Diagnostic Test Working Group

The Honorable Larry Bucshon, M.D.
U.S. House of Representatives
Washington, DC 20510

The Honorable Orrin Hatch
U.S. Senate
Washington, DC 20510

The Honorable Diana DeGette
U.S House of Representatives
Washington, DC 20510

The Honorable Michael Bennet
U.S. Senate
Washington, DC 20510

August 20, 2018

Re: DTWG Comments on the Diagnostics Accuracy and Innovation Act

Dear Representatives Bucshon and DeGette, and Senators Hatch and Bennet:

The Diagnostic Test Working Group (DTWG) applauds Representatives Bucshon and DeGette and Senators Hatch and Bennet on their continuing work to build consensus around efforts to enact comprehensive legislative reform of diagnostics oversight, such as the discussion draft of the Diagnostics Accuracy and Innovation Act (DAIA). DTWG is a coalition of leading *in vitro* clinical test manufacturers and laboratories. DTWG members are committed to advancing patient care through the development, manufacture and performance of high quality, high value diagnostic tests. DTWG members support the mission of FDA and CMS to provide physicians and patients access to analytically and clinically valid in vitro clinical tests using risk based, least burdensome principles.

DTWG members have been instrumental in advancing a consensus-based approach to the regulation of *in vitro* clinical tests (IVCTs). This approach puts patients first and balances the needs of all stakeholders. DTWG appreciates the hard and bipartisan work put in by both the House and the Senate in advancing this initiative.

This document sets forth a summary of DTWG's preliminary views on the relative merits of FDA's newly proposed legislative language ("FDA language") and DAIA. The accompanying chart provides substantially more detail and also addresses questions or concerns not listed in this summary. These documents should be considered together.

DTWG stands ready to help in any way possible.

1. General Comments

    a. Utilize DAIA as the framework for legislation

DTWG strongly urges Congress to use DAIA as the framework for legislative action. DAIA is the product of extensive discussion and input from stakeholders, including FDA, such that we believe there to be greater consensus regarding DAIA's specific wording. Additionally, DAIA has been publicly available for well over a year, with earlier versions available since 2015,

giving all stakeholders the opportunity to review the language in detail, and to assess the draft for any unintended consequences or inconsistencies. It is important to note that FDA has already had substantial input into the DAIA language, including as part of several meetings called by Congress, along with multiple stakeholders. As such, a number of DAIA's current provisions reflect and incorporate numerous significant compromises in response to FDA input and discussions.

Unlike the DAIA, the FDA language uses device-specific terminology and concepts and incorporates numerous cross references to device provisions. A complete, comprehensive, and clear regulatory structure—as set out in the DAIA—is critical to support understanding and certainty for the thousands of labs that do not have experience with FDA regulation and would potentially be subject to DAIA requirements. A clear, comprehensive structure will support their understanding and ultimately advance compliance.

In DAIA, Congress has wielded the pen with the expert assistance of legislative counsel, and should continue to do so. By using DAIA as the starting point for further discussions, we reduce the risk of inadvertent drafting errors and unintended consequences, maintain the role of Congress, and benefit from all stakeholder input to date. Integrating valuable ideas from FDA or other stakeholders into DAIA's existing and carefully developed framework is the most appropriate path forward.

Finally, DAIA is a complete bill with cohesive elements. The FDA draft is missing key elements found in DAIA such as timelines for approval, an appropriate transition process, standards recognition, user fees, and a list of generally applicable provisions of the Food Drug and Cosmetic Act. Furthermore, DAIA's classification, reclassification, and appeals processes are more comprehensive.

b. Avoid incorporating device provisions

One of the key drivers for DAIA is the recognition that IVCTs and therapeutic devices have key fundamental differences, rendering therapeutic device regulations, terminology and concepts inappropriate and unsuitable with respect to IVCTs. Unfortunately, although FDA recognizes that IVCTs and therapeutic devices are different, in multiple places the FDA language incorporates device provisions,[1] sometime with just the notation that such provisions should be interpreted in light of IVCTs. DTWG agrees with the approach in DAIA that provides for IVCT focused regulations and gives FDA and stakeholders three years to develop such regulations. DTWG strongly urges that the DAIA approach be maintained and that the legislation not include the incorporation of existing device specific provisions.[2]

c. Specific wording edits

[1] This comment applies to multiple provisions within the FDA language. In the interest of brevity, we will not repeat this important comment every time the FDA language improperly incorporates device provisions.
[2] As a matter of drafting, we also suggest that DAIA not incorporate or reference specific sections of the Code of Federal Regulation. Such regulations may change or be renumbered. Such evolution creates statutory interpretation issues, adds burden to Congress, and creates uncertainty.

