Diagnostic Test Working Group

The Honorable Frank Pallone
U.S. House of Representatives
Washington, DC 20510

The Honorable Greg Walden
U.S. Senate
Washington, DC 20510

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

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

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

February 15, 2019

Re: DTWG Comments on the Verifying Accuracy Leading-edge IVCT Development Act (VALID)

Dear Representatives Pallone, Bucshon, and DeGette, and Senators Walden and Bennet:

The Diagnostic Test Working Group (DTWG) greatly appreciates the time and effort that you and Senator Hatch have invested in the Verifying Accuracy Leading-edge IVCT Development Act as part of your continuing commitment to finding a legislative solution to the challenges associated with regulating *in vitro* clinical tests (IVCTs).

DTWG has long supported the development and advancement of a consensus-based legislative framework to regulate IVCTs. We support a risk-based approach to the oversight of IVCTs to best advance patient care and innovation. DTWG appreciates your continued commitment to advancing a new legislative framework for diagnostic oversight based on collaboration and input from a range of industry, laboratory, patient, and provider stakeholders.

This document provides a summary of DTWG's comments on the December 6, 2018 Discussion Draft "Verifying Accuracy Leading-edge IVCT Development Act" (VALID). The accompanying redline of the discussion draft provides more detail, and these documents should be considered together. We are optimistic that the VALID framework can be reasonably adapted to provide an efficient, effective model for diagnostic regulation. We hope our detailed comments will support such a process and we look forward to working with you to advance the process.

I. Precertification

Precertification when properly constructed, can help advance innovation and patient access to high value IVCTs while eliminating unnecessary regulatory burden.[1]

[1] If on the other hand, Congress prefers to utilize a pilot precertification program (which DTWG would also support), we will likewise work with Congress and stakeholders to craft an effective and efficient pilot precertification program.

As such, the following principles are critical to help ensure that any IVCT precertification program is successful:

1. Precertification must be simply an alternative way of demonstrating a reasonable assurance that an IVCT is analytically and clinically valid, and it should not be viewed as raising or lowering the regulatory standard.
2. Precertification should be an optional pathway.
3. Precertification does not negate the importance of a risk-based regulatory system that utilizes well-understood risk classes.
4. Precertification must be structured in a way that will work in the real world for all different types of IVCT developers.

Furthermore, there are several core components to a precertification program: the scope of precertification, the assessment process and criteria, and utilization of a risk-based approach using quality systems, which we describe below. There are other important issues related to precertification (*e.g.*, method of assessment and how precertification can be revoked and transferred) that are not addressed in the discussion draft, which we stand ready to work with you to address.

I.A. Scope of Precertification

Precertification scope should be based upon IVCT technology or discipline, and clearly provide each developer with the flexibility to determine when to seek precertification.

Categories: VALID defines the scope of precertification through its "test group" concept (*see* Section 587(11)). The test group definition is too narrow to support a viable precertification program. VALID's test group concept could require the creation of hundreds of separate precertifications within one developer. As a result, each precertification would cover so few IVCTs that its value would be minimal and the burden of obtaining each precertification high. Likewise, FDA would be overwhelmed by precertification requests.

Defining the scope of a precertification by some combination of IVCT technology or clinical discipline strikes an appropriate balance, provides consistency, and ensures flexibility. We believe that approximately ten clinical disciplines, based upon the State of New York's test categories, could be identified and used to define the scope of precertifications (*e.g.*, disciplines such as Cytopathology, Hematology, and Parasitology).[2]

Exclusions: The current draft language excludes large sets of IVCTs from precertification. For example, so-called "cross-referenced" IVCTs are not precertification eligible. These blanket exclusions are not risk based and would result in many IVCTs being ineligible for precertification. In fact, one stakeholder has estimated that perhaps 80% of its laboratory test protocols could be deemed to be cross referenced IVCTs under the current draft and thus ineligible for precertification. DTWG proposes that all IVCTs that meet the definition of high-risk with mitigating measures should be eligible for precertification unless specifically identified by FDA as ineligible and with necessary justification and opportunity for public comment.

