LEAVITT PARTNERS

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DTWG

The VALID Act Key Open Policy Issues & Questions

We applaud the sponsors and their staff for their hard work on a bipartisan and bicameral bill intended to advance patient benefit, promote innovation, and provide predictable regulatory requirements. We look forward to working with Congress, FDA, and other stakeholders to improve and advance this important initiative.

The following are DTWG's preliminary thoughts, highlighting key aspects of VALID that we support and others that need further refinement. We have not yet done a redline and are continuing our review of the bill and our conversations with other stakeholders.

Our comments are based on the need to implement the following key principles. We believe that there is a general consensus around these principles. Any substantive provisions should be assessed using these principles:

Key Principles of Diagnostic Reform and Oversight

- Advance patient care.
- Provide a simple yet comprehensive regulatory framework for Vitro Clinical Tests (IVCTs), separate and distinct from the current regulatory framework for medical devices.
- Apply the same regulatory principles to the same activity regardless of the identity of the entity developing or performing the test.
- Establish clear, consistent, non-overlapping lines of jurisdiction based on activity
    - Any premarket review of test development would be regulated exclusively by an appropriate center at FDA.
    - Laboratory operations would be regulated exclusively under CLIA,
    - The practice of medicine would be regulated exclusively by the States.
- Provide a risk-based regulatory framework that differentiates regulatory burden depending on the test's risk profile of high, moderate, or low risk.
- Advance diagnostic innovation.
- Create a certain and rational system for regulation of IVCTs.

- Provide appropriate grandfathering provisions that establish clear, objective standards to enable predictable ongoing access to existing tests while protecting patients against tests that pose legitimate threats of harm.
- Establish a reasonable transition period for compliance with any new applicable requirements to allow for appropriate certainty and planning.
- Utilize a least burdensome regulatory structure.

Positive Features of the VALID Act (VALID)

Comprehensive legislative reform is needed to advance patient access to innovative diagnostic tests, ensure rational regulatory processes and provide certainty for all stakeholders. While additional discussion is necessary, as laid out below, we appreciate the hard work of Representatives Bucshon and DeGette, Senators Burr and Bennet, FDA and other stakeholders to find a constructive path forward to ensure patient access to accurate and reliable diagnostic testing through appropriate regulatory oversight.

The introduced text of VALID is an important step in developing and passing diagnostic test reform. We look forward to continuing our work with Congress, FDA, and other stakeholders to improve and advance this important initiative. The goal of all stakeholders is to promote innovation and protect patients. Diagnostic test reform will advance these important objectives.

Subject to some remaining issues discussed further below, key areas of positive progress in VALID as compared to the December 2018 discussion draft include:

- Improved separation of IVCTs from current medical device regulations.
- Several of the definitions have been improved.
- Pre-emptive language prohibiting state, tribal, or local governments from creation of IVCT laws and regulations that conflict with or are in addition to VALID.
- Efforts to avoid duplicative regulation between FDA and CLIA.
- Exceptions to submission requirements for modifications are heading in the right direction to establish appropriate levels of oversight. In particular, the specimen stability exception is quite valuable.
- Expanded grandfathering provisions provide greater certainty for IVCTs currently on the market.
- A breakthrough pathway establishing a program to address unmet patient needs.
- Technology certification needs additional clarification but is substantially improved over earlier concepts.

Open Issues and Challenges

Definitions

Clear, objective, comprehensive, and consistent use of definitions is crucial for all parties to understand regulatory expectations and legislative intent. VALID includes definitions of several key terms such as analytical validity, clinical validity and IVCT.

However, several definitions are unclear or create other problems. Other definitions are missing. For example:

- Several definitions include unclear and subjective terms such as "sufficiently".
- Several terms in Section 587J, Quality Requirements, are not defined and are not commonly used in clinical laboratories, (e.g., design controls, acceptance activities). They should be defined and be pertinent to lab test development, not medical device development.
- "Indications for use" is a new definition of a concept formerly called a "test group". Use of the term is very confusing and raises concerns in addition to those previously expressed about a "test group". Currently, "indications for use" is a term of art with a very different meaning in the context of existing FDA regulation of medical products.
- The Inclusion of "advertising" in several definitions has the effect of expanding FDA jurisdiction inappropriately.
- Since there are situations in which laboratory developed tests and manufactured test kits need to be differentiated for the purpose of appropriate regulatory oversight (as FDA has acknowledged in its guidance for COVID-19 tests), VALID should adopt the "laboratory test protocol" and "finished product" definitions from DAIA and modify the definition of IVCT to acknowledge their existence as subparts of the IVCT definition, as in DAIA.

