AdvaMedDx Comments on the VALID Act
(Verifying Accurate Leading-edge *In vitro* clinical test Development Act)

On behalf of AdvaMedDx, a division of the Advanced Medical Technology Association, thank you for your role in introducing the bipartisan VALID Act in the House and Senate, and for giving us the opportunity to provide our comments. We sincerely appreciate the efforts of the bill sponsors and Congressional supporters to advance public health through modernizing the regulatory framework for diagnostics.

About AdvaMedDx:

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease, and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted policy organization that deals exclusively with issues facing *in vitro* diagnostics companies in the U.S. and abroad. Our members include manufacturers engaged in the development of innovative diagnostic tests supporting patient care and advancement of precision medicine.

Background – The Need for a Modernized Regulatory Framework:

Diagnostic technologies are advancing more quickly than ever, leading to more rapid and precise identification of disease and direction to appropriate treatment. But the current regulatory framework for clinical tests is fragmented, outdated, and has not kept pace with scientific and technological changes. Neither CMS nor FDA are currently operating with a regulatory framework that is tailored specifically to diagnostics.

AdvaMedDx strongly supports establishment of a single, modernized, diagnostics-specific, risk-based regulatory framework for all *in vitro* clinical tests (IVCTs), regardless of where developed, separate from medical devices, and overseen by FDA. Such a framework would help speed the pace and reach of cutting-edge diagnostics, allowing patients to benefit more broadly, rapidly, and confidently from the latest diagnostic technologies. We believe that the recent COVID-19 pandemic has underscored the vital role of diagnostics for public health, and showcases the need for FDA oversight that is nimble, flexible, and allows for confidence in testing results.

The VALID Act – Key Provisions and Policies:

We appreciate the extensive undertaking in development of the VALID Act. We are pleased with the adoption of definitions and standards that are appropriate and tailored to *in vitro* clinical tests, such as “analytical validity” and “clinical validity”. While we recommend additional revisions, the bill recognizes the need for important concepts of high risk, low risk, and mitigating measures that relate specifically to diagnostics. We are pleased that the legislation provides a robust Technology Certification program to include authorization of IVCTs within multiple subspecialties if they use a single technology. We support the use of change control protocols, whereby the agency and a developer could agree in advance that certain changes that would

otherwise require supplemental review would not require supplemental review so long as certain criteria are met. We also note the inclusion of the pro-innovation and longstanding replacement reagent and instrument family policy.

In our specific redline feedback, our comments include the following priority areas:

I. A risk-based approach to IVCT oversight and review;

II. The need for appropriate flexibility within the Technology Certification program.; and

III. Appropriate supplemental review of changes that are significant and clinically meaningful.

Revisions to accomplish these priorities are particularly important, and many of our comments relate to the definitions, framework, and overall premarket regulatory approach generally tied to these thematic areas. We have included an overview of the feedback along with a specific redline. While we have strived to provide detailed feedback on these priority areas, we also offer feedback on other areas, including technical or clarifying language. We welcome the opportunity to provide additional comments, and to discuss our feedback in one or more future meetings.

I. Ensuring a Risk-Based Approach to IVCTs and IVCT Submissions:

Fundamental to a modernized regulatory framework is the principle that risk must be the primary determinant for how IVCTs are regulated. IVCTs should be regulated based on the risk of particular IVCTs, taking into account the intended use of the IVCT and all surrounding circumstances that can either heighten or mitigate the risk of use of that particular technology for that particular use. A risk-based framework means regulatory rigor would be appropriately focused commensurate with potential risks, and most heavily focused on high-risk tests.

To be risk-based, regulation should not be based on an artificial or static categorization of IVCTs, such as "Direct-To-Consumer," "home use," "cross-referenced," or "first-of-a-kind." Locking tests into categories will not allow the regulatory framework to adapt as technology and clinical practice evolves, and would easily become outdated. To better illustrate the challenges of regulating based on category instead of individualized risk, please consider the following examples:

A. Antimicrobial susceptibility tests (ASTs) have been on the market for decades and FDA has cleared thousands of these tests. ASTs are a recognized tool in the fight against antibiotic resistance. Because ASTs merely mention another therapy, e.g., an antibiotic, in the labeling, under the legislation, we believe they could be considered "cross-referenced." This could be subject to the most burdensome level of review and excluded from Technology Certification, despite their clear value to public health, Congressional efforts to streamline the regulatory process for these tests, the long history of safe and effective use, and relatively low risk. Additional examples of IVCTs currently regulated as moderate risk that would appear to fall within "cross-referenced" that we do not believe should be subject to the most burdensome level of review include urine and blood tests for

drugs of abuse and tests to asses circulating pharmaceutical levels used to ensure proper dosing (common for products like anticonvulsants, vancomycin and digoxin).

B. Blood glucose monitoring systems (BGMs) have been an important part of diabetes treatment, both in the point-of-care (POC) setting and for use at home. Under the legislation, we believe that while both POC and home use BGMs would, and should, be subject to review, the tests intended for the POC setting would be eligible for Technology Certification, but those for use at home would not. We believe such a disparate treatment of such extremely similar IVCTs, which utilize the same technology for the same intended use only in different settings, both of which potentially should be eligible for Technology Certification, highlights the difficulties of a category-based approach.

All IVCTs have the potential to be high- or low-risk depending on the particular circumstances surrounding use of the IVCT. A fully risk-based approach serves the public health by applying calibrated oversight to IVCTs based on their level of risk. It would align FDA's review resources with protection of patients.