[2] New York State Dept. of Health, CLEP Guide to Program Requirements and Services, at 26-34, *available at* https://www.wadsworth.org/sites/default/files/WebDoc/CLEPGUIDE_July2018_FINAL.pdf.

Flexibility: Each eligible developer should have the flexibility to determine the one or multiple technologies or disciplines that it seeks to have precertified. A single streamlined application process should be used if precertification of multiple technologies or disciplines is sought simultaneously. In addition, if a developer chooses not to undergo precertification, they should have access to a streamlined premarket review.

I. B. Assessment Criteria and Process

The assessment criteria used to determine whether an applicant for precertification receives precertification should be designed to provide confidence in the developer's FDA-related processes, and should be based on applicable FDA regulatory requirements (not a different set of regulatory requirements). The assessment itself should be designed to confirm that the applicant has quality system processes in place to demonstrate its ability to meet applicable FDA regulatory requirements. The benefits of precertification must be tangible and should be based on (i) risk classification, and (ii) the scope of a quality system.

Precertification should serve as an alternative, quality system process-oriented way in which a developer provides a reasonable assurance that the IVCTs it develops are analytically and clinically valid.

The process and submission requirements for becoming precertified should be focused and follow least burdensome principles. The current draft language in VALID should be revised to eliminate unnecessary burden and to extend the renewal timelines for precertification. As drafted, a precertification application would require a PMA type submission for a specific IVCT in addition to voluminous information on quality systems. The burdens of such a submission, considered in light of the limited benefits of precertification, will lead many developers to forego precertification.

The precertification assessment should focus on the developer's general quality systems applicable to the IVCTs within the eligibility scope.

DTWG has consistently advocated that FDA's limited resources should be targeted at the areas where it adds the greatest value, which is primarily related to high-risk IVCTs (as defined in Section 587(7)(B)). We agree with VALID that precertification should only include IVCTs that are high-risk mitigated.

Precertification processes should include the following:

- If a developer desires to offer a new IVCT (*i.e.*, an IVCT for which it would otherwise make a premarket submission) within the scope of a precertification, standard premarket submission and review processes should not apply. Instead, the developer should be permitted to offer the new IVCT upon listing the IVCT with FDA, perhaps utilizing FDA's CTIS concept.
- Precertification should not alter the post-market adverse event reporting or monitoring requirements or processes for an IVCT that is high-risk mitigated as set forth in Section 587(7)(B)(2). Modifications to an IVCT that has been precertified should be permitted without a submission, as long as the IVCT as modified remains within the scope of the precertification.

- Precertification should not be withdrawn absent serious, repetitive non-compliance within the scope of the actual precertification that presents a serious risk to public health. There must also be due process procedures before precertification can be withdrawn.
- Low risk IVCTs are not subject to precertification or individual premarket submissions.

Multiple stakeholders coming from different parts of the diagnostic world have overwhelmingly concluded that the current approach to precertification will not be something they can utilize for any number of reasons including those listed above.

II. Modifications

The majority of laboratory developed tests today are modifications to FDA-approved or cleared in vitro diagnostics. Additionally, streamlined modification processes are essential for any IVCT developer. To ensure continued innovation and patient safety, DTWG believes modification submissions should be limited to those that create **new intended uses** or which have a meaningful clinical impact.

As currently drafted, VALID's modification framework and the reliance on the concept of "test group," causes a submission for a much broader scope of changes, essentially any change to any element of a test group, without regard to the impact of that change on actual patient risk or product performance.

A submission requirement for a modification to an IVCT should be triggered only by a change in an IVCT that creates a new intended use — one that is either high risk or high risk mitigated (as defined in 587(7)) — or which has a meaningful clinical impact. Requiring submissions for such other modifications adds substantial burdens and barriers to innovation without furthering patient safety and is not a good use of FDA resources. Similarly, submissions should not be required for modifications to IVCTs that are within the scope of precertification.