Jurisdiction

There should be clear, non-overlapping jurisdictional lines that recognize the distinct roles of FDA, CLIA, and states. The jurisdictional structure, which is foundational to stakeholder consensus, is built upon a clear distinction between IVCT development activities, which are solely regulated by FDA, and laboratory regulations, which are solely regulated by CMS (i.e. CLIA).

Modernization and harmonization of CLIA with VALID 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 non-duplicative manner. Moreover, there should be a distinction between FDA oversight of CLIA laboratories that register with the FDA as developers and those CLIA certified laboratories that do not develop IVCTs but do run clinical diagnostic tests. The latter CLIA laboratories should not be subject to FDA oversight, except for cause such as violation of the VALID Act, while only IVCT developmental activities of registered CLIA laboratories should be

subject to FDA oversight since many of these labs will also be conducting diagnostic tests just as any other CLIA lab would do.

One challenge is that VALID grants FDA new authority to oversee certain activities currently governed by CLIA, such as purchasing controls. Presently, CLIA authorizes clinical laboratories to purchase reagents, controls and other items needed to run a clinical test from various manufacturers as long as the laboratory has processes in place to verify or validate the items used. The concern with FDA's proposed approach is that FDA may attempt to limit the ability of clinical laboratories, especially laboratories that are not IVCT developing laboratories, to do this, thus conflicting with CLIA and potentially limiting the ability of clinical laboratories to enter purchasing agreements with various suppliers.

Although VALID attempts to prohibit FDA from issuing or enforcing "regulations" that are duplicative of regulations under CLIA, it does allow FDA to regulate through duplicative "guidance". As drafted, FDA could take the position that the FDA purchasing controls, for example, are not duplicative of CLIA processes and then could use the guidance as a justification to independently inspect CLIA laboratories and take enforcement action against them because the laboratories followed CLIA and not an FDA guidance. Therefore, although the VALID text says that quality requirements must avoid duplication of regulations under CLIA, VALID already includes duplicative requirements. This is most notable regarding duplicative inspection and enforcement authority by FDA over clinical laboratories that are not developing IVCTs and is contrary to the sponsors' stated goal of avoiding duplication.

VALID, as drafted, makes no amendments to CLIA. Thus, various CLIA requirements that currently overlap with new authorities granted to FDA under VALID will continue to overlap and cause confusion. For example, CLIA requires all CLIA certified laboratories to establish the performance characteristics of their tests such as the analytical validity of the tests they perform in the CLIA certified lab. CLIA regulations and interpretive guidelines specify the way this test development activity is to be performed. VALID grants FDA authority for premarket review of the analytical (and clinical) validity of IVCTs developed in those high complexity CLIA certified laboratories that register with the FDA as IVCT developers. However, most CLIA certified laboratories will not be registered as FDA developers, but will be running the IVCTs for diagnostic purposes. Overlap and conflict occur in this scenario as CLIA requires all CLIA certified labs to establish their own performance characteristics of the tests they run, while VALID also requires the developer (e.g. CLIA certified laboratory) to demonstrate analytical validity. This is an example of duplicative requirements.

Additionally, some provisions appear to grant FDA authority to regulate certain aspects of the practice of medicine, rather than leaving such oversight exclusively to the States. For example, in the case of recalls VALID outlines a process in SEC. 587Z (d)(3)(B)(iii) that requires developers to provide notice to individuals about risks associated with the use of a recalled in vitro clinical test. Informing individual patients about the risks applicable to that patient is part of the practice of medicine.

IVCT Classifications

First, DTWG strongly supports a risk-based classification and oversight system. On occasion, FDA has stated that VALID should not be risk based. We disagree and urge the sponsors to continue to employ risk-based concepts.