We have not attempted to edit either bill or to make specific wording edits or suggestions. Once we understand FDA's intent, the views of other stakeholders, and policy decisions from Congress, DTWG will provide specific wording suggestions. We believe that there are numerous places where wording changes or clarification will be needed once policy questions have been resolved. For example, at some places the term "in vitro clinical test" is used, in other places the FDA language uses the more generic (and potentially inaccurate) term "test". Likewise, FDA's proposed language inappropriately uses the term "safe" and "safety" throughout, which undercuts DAIA's recognition of analytical and clinical validity as the standard for approval.[3] This occurs despite FDA's recognition that analytical and clinical validity is the appropriate standard.

Given the need to carefully review wording after clarifying policy matters, DTWG's positions are contingent on acceptable wording being developed – preferably in a cooperative manner. In the meantime, DTWG will continue to review wording.

d. Core Principles

It is important to keep in mind the core principles of DAIA when considering possible changes. These core principles include:

- Patients come first;
- IVCTs are different from therapeutic devices;
- Systems and processes should be tailored to IVCTs;
- The same activity should be regulated the same way;
- There should be clear, non-overlapping jurisdictional lines that recognize the distinct roles of FDA, CLIA, and states;
- Innovation needs to be supported, including through appropriate modification provisions;
- Least burdensome principles must be utilized;
- Appropriate grandfathering and transition provisions are needed;
- Utilization of rulemaking for substantive provisions; and
- Risk based regulatory structure with appropriately stratified and transparent risk classifications.

As stakeholders consider possible revisions to DAIA, those alterations should be assessed using these principles. Changes which do not satisfy these core principles should be rejected.

e. Clinical Laboratory Improvement Amendments (CLIA)

Modernization and harmonization of CLIA with DAIA is important to ensure complete regulatory coverage and consistent provisions, while maintaining clear and distinct jurisdictional boundaries. FDA and CMS have complementary expertise that should be leveraged in a nonduplicative manner. The jurisdictional structure, which is foundational to industry consensus, is built upon a clear distinction between IVCT development activities and laboratory operations.

[3] Again, these comments are important but will not be repeated each place within the FDA language which uses inappropriate language.

Each should be distinctly and solely regulated by FDA and CMS respectively. We recognize that FDA is not speaking for CLIA. However, these CLIA improvements are a necessary part of the overarching framework and should not be swept aside.

2. Key Issues

The following is a discussion of key policy or drafting elements in the FDA language. More detail is provided in the accompanying chart which discusses each provision of the FDA language, and also gives a citation to the parallel provisions in DAIA.[4]

These comments are conceptual and are based on an initial review of the FDA language. Our comments are based on our review of the document and discussions with other stakeholders. There are a number of provisions which are unclear to us and so further explanation from FDA will be valuable. DTWG will continue to review the FDA language and we anticipate providing additional thoughts on the FDA language in the near future.

These summary positions are explained in more detail in the accompanying chart.

a. Preamble

DTWG agrees with the statement of legislative purpose set forth in the FDA language. However, in light of the key issues described in greater detail below and in our accompanying chart, FDA's proposed text itself undercuts the goals set forth in the preamble. While DTWG is supportive of FDA's stated objectives, if Congress decides to include a preamble or statement of legislation purpose, wording changes will be desirable.

b. Jurisdiction

DAIA carefully establishes three specific jurisdictional categories: (1) FDA regulation of test development, (2) CLIA regulation of laboratory operations, and (3) state regulation of the practice of medicine. DAIA preserves these clear jurisdictional lines, avoiding overlapping or duplicative regulation.

Unlike DAIA, the FDA draft language proposes a system of regulations that intrudes into territory already regulated through CLIA or by state authorities. Absent DAIA's clear and distinct jurisdictional lines, the FDA language asserts jurisdiction over CLIA regulated activities in a number of places. For example, in the Quality Systems portion of the FDA language, FDA proposes that it have overlapping jurisdiction with CLIA with respect to certain laboratory operations, including purchasing controls, acceptance activities, and corrective and preventive activities (CAPA).