III. Premarket Review & Classification

DTWG believes that the approach to premarket review in VALID should be risk-based and agree that it should reflect a consideration of whether FDA's premarket review adds value. VALID creates several pathways to market based on risk classification. For high risk IVCTs without mitigation, VALID mandates individual test review, with requirements similar to what is currently in a PMA submission. High risk IVCTs which have their risk reduced through mitigating measures have the option of the precertification pathway or, as set forth in Section 587B(b)(3), utilizing a more stream lined premarket submission (thus following the VALID policy of using FDA review when and how it adds value). DTWG believes all low-risk tests should be exempt from premarket review.

In order to more closely follow the VALID policy of utilizing FDA review only when it adds value, DTWG suggests:

(1) VALID take a risk-based approach to when an IVCT requires review.
(2) Premarket review requirements for high-risk IVCTs should not require quality system and manufacturing information, which can be assessed outside of a product review. There should not be IVCT types, such as cross-referenced or first-of-a-kind, that automatically

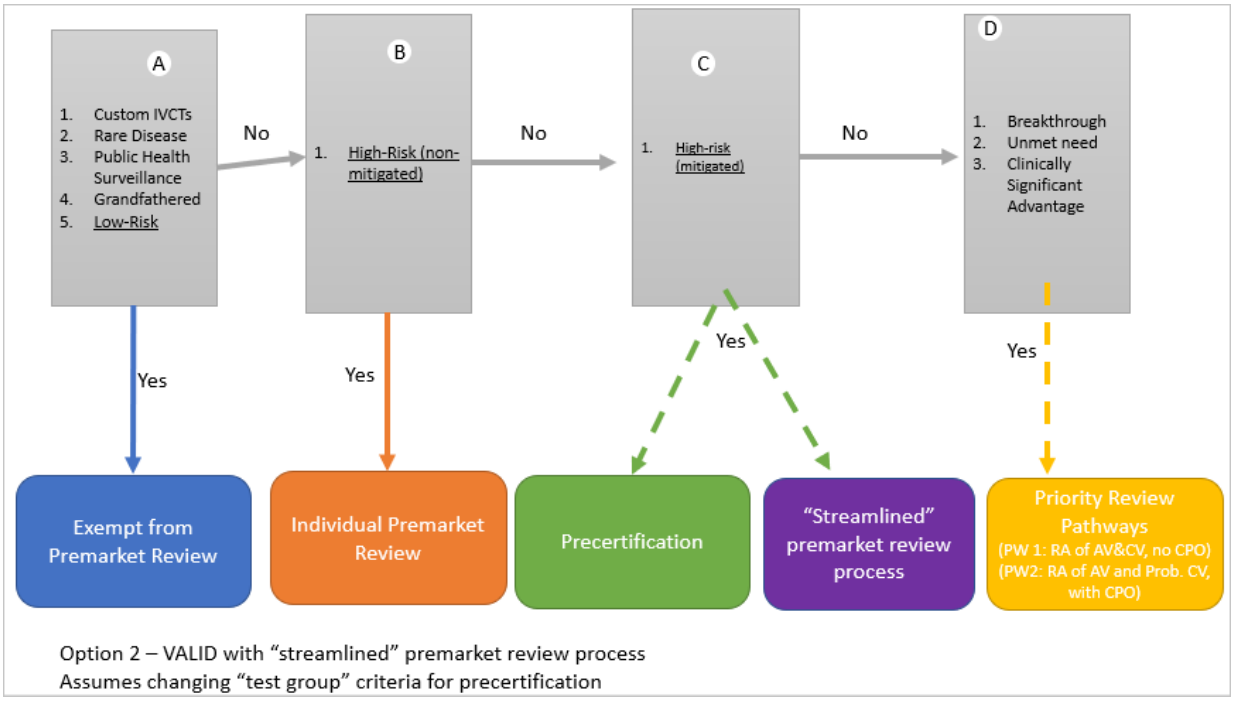
are deemed high-risk and require review. Such an approach does not incorporate an actual risk evaluation of these IVCTs.

(3) IVCTs that meet the definition of high-risk mitigated should have the option of undergoing precertification or an individual streamlined premarket review. We disagree with categorical exemption of IVCTs, such as those for home use, from precertification.