However, VALID proposes moving from a three-tier, risk based classification system to a two-tier classification structure which fails to recognize moderate risk tests and will result in the "up-classification" of a significant number of IVCTs to a high risk classification that otherwise would have fallen into a moderate risk category. Unless meeting a specific exception, all IVCTs subject to review default to the high-risk classification. This results in unnecessary and non-valued added regulation.

While DTWG appreciates the innovative thinking in VALID, we believe that a risk classification system needs more than two categories to implement a risk-based approach to regulating IVCTs, and that the classification system should be as clear and transparent as possible. DTWG supports a three-class system with transparent and clearly defined parameters for each classification based on realistic risk assessments. Under VALID tests that are neither high risk nor low risk default into either an undefined "high risk with mitigations" category, or an IVCT subject to expedited review or a technology certification pathway. This process provides unclear guidance to IVCT developers and does not allow developers to adequately plan for test development. Further, a substantial amount of discretion is left to FDA reviewers as there is no specific regulatory pathway for them to follow in determining what mitigations are enough to lower the risk level of an IVCT, or which submission requirements must be met by developers to get approval for the IVCT. (Even FDA's terminology can result in in confusion. What will the IVCT be called – a high risk test that met mitigations?)

DTWG supports risk-based regulation – a concept that that FDA has also long espoused. Categories such as "first in kind" and "cross-referenced IVCT" are "risk neutral" classifications, meaning that but for the fact the test is in one of these artificial categories, a truly low risk test would be regulated as a high-risk test. The high-risk category requires full premarket review and even the FDA proposed abbreviated high-risk pathway also requires a major submission, thus putting some otherwise low risk tests into an unreasonable regulatory review process. The high-risk category also triggers burdensome modification reporting requirements. These non-risk-based classifications should be eliminated, and each IVCT should be evaluated and regulated based on its realistic risk profile unless subject to an applicable exemption.

Inappropriate risk classifications lead to non-value-added regulatory requirements. Such requirements add unnecessary cost to the health care system and reduce innovation.

Submission Requirements

Submission application requirements seem excessive and do not follow the least burdensome philosophy or regulatory requirements. In particular, 587B(c)(2)(B) seems burdensome, essentially conducting a market and clinical analysis of any similar tests and of other methods such as physician observation. It is also unclear what the difference is between section (iii) of

that clause and 587B(c)(2)(H). For another example, the requirement to discuss the data in each literature reference (see 587B(c)(2)(D)) is a time consuming and excessive activity for little or no value.

The amount of information required for registration and listing is also excessive (see 587I(b)(2)). The information in the registration and listing system should be limited to that information that is needed to identify the IVCT, its intended use and the identity of the developer. Much of the other information will be available in the laboratory's test catalog and is redundant, leading to unnecessary clerical burden for the developer. Additionally, annual reporting requirements are too broad and burdensome without adding value.

The deadline for approval of a premarket submission is too long at 90 days (see 587B(g)(1)(A)). Earlier FDA had taken the position that 75 days was sufficient.

The Humanitarian IVCT exemption should be based upon the prevalence of the disease in the entire U.S. population and not based on how many doctors might use a particular test.[1] It is essentially impossible for the developer to know how many people may use a test and the present language seems to place a burden on an IVCT developer to know what is almost impossible for the developer to know. For example, some physicians may order tests to rule out diseases in arriving at a diagnosis of their patient. This type of medical procedure and practice should not be used to exclude an IVCT from a rare disease or humanitarian use exception that could be detrimental to patients who have the rare disease.

Modifications

VALID should maximize the role of existing CLIA quality system requirements for laboratory operations, maintain clear jurisdictional lines between CLIA and FDA requirements and processes and reduce unnecessary submissions to FDA. Having a logical and balanced modifications system is a key element to having a successful IVCT system where the government agencies are not overwhelmed with non-essential modification submissions or where clinical laboratories and manufacturers are not being subject to excessive regulatory oversight. Premarket review of modifications should be limited to only those modifications that would have meaningful clinical impact on the patients on whom the test is performed or that significantly modifies the test's intended use. Other, less impactful modifications should be handled pursuant to CLIA or IVCT/VALID quality system requirements thus providing an appropriate balance for innovation and patient protection.

