification. ACLA recommends that high-risk tests be eligible for precertification, or, at a minimum, that high-risk tests are eligible under the program for a reduction in premarket review requirements, such as summary review instead of full review, no premarket submissions for modifications, or an expedited review pathway.

Finally, FDA's proposed precertification program would exclude those individuals who have committed a "significant violation" of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.[57] The TA does not define "significant violation." ACLA requests greater clarity on this term. Furthermore, by disqualifying from the precertification program those laboratories that fail to maintain CLIA certification, the program could exclude laboratories that have temporary gaps in certificate renewal by no fault of their own, but rather because of government administrative delays.[58] We understand that such delays commonly occur.

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[55] FDA TA, page 31.

[56] *See id.* at 28.

[57] *Id*. at 27.

[58] *See id*.

I. Application of Device Requirements

ACLA has concerns over the FDA TA approach to a variety of device-centric regulatory requirements that would apply to IVCTs. While the issue is broader than just FDA QSRs, the TA's treatment of QSRs is illustrative. As stated above in section II.A.1, the TA proposes that until regulations are amended, device QSRs will apply to IVCTs. There is no deadline by which FDA is required to amend Agency regulations after enacted legislation. The default, therefore, is that these medical device QSRs will apply to IVCTs, including laboratory IVCTs, and could continue to apply indefinitely.

ACLA strongly opposes this approach. IVCTs, including LDTs, are not devices. Like the FDA's 2014 draft guidance, the TA is attempting to fit the square peg of IVCTs into the round hole of a medical device framework that was never designed for them. By contrast, DAIA creates a new framework specifically designed for IVCTs.

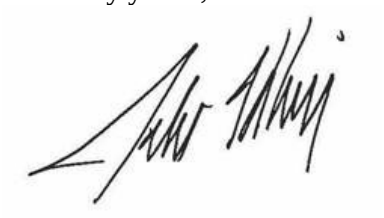
Further, laboratory operations are subject to, and should remain being regulated solely under, CLIA. It is important to avoid imposing unduly duplicative regulation under two statutory frameworks. As such, there should be clear boundaries and transparent coordination between FDA regulation of IVCT development activities and CMS regulation of laboratory operations.

ACLA also believes that quality requirements should account for differences between IVCTs that are finished products and IVCTs that are laboratory test protocols. Although we generally support the TA's approach to require limited FDA-regulated QSRs for certain CLIA-certified high-complexity laboratories that develop tests for use within their own laboratories, and to CLIA-certified high-complexity laboratories that distribute protocols to other CLIA-certified high-complexity laboratories under common ownership, we still have reservations. Specifically, ACLA continues to take the position that changes to suppliers or equipment should be regulated only under CLIA, except to the extent that such a change has a meaningful clinical impact or changes the intended use of a test.

III. 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

Attachment 1

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").