(4) IVCTs that meet the definition of low risk should be exempt from premarket review.

DTWG's proposed changes to VALID also provide for a distinct approval process to facilitate access to important IVCTs where the developer demonstrates either a reasonable assurance of analytical validity and clinical validity, or demonstrates a reasonable assurance of analytical validity and probable clinical validity, provided the developer and FDA agree to specific post-market obligations. This pathway will be available for IVCTs that meet criteria related to unmet medical need, a breakthrough technology, or a clinically significant advantage over previously approved, cleared, or otherwise legally marketed IVCT.

See graphic below:



IV. Clinical Laboratory Improvement Amendments (CLIA) & Jurisdiction

Harmonization of existing CLIA with new regulatory oversight proposed in VALID is essential to ensuring complete regulatory coverage and consistent provisions, while also maintaining clear and distinct jurisdictional boundaries and avoiding duplicative regulation. The framework must have a clear distinction between IVCT development activities and manufacturing activities as compared to laboratory operations. Each of these activities should be distinctively and solely regulated by FDA and CMS respectively.

The framework should preserve clear jurisdictional lines that distinguish between (1) FDA regulation of test development, (2) CLIA regulation of laboratory operations, and (3) state regulation of the practice of medicine. DTWG understands the desire to limit the number of

changes to CLIA. While it may not be feasible to completely modernize CLIA at this time, it is our firm belief that there are some limited ways in which CLIA must be harmonized to the framework (or a similar approach) to ensure successful implementation. VALID seeks to establish a complete regulatory scheme based on both the FDCA and CLIA, and cross-referencing will therefore be necessary to both.

Without some clarifying amendments to CLIA, regulated parties will be subject to duplicative, overlapping and inconsistent regulation. For example, CLIA currently states that IVCT validity is under CMS jurisdiction. Without changes to CLIA, this would conflict with the new FDA jurisdiction over analytical and clinical validity of IVCT development. Likewise, under CLIA, CMS has jurisdiction over laboratory operations, including personnel and purchasing controls. Without some conforming amendments, both FDA and CMS may have jurisdiction over the same activity. It is essential to ensure that FDA authority not extend to laboratory operations.

The attached redline contains the current language of CLIA, redlined to show those changes DTWG believes are necessary to ensure clear jurisdictional lines and the elimination of any potential regulatory gaps. While DTWG appreciates that broad improvement of CLIA may not be possible in this framework, at a minimum, some CLIA harmonizing amendments as we have provided are critical to ensure appropriate jurisdictional lines and distinguished roles between FDA and CMS.

V. Transition

Any transition provision should address timing for the transition, required actions, and rule sets for handling new or modified IVCTs developed during the transition phase. The basic approach advocated by DTWG utilizes the policies in VALID as the foundation for a transition process that brings certainty and balance to the IVCT regulatory system. We suggest defined timelines and a transition process that calls for: (1) a certain process for the development of implementing regulations, (2) clear timelines for completion of the transition, and (3) a process for permitting continued patient access and innovation while ensuring that any IVCT that truly does hurt patients is removed from the market.

VI. Grandfathering

Grandfathering is necessary for patient access and to prevent disruptions in the health care system. Carefully crafted grandfathering provisions must provide clarity and predictability to developers, while also providing FDA with appropriate oversight authority to ensure patient protections. Further, any removal of grandfathered IVCTs must be based on true and significant public health risks and established using objective criteria and clear processes as we have suggested.

VII. Device Regulation

The fundamental distinction between IVCTs and therapeutic devices is essential to any regulatory system for IVCTs. VALID establishes a new, distinct regulatory system for IVCTs, and we identify instances where legislative language, provisions, and processes in VALID should be further tailored to address the distinct functions of IVCTs. In addition, the new framework should not incorporate or directly cross-reference device provisions, and should require notice and comment rulemaking over a period of at least three years to ensure stakeholder input and transparency to establish this new system.

VIII. Parts, Components, and Accessories

The current approach in VALID to the oversight of parts, components and accessories will create unnecessary regulatory burden and will slow innovation.