VALID would require submission of a modification to an IVCT (including a grandfathered IVCT) for premarket approval if, among other things, it "affects" the analytical or clinical validity of such test. The term "affects" could be subjectively interpreted by FDA to require broad submission of modifications that do not have a meaningful clinical impact or change the

[1] DTWG supports either the 8,000-patient threshold established in 21st Century Cures or the 10,000-patient threshold established in VALID

intended use of the test. That provision should be revised to narrow its application more objectively to include changes that have a meaningful clinical impact or change the intended use of the test as stated by the developer.

The inclusion of an exception for specimen-related modifications made to extend specimen stability is very important to patients, laboratories and IVD manufacturers and impacts a large percentage of modifications that IVCT developers and users deal with every day. The inclusion of an exception for modifications made pursuant to an approved change protocol is also helpful. However, other changes to IVCTs should also be relieved of having to undergo FDA review, such as changes made pursuant to recognized standards. If FDA or other standards organizations have recognized a standard, and a modification is made in accordance with that standard, it would create unnecessary work for both the Agency and the developer to submit that modification for premarket review.

The requirement of an annual report listing all test modifications (see Section 587B(k)), including validation data "as applicable" is overly burdensome and not in the spirit of the least burdensome regulatory requirements. Many laboratories have a large and dynamic test menu, and manufacturers offer many IVCTs; collating modification information annually on this large number of IVCTs for submission would be a tremendous clerical burden for no benefit. Remember that developers must keep such documentation on file and FDA has the authority to review that documentation during inspections. We are also concerned about discretion explicitly granted to the Secretary to require additional information in the annual report with no limitations. There need to be some criteria and limits on such power.

The "changes being effected" (or "CBE") provision also does not fit IVCTs. The CBE provision is intended for safety related changes. The IVCT standard for approval and physician access to IVCTs is not "safety" (as that concept does not fit the role of IVCTs) but rather analytical and clinical validity. The CBE provision should be struck.

Technology Certification

The technology certification (tech cert) pathway, while improved from previous drafts, still contains so many exceptions that its narrowness raises questions about its utility. As discussed previously, there should be a clearly defined pathway for moderate risk tests apart from tech cert as tech cert will not be viable for several developers and several IVCTs will not fit within tech cert requirements. Tech cert could serve as an alternate for those moderate risk IVCTs (otherwise now called high risk with mitigations) that meet the requirements to go through the tech certification process.

Several aspects to tech certification should be clarified:

- It is unclear why these specific categories for tech certification were selected and the process and criteria for creating more categories.

- How is tech certification lost? What are the criteria for losing tech certification and what is the process? What is the effect of losing tech certification on IVCTs in the market pursuant to a tech certification order?
- It is unclear what happens if a tech certification timetable expires and the laboratory does not have another representative test to submit. Further, if an IVCT has obtained the tech certification and the developer remains in good standing, why should the certification be at risk based on a timetable or lack of a different representative test to submit?
- First-of-a-kind and cross-referenced tests should be eligible for tech certification if these concepts are not eliminated as we prefer. DTWG has not heard a reasoned explanation for the exclusion of these IVCTs. In fact, these classifications should be eliminated (See, above comment on risk classifications.)
- There are a substantial number of open questions regarding the role of tech cert in real life. For example, are all tests that were introduced under a previous tech cert order considered approved, or would the lab need to submit one of those tests as their next representative test? If the latter, the value of tech cert is significantly diminished. What if the developer chooses not to seek a renewal of its tech cert order? Are the IVCTs introduced under the previous tech cert order still considered to be approved? We would prefer that tests marketed under a given tech certification remain approved without further submission, and the laboratory would reapply for a tech cert for the given technology the next time they want to market a new test in that category.
- Several business issues such as licensing, corporate mergers and acquisitions and sales of IVCT rights remain open as to how these would affect the standing of a company for tech certification eligibility.

Tech certification is a completely new regulatory process and some time and experience is needed to determine how it should work. The final legislation, if it includes a tech certification process, should consider how to provide a process to adjust the tech certification process to address lessons learned.

General Exemption Authority

The current legislation gives the Secretary the unlimited ability to exempt certain IVCTs/developers from all the obligations or requirements under VALID. No criteria or process is laid out. Giving the Secretary and FDA such unfettered authority raises questions about protecting public health and giving unfair advantage to some entities or sectors that are, at that time, popular with HHS and FDA. Our strong preference is to delete this section.