Granting FDA authority over laboratory operations undercuts core principles at the heart of both DAIA as well as CLIA, and renders the impact of this regulatory scheme more burdensome for laboratories and the regulatory agencies. In addition, its duplicative nature defies efficiency, forcing overlapping resources and responsibilities at CMS and FDA. DTWG urges Congress to

[4] Because the FDA language is organized differently in some places than DAIA, there is not perfect alignment of provisions. We have tried to note where DAIA contains corresponding concepts.

keep the carefully negotiated and crafted provisions of DAIA that establish clear and non-duplicative jurisdictional lines.

c. Definitions

DAIA includes meticulously constructed definitions of key terms such as analytical validity, clinical validity and IVCT. Having clear and correct definitions is critical to the rest of DAIA. The definitions in DAIA incorporate input from all stakeholders, including FDA. FDA now seeks to rewrite these.

As an initial matter, it remains unclear what substantive issues are resolved through the FDA revisions of these core definitions, which were produced through years of collaboration and discussion. The DAIA language was developed through a consensus, multi-stakeholder process, over multiple years, in which FDA had ample participation and is in fact consistent with FDA's current use of these terms.

Second, a number of the definitions proposed by FDA are unclear or create other problems. For example:

- FDA's definitions consistently fail to distinguish or clarify that the relevant intent is the intent of the developer. This is particularly critical in the context of intended use, which triggers requirements set forth in DAIA;
- FDA's definitions repeatedly include unclear terms such as "test";
- Some FDA definitions include terms that implicate the practice of medicine (e.g. "diagnosing");
- Several definitions use language that incorporates vague and subjective standards, such as the repeated inclusion of the term "adequately" or "adequate" (e.g. inclusion of "adequately" in the definition of analytical validity).

The accompanying chart provides further examples and details.

Finally, FDA's definitions undercut other parts of DAIA. For example, the inclusion of parts and components in the definition of IVCT undermines DAIA's broader policy that parts and components are best regulated via quality systems.

For these reasons, we urge that DAIA's existing definitions be used.

d. Grandfathering

Grandfathering is a critical issue. Following stakeholder input, DAIA struck a balance that addresses patient needs, lab needs and industry needs. In its proposed language, FDA seems to revert to the definition it advanced as part of the draft 2014 guidance. FDA's grandfathering approach will cause confusion, take a number of laboratory developed tests out of the hands of physicians and patients, and will disrupt the balance of interests expressed in DAIA.

For example, FDA's grandfathering provisions are limited to laboratory developed tests (LDTs) that are both developed in a specific CLIA licensed lab, as well as used in that specific lab. Under FDA's approach, an academic medical center would not be able to use a test in a different

physical location that is still within the same AMC. Other labs composed of multiple facilities under common ownership and control would not be able to use tests developed by a research and development center. In practice, labs will have to ship samples back to one arbitrary location, yet there is no valid purpose or patient benefit for this process. Simply put, the FDA proposal will increase costs while adding no value, and ultimately reduce physician use and patient access to existing tests.

FDA's proposed grandfathering provisions are also impracticable with respect to its reliance upon the CLIA licensing system. FDA's proposal is based on the CLIA licensing system and the supposition that those licensures are static. Over time organizations, including academic medical centers, may undergo restructuring, labs may merge or separate, or engage in other regular business activities that would require new CLIA licensing. Under FDA's proposal such normal activities will not be possible. The FDA's grandfathering language is undermined by its own modification provisions, which, compared to DAIA, significantly expand the situations under which a submission would be required for a grandfathered test, thereby negating its grandfathered status.

The FDA's grandfathering provisions also lack clarity – depriving patients, physicians and labs of certainty. FDA's "claw back" standard with respect to mandating information submissions for grandfathered IVCTs is highly subjective and overly broad, resulting in potentially voluminous and burdensome information submission by labs. The FDA proposal does not require any showing of patient harm before FDA can mandate a submission. This approach creates substantial uncertainty and can be used by FDA to bypass the statutory provisions permitting grandfathered IVCTs to remain available to patients and physicians absent rare situations involving true risk to patients.

DAIA's current grandfathering provisions, which already incorporate several significant compromises in response to FDA input, should be retained.

e. Timelines

Timelines for FDA action on submissions are critical. The timelines in DAIA were carefully constructed after discussions with all stakeholders and reflected compromises in response to substantial FDA input. Not only does the FDA proposed language completely eliminate DAIA's thorough and structured timelines, it also neglects to provide for any alternative timelines.