In addition to serving the public health, our recommendations are designed to provide greater predictability and to create a paradigm that can serve for years to come. Certain uses of tests that may be cutting-edge today may be well-established and commonplace in the future. Putting into law an approach based on arbitrary categories is not well suited to the changing advances we expect to see in the future. This has proven to be the case with regulations that were promulgated in the late 1990s outlining device types and technologies that FDA would always treat as not low risk and therefore subject to premarket review, regardless of the particular risk posed by a specific device within that category.

Nearly two decades have passed since FDA first promulgated these "limitations on exemption" provisions, which specified multiple device categories that FDA would treat as not qualifying as low risk. During that time, we have seen tremendous advances in technology, scientific and medical knowledge, and the availability of standards and guidance, yet those limitations remain. Many technologies and device types that were new and innovative in the late 1990s are now well-characterized. For example, point-of-care devices, one of the categories of devices that FDA does not treat as low risk under these regulations, are now an integral and recognized part of medical practice and are subject to strict performance standards. Categorically limiting a device as moderate or high risk simply because the device is used at the point-of-care no longer makes sense and does not support the public health in today's health care environment.

Our suggested revisions seek to further advance a stratified, risk-based approach by providing a consistent application of these principles, such that FDA's oversight is focused on higher-risk tests, risk-based regulatory requirements are outlined more clearly and appropriately for each type of application, and the nature of premarket review is more clearly tailored based on what is needed to show analytical and/or clinical validity for a particular type of IVCT.
Suggested revisions include:

A. Definitions to clarify the criteria for high risk and low risk tests, as well as "first of a kind" tests.

B. Expanded list of possible measures that could be used to mitigate risk, based on our collective experience.

C. Changes to the submission requirements for those IVCTs that require premarket review.

D. Removal of exclusions to participation in Technology Certification that are based solely on falling into a category such as Direct-To-Consumer, or home use, and propose a more specific linkage between the development of mitigating measures for a test and eligibility for the Technology Certification pathway.

E. A streamlined re-designation pathway to move IVCTs to better reflect the risk profile.

Our proposed changes would achieve a more fundamentally consistent, risk-based approach, and provide continuity in availability of generally well-established, lower-risk diagnostics.

II. Technology Certification Program:

AdvaMedDx supports the inclusion of the voluntary pathway for test developers with robust quality systems to allow for smart reviews and more efficient consideration of innovative technologies. We think this pathway, Technology Certification, holds great promise to support accurate, high-quality, cutting-edge diagnostics. Through leveraging the regulatory apparatus to keep pace with scientific advancement, a Technology Certification program for diagnostics can both promote excellence in quality while maintaining the highest standard for ensuring analytically and clinically valid tests for patients.

We commend the sponsors for including the Technology Certification program in this legislation, especially in light of many of the lessons we are learning during the COVID-19 pandemic. However, we believe it can be further improved upon by ensuring that it is not overly rigid and will withstand the test of time as diagnostic technologies continue to evolve, and there is greater understanding of innovative tests and how they can be used effectively. We believe it is important that certain test types not be preemptively excluded from eligibility. Moreover, the appropriate use of this program is an important element of FDA's ability to oversee review of a likely influx of IVCTs and respond to emerging public health needs. To be successful, Technology Certification must strike an appropriate balance between ensuring high standards and leveraging existing quality systems already in place to protect patients and public health.

Essential to success of the program is eliminating the default statutory disqualification from Technology Certification, including home use IVCTs and Direct-To-Consumer IVCTs, where IVCTs are automatically disqualified from participating in Technology Certification without consideration of the particular risk posed by the specific IVCT. Instead, AdvaMedDx recommends that IVCTs should only be ineligible for Technology Certification if they are high risk or mitigating measures for the test cannot be established. This approach is consistent with our discussion above about the need for use of risk as the dominant determinate of regulatory requirements.

III. Modifications:

We also seek revisions to regulatory pathways in VALID to facilitate certain modifications to approved tests in a timely fashion. These would help keep pace with science and ensure high-quality products. Across all review pathways (including Technology Certification), it is important that any reform to the regulatory paradigm for IVCTs provide a more effective and predictable approach regarding what changes to a marketed test require a new review, and the nature of that review.

We recommend clarifying that only significant, clinically meaningful changes to an approved IVCT would require supplemental review. We propose certain types of changes that would not warrant supplemental premarket review because the risk these changes could pose is minimal.

Other Comments:

We have offered other technical suggestions, clarifications, and potential enhancements to the legislation, including the following:

1) Reducing duplication by deeming IVCTs approved for use in a non-moderate, non-high complexity laboratory context as CLIA-waived.

2) Ensuring appropriate appeals procedures consistent with appeals of significant decisions for medical devices.

3) Ensuring sufficient opportunity for comment in, and transparency regarding, FDA development of policies and issuance of orders.

4) Providing language to facilitate the use of IVCT master files.

5) Ensuring appropriate adverse event reporting requirements and quality system requirements, consistent with existing statutory requirements.

6) Providing additional transparency for tests offered during the transition period, and reducing the transition period by a year to the third fiscal year following enactment.

7) Providing assurances of transparency and opportunity for engagement and feedback of interested stakeholders in collaborative communities when FDA intends to obtain advice or recommendations.

8) Suggesting updates to emergency use authorization (EUA) provisions specific to IVCTs, and providing additional emergency authorities for FDA in response to lessons learned during the COVID-19 pandemic.

Conclusion:

Our redline edits follow, which are intended to address priority areas noted in our summary of comments. AdvaMedDx appreciates this opportunity to provide our feedback, which we hope you will find useful as you update and refine the VALID Act. We also would welcome opportunities to meet with you to discuss our comments further. We view this effort as vital and look forward to working with you and other stakeholders to advance diagnostics regulatory reform.