While some flexibility is needed for implementation, such as to address inherent differences between laboratory test protocols and finished products, VALID should apply equally to all entities engaged in the same activity and be bounded by clear, objective, and appropriate criteria and processes.

Transition & Grandfathering

We are grateful for the improvements in the grandfather provision, including expanding grandfathering to all IVCTs that are first offered to the public right up to the time of enactment (rather than 90 days prior to enactment). This includes those tests that were developed within a CLIA certified high complexity lab and further includes those tests that were performed in a high complexity CLIA laboratory under common ownership with the developing lab. We also appreciate the expansion of the grandfather exemption in VALID to include an exemption from the entire subchapter except for the claw back provision, registration and listing, and adverse event reporting requirements.

We are supportive of several of the changes made to the "claw back" provision that now requires FDA to have valid scientific evidence of a health problem with a grandfathered test before initiating an inquiry about its analytical or clinical validity. Further, the VALID update authorizes FDA action to recall and/or pull a grandfathered IVCT from the market when the FDA finds that 1) there is insufficient valid scientific evidence to support the analytical or clinical validity of the IVCT *and* that the IVCT is being offered with materially deceptive or fraudulent analytical or clinical claims; *or* 2) that it is "reasonably possible" that the IVCT will cause serious adverse health consequences; *or* 3) that there is sufficient valid scientific evidence that a specimen receptacle did not perform as intended and will not support the analytical validity of tests with which it is used, or it is not safe for use.

Many of these provisions represent positive improvements from prior drafts; however, the "reasonably possible" standard is still too speculative and subject to abuse of discretion by the Agency. That standard should be "reasonably probable", such that if the other provisions of the claw back provision are not applicable, a grandfathered test could only be pulled from the market if it is "reasonable probable" that the IVCT will cause serious adverse health consequences.

The transition period under VALID ends on the effective date, which is currently defined as the first day of the fourth fiscal year that begins after the date of enactment, which amounts to a 3-4-year transition period, depending on when the bill is enacted (e.g., if the bill is enacted on September 30, 2020, the effective date would be 10/1/23, 3 years and 1 day after enactment). Laboratories and test kit developers need a predictable period for transition, and 3 years is probably not enough time. Further clarity on the transition provisions would be beneficial.

A 4 or 5-year transition would be more reasonable for the major changes stakeholders will need to make. There must be time for FDA, following APA processes, to develop new rules and implement regulations and then additional time for stakeholders to come into compliance with those new requirements. The timeline suggested by DTWG in past discussions is consistent with timelines for other major changes such as the Quality System Regulations in the late 1990's.

During the transition period between enactment and the effective date, as currently set forth in VALID, FDA would have the authority to apply all device regulations to all transitional IVCTs, including laboratory developed tests (LDTs) or laboratory test protocols introduced between

enactment and the effective date. While we recognize the desire to begin implementing some additional oversight during the transition period, the application of device authorities to laboratory test protocols during the transition period is not an appropriate way to accomplish that objective. One of the primary purposes of diagnostics reform is to avoid application of device regulation to IVCTs, for which the device framework was never intended.

We would support some incremental regulation of transitional IVCTs during the transition period, such as early implementation of certain VALID requirements like adverse event reporting that would otherwise become effective on the effective date; but we do not support application of current device authorities to IVCTs including LDTs or laboratory test protocols, to be followed by a subsequent transition to IVCT regulation upon the effective date.

Emergency Use

We appreciate the last-minute revision of VALID to seek to codify FDA's February 29 guidance enabling LDTs to be offered to help meet the testing needs of the country during a declared emergency prior to issuance of an EUA under certain conditions. This provision will need to be expanded to incorporate subsequent guidance from FDA, as well as some potential lessons learned from the COVID-19 pandemic, including the need to import needed products more easily into the USA.

Overall, the EUA provisions should be reassessed given the ongoing experience with COVID-19. Lessons learned should be incorporated into VALID.

However, it is also important to understand that in the greater scheme of things, the deregulatory nature of this specific provision is a very small portion of overall regulatory oversight. We must ensure that the prevailing effect of VALID in its entirety does not increase non-value-added regulatory burdens on stakeholders as compared to the status quo.