Given that DAIA's timelines are the result of a consensus approach, and that FDA's proposed language fails to provide alternative timelines, DTWG suggests that the DAIA timelines be used.

f. Number of Classes

FDA proposes moving from a three-class system in DAIA, comprised of high, moderate, and low risk IVCTs, to a two-class structure. DTWG is concerned that FDA's binary structure, which fails to recognize moderate risk tests, will result in the "up-classification" of IVCTs that would have fallen into DAIA's moderate risk category. FDA's proposed definitions of high and low risk further compound this concern by including subjective elements, making it virtually impossible for stakeholders to understand which moderate risk tests will be up-classified and

which will be down-classified. The opportunities for unintended consequences in this scenario are tremendous.

While DTWG appreciates the innovative thinking of FDA, we believe that a risk classification system needs more than two categories in order to implement DAIA's risk-based approach to regulating IVCTs, and that the classification system be as clear and transparent as possible. DTWG supports a three-class system with clear and transparent classification based on risk.

g. Administrative law protections

Various provisions in the FDA language eliminate stakeholder input and administrative law protections. See, for example, language circumventing the procedural protections of the Administrative Procedures Act in § 587(e)(2)(C), § 587E(b)(1)(B), and § 587F(b).

DTWG believes that opportunities for stakeholder input, transparency by FDA, and maintenance of administrative procedural protections, are all critical to the success of FDA's regulation of IVCTs. Congress created these procedures to formalize administrative practice and integrate due process into agency action. See Wong Yang Sung v. McGrath, 338 U.S. 33 (1950). DAIA recognizes the importance of these protections and incorporate the APA's provisions. We should not bypass congressional intent by allowing FDA to circumvent them.

Furthermore, these administrative law provisions also help ensure that Congress remains the policy making body of the federal government. To the extent that authority is legitimately delegated to FDA, the process of developing regulations ensures adequate stakeholder input, agency accountability, and permanence. Agency guidance is non-binding and thus does not provide regulated parties with the same protective level of certainty, transparency, and administrative process compared to regulation. While agencies have a legal obligation to respond to stakeholder comments on proposed rules, they have no such obligation or accountability when guidance is used instead. DTWG urges that due process and administrative law requirements of DAIA remain.

h. Accessories

DTWG disagrees with the approach to accessories taken in FDA's proposed language.

The FDA conflates parts, components and accessories as one category when those articles are quite different. We believe that this may be based on FDA's prior approach in the 2014 draft guidances and past interactions with manufacturers in which FDA treated parts, components and accessories through a forced linkage with manufactured in vitro diagnostics (IVDs) (a so-called test system approach). Among other problems with this approach, the draft FDA language is contrary to the accessory provisions in the 21st Century Cures Act (Cures).

Until recently, FDA has sought to force a "systems approach" to premarket review and regulation of IVDs. Under that approach, all components, accessories and stand-alone devices associated with an IVD system have been regulated the same as the highest risk device element of the system. For example, when an automated clinical analyzer measures a specific analyte, FDA has treated the analyzer, the associated reagents, software, and in some cases pre-analytic

devices as a test system subject to the highest of the device classifications associated with the system. This means that everything within that system (including class I pre-analytics and analyzers, which, in general, are considered low-risk and require no review) have been subject to requirements for premarket approval.

To prevent such an approach, which forces high-risk requirements onto low-risk products, Congress recently changed the law in the 21st Century Cures Act to require that FDA regulate accessories, which are finished goods, based on the risks of the accessory when used as intended, and the level of regulatory controls necessary to provide a reasonable assurance of safety and effectiveness of the accessory. These changes ensure continued innovation in lab automation that improves patient care and has potential to lower health care costs.

In addition, Cures amended the Federal Food, Drug and Cosmetic Act (FD&C Act) to remove from the definition of device different types of low-risk software functionality. This included for example laboratory work flow automation, medical device data systems, and certain low-risk clinical decision support software that may have been regulated as part of a clinical laboratory test system under FDA's prior interpretation. FDA's proposed language could, in effect, pull this software back under the IVCT regulation, circumventing the advances made in Cures.

Additionally, in Cures, Congress provided for accessories to be regulated separately, based on their own risk. Congress further clarified the treatment of accessories in August 2017, including language in the FDA Reauthorization Act that amended the FD&C Act, to clarify that FDA "shall classify an accessory. . . based on the intended use of the accessory, notwithstanding the classification of any other device with which such accessory is intended to be used.'' This language mandates that FDA classify products that are accessories accordingly, regardless of their use within a test system.