True parts and components, by definition, are not finished IVCTs that can be used for patient care. As such, quality system regulations, particularly supplier controls, are the appropriate mechanism for ensuring compliance. By using quality systems as the oversight system for parts and components, and an appropriate regulatory pathway commensurate with patient risk for finished products, FDA will have visibility into all aspects of the process and the ability to assess the actual use of a part or component, all without having duplicative or non-value-added regulation. Otherwise, FDA could be flooded with multiple submissions for the same part or component, one at the time of distribution of the part or component, and another at the time of the incorporation of the part or component into any finished product.

Accessories, on the other hand, are finished products and should be classified as IVCTs based on their own risk. This approach avoids uncertainty and provides the correct level of oversight. Accessories should be assigned the same risk classification as the IVCT with which the accessory is used.

Part of the confusion arises from VALID's incorporation of a "systems approach" in which multiple finished products being used in the same patient centric interaction are treated as one. This approach confuses the regulatory concept of "component," with FDA considering each finished product as an element or component of the overall system. As a result, it treats pre-analytics, platforms, accessories, and potentially even non-IVCTs, under the same risk classification, even when the specific finished IVCT may be lower risk, exempt, or subject to enforcement discretion. In addition, this approach is counter to policy enacted through 21st Century Cures Act and will impede innovation. In support of the policies underlying VALID, DTWG continues to believe that platforms should be low risk and that all other IVCTs should be reviewed based upon the risk profile of that IVCT. Any other approach would add unnecessary regulatory burden and delay IVCT development and innovation.

DTWG has attempted to address these issues through its revised definition of IVCT to include finished products and laboratory test protocols, and by adding new definitions for parts, components, and raw materials as well as a definition of accessories. We have also added new language related to regulation of platforms and platform families.

IX. Scope of FDA's Discretion: Standards for Implementation and Rulemaking versus Guidance

A clear and predictable regulatory structure is critical to support understanding and certainty for all stakeholders. Large and small developers are making multi-year commitments and require clarity and certainty.[3]

[3] This is particularly true for the multitude of laboratories that do not have experience with FDA regulation and would potentially be subject to VALID's requirements as drafted.

In addition, VALID provides FDA with tremendously broad and general flexibility to implement or impose vague standards (*e.g.*, the Secretary may, upon the initiative of the Secretary require a test group to go through full premarket review even if it is otherwise eligible for an alternative statutory pathway; the Secretary may expand the scope of adverse event reporting as it determines necessary; premarket approval is based on FDA's discretionary view of "adequate" validity). Additionally, VALID vests FDA with broad discretion, does not require rulemaking, and calls for much of the Act's implementation to be effectuated through guidance, a procedural mechanism that is by its nature non-binding and lacks important procedural protections afforded through the Administrative Procedures Act.

All stakeholders need clear, detailed, and predictable standards. Furthermore, any regulatory scheme implemented by guidance would fail to ensure that regulatory standards and approach will remain consistent over the long term regardless of change in Administration.

X. Technical Edits

Finally, we note two specific technical edits that are incorporated in our redline edits. Although we may not have edited every provision, we do believe two universal edits are needed.

1. VALID should always use the term "in vitro clinical test" and not "test." Simply referencing "test" when the defined term is "in vitro clinical tests" will create interpretation issues as to the intended scope of the term "test."
2. VALID should always clarify that the relevant intended use is that of the developer by using "intended by the developer." In some places the text instead simply references "intended use." Intended use is determined by the developer, and that should be made clear in the legislative text.

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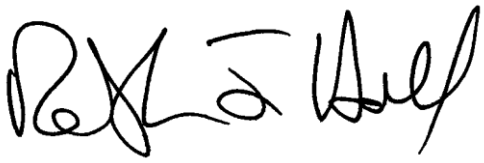
Thank you very much for your consideration of our comments and recommendations. If you have any questions, please feel free to contact me at: 651-261-3467 or Ralph.Hall@leavittpartners.com.

Best regards,



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On behalf of the Diagnostic Test working Group (DTWG)