Use of Guidance Rather than Rulemaking

VALID authorizes FDA to issue regulations, but also leaves FDA discretion to implement numerous sections of the new framework with guidance. Our experience has been that when given the choice, FDA will choose guidance over regulations (e.g., draft guidance on regulation of LDTs as devices). Definitionally, guidance is not law, but should merely be an expression of the Agency's interpretation of the law or pertinent information for stakeholders how to do things in compliance with the law and its regulations. The rulemaking process should not be abrogated by using guidance as rulemaking is required under duly enacted law and provides for more input from stakeholders, requires an assessment of economic burdens and provides meaningful due process for all stakeholders.

In addition, it is inappropriate to use guidance, which by definition is non-binding, for matters that should be obligatory and well defined for all stakeholders. In a number of cases, FDA proposes using guidance for matters for which there should not be discretion or permitting differing legal approaches. For example, as drafted, VALID requires FDA to issue final guidance prior to the effective date of the Act on premarket review requirements, technology

certification review requirements and applicability, all of which are substantive policy areas that should be addressed through formal notice and comment rulemaking, not sub-regulatory guidance. In fact, it should be the other way around; first, FDA should use the rulemaking and regulation promulgation to create the implementing requirements, and then FDA can use guidance that illustrates how the Agency intends to interpret the rules and regulations and to provide instructional help to stakeholders so they understand the agency's perspective.

Therefore, guidance may be appropriate in certain instances where non-substantive procedural clarification is involved (e.g., what kinds of forms to use for a process for which the policy has already been established through more formal mechanisms), but not for substantive policy making either intended to become, or having the effect of, binding obligations.

User Fees

DTWG understands the value and reason for implementation of an FDA user fee program to help fund these activities, and the inclusion of a cap at 30% of program costs is particularly helpful, especially since laboratories are already subject to CLIA fees, to which these FDA user fees would be added under VALID. However, significant clarifications are needed to clarify the expectations and timelines for the proposed user fee collection system. Upon review the user fee timeline and structure is unlike any FDA user fee structure currently in place and requires significant additional dialogue with potential fee-paying entities.

Also, it appears that some of the dates in the user fee provisions (as we read the language) do not line up. For example, it is unclear how FDA and stakeholders can transmit recommendations to Congress by January 1, 2021. The regulations will not have been adopted by that time.

Additional Topics for Discussion

- In several cases, VALID references device provisions (see, for example, the transition section and 587Q(b)). Because IVCTs are separate from devices, all device references should be removed except to the extent necessary for oversight of manufactured test kits (finished products) during the transition period since they would already have been subject to such requirements prior to enactment. To the extent that similar provisions should apply to IVCTs, relevant language should be added to VALID as new IVCT-specific requirements.
- Past drafts included an Approval with Confirmatory Postmarket Obligations (AWCPO). This concept is important to many stakeholders and re-inclusion should be considered.
- In several cases, FDA appears to be using VALID to address Constitutional issues relating to IVCTs. Of course, a statute cannot overturn Constitutional rights and obligations; thus, this legislation is not the appropriate place to address such issues. Further, by adding these provisions to VALID, FDA may be seeking to address recent court cases or legal challenges. Any effort to address these issues has ramifications much broader than diagnostic tests and should not be addressed in the middle of a major legislative initiative focused on diagnostic tests. For example:

- FDA appears to be trying to address interstate commerce issues raised by stakeholders in both the diagnostic test area (objections to FDA's proposed 2014 draft guidance on LDTs) and in the non-diagnostic test area (regenerative medicine issues).
- Likewise, FDA seems to be trying to address 1st Amendment issues indirectly in this legislation. FDA has promised guidance on this issue for all product areas for years. This legislation should not be used to bypass this commitment.

- Stakeholders are also confused by what appears to be inconsistencies in FDA's regulatory positions. One key inconsistency exists between FDA's positions in VALID and draft IMDRF risk-based classification guidance. FDA has been advocating a 2 class/non-risk-based approach in VALID, yet FDA is a key member of the IMDRF effort that led to the draft guidance calling for a 4 class/risk-based approach. DTWG supports a risk-based, multi class diagnostic test classification system.

Conclusion

DTWG appreciates the opportunity to provide these thoughts. Please contact us with any questions or if we can be of any assistance.