The approach that FDA takes in its proposed bill essentially undoes these important provisions, allowing FDA to treat accessories that are used with other IVCTs as test systems. Language throughout FDA's proposed provisions (e.g., definition of analytical validation) confirms that FDA intends such an approach. Given experience, this would slow the availability of innovative new IVCTs that have the ability to be used as accessories, to the detriment of public health.

DTWG urges the retention of the accessory, parts and components language in DAIA.

i. Platforms

DTWG disagrees with the approach to platforms taken in FDA's proposed language.

FDA's treatment of platforms as anything but low risk, is equally as concerning as its tactics with respect to accessories. The availability of platforms is needed to spur innovation by all developers of IVCTs. Platforms themselves do not carry the risk. It is the tests and test application software that carries the clinical claims, and the clinical risk. Indeed, FDA recently has exempted from FDA review a number of platforms, recognizing just that. For that reason, DAIA wisely provides that platforms shall be low risk to enable developers access to platforms on which to develop IVCT tests. We strongly believe this is the appropriate approach.

j. Modifications

Having a logical modifications system is a key element in any successful IVCT system. DAIA carefully balances the need for FDA oversight of modifications to an IVCT, with the need to ensure improved IVCTs are available to physicians and patients in a timely way that avoids non-value-added burden to developers and FDA.

DTWG supports the "change protocol" concept in the FDA language, but FDA's language dropped a number of important modifications provisions found in DAIA that would enable innovation, while still ensuring IVCTs retain analytical and clinical validity. DTWG believes that it is critical to include the other modification provisions in DAIA which, for example, address specimen changes and use of quality systems to assess modifications.

The DAIA provision maximizes the role of quality systems, maintains clear jurisdictional lines and reduces unnecessary submissions to FDA.

k. Precertification

DTWG is very interested in the concept of precertification. We applaud FDA's innovative thinking in proposing a "precert" process. Precert is a significant policy change as it shifts the regulatory focus from a product specific approach to a process or organization centric approach, making it all the more critical that precert be properly designed. Precert raises many substantive as well as procedural questions. Additionally, not all stakeholders share the same level of familiarity with the concept and approach of precert, and comprehensive review and discussion is needed in order to ensure that FDA's precert program is built through consensus and collaboration.

Given the above considerations, DTWG suggests that Congress authorize a voluntary pilot precert program for IVCTs. Such a program would have a defined size, entry criteria and processes. The program should include industry and different types of laboratories and should have a defined time frame. At the end of the pilot, a report should be submitted to Congress and the public. Congress and other stakeholders can review that report, its findings, the experience of pilot program participants and stakeholder reactions. Armed with this data, Congress can then assess the value of the precertification concept, and determine if and how to create a more formal precert.

The pilot should be timed in coordination with the transition to DAIA's new system, and the next user fee authorization, so that Congress will have concrete data as well as an established legislative vehicle converging at the same time to further support the enactment of any precert program. Additionally, starting a full precert program now will miss the opportunity for key stakeholder input, while also requiring developer compliance with obsolete and soon to be replaced device regulations, rather than final IVCT regulations.

l. Collaborative Communities

DTWG is working to understand the Collaborative Communities provision and the rationale behind it. While DTWG supports FDA interaction with stakeholders within the context of

appropriate boundaries and transparency, it appears that the primary purpose of this provision is to eliminate the requirements of the Federal Advisory Committee Act (FACA). DTWG believes that FACA provides important protections and transparency, but we are open to additional discussions once we understand FDA's objective.

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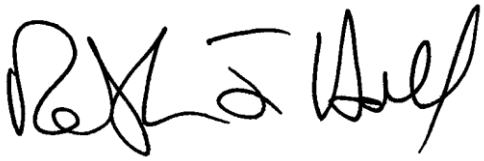
DTWG thanks Representatives Bucshon and DeGette, and Senators Hatch and Bennet for their hard work on legislative efforts to reform oversight of diagnostics, such as DAIA. In order for patients and health professionals to make appropriate decisions about their health, it is vital that they be able to trust the tests they use to be high quality, accurate, and reliable. This trust can only be achieved through comprehensive diagnostic reform that provides a predictable and timely path to market for developers while regulating tests based upon the risk to patients and not where the test is developed. We are prepared to support your offices and the committees in any way we can to help enact this important legislation.

Thank you very much for your consideration of our comments and recommendations. If you have any questions, please feel free to contact me at: 651-261-3467 or Ralph.Hall@leavittpartners.com.

Best regards,



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On behalf of the Diagnostic Test working Group (DTWG)