AdvaMedDx
Vital Insights | Transforming Care

AdvaMedDx Comments on
FDA Technical Assistance (TA) on
Diagnostic Accuracy and Innovation Act (DAIA) House Discussion Draft

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association, we applaud Congressional efforts to support critical reform to modernize the regulatory framework for all diagnostics, including laboratory developed tests (LDTs) and *in vitro* diagnostics (IVDs). 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* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostic tests supporting patient care and the advancement of precision medicine.

The diagnostic industry is a cornerstone of the modern health care system with rapid advances for patients paving the way for more personalized, targeted patient care. Diagnostics reform will represent a major step forward for patients and public health in the U.S. We greatly appreciate the Food and Drug Administration's (FDA) efforts to develop technical assistance (TA) on the Diagnostic Accuracy and Innovation Act (DAIA) as a significant, positive step in enacting comprehensive legislation reform. In that vein, we urge Congress to continue this forward momentum and move swiftly to advance diagnostic reform legislation so that comprehensive reform may be enacted in 2018. Through these efforts, we can harness critical opportunities to provide high quality diagnostics for patients and ensure efficient effective regulation that keeps the pace of tremendous scientific progress in the field while implementing reforms reflective of the unique way diagnostics are used in healthcare today.

Thank you for the opportunity to provide our comments on this critical topic. AdvaMedDx strongly supports FDA oversight of all diagnostics under a rationale risk-based approach that promotes the public health and diagnostic innovation for patients. Notably, we thank FDA for its constructive engagement on efforts to develop a framework that is tailored for diagnostics and that regulates all clinical diagnostic tests under a consistent approach, regardless of where a test is developed. Such framework is vitally important to ensure a consistent and predictable pathway for developers as well as timely patient access to cutting-edge diagnostic technologies.

Below you will find our initial feedback on the FDA TA, which is focused on 1) priority concepts critical to AdvaMedDx members for reform and 2) additional provisions that merit further review (in below chart). We welcome additional opportunities to provide technical review and feedback. We look forward working with Congress, FDA, and the broad range of stakeholders committed to advance diagnostic reform this year.

Upon initial review of the TA, we strongly support the following key concepts reflected in the TA and in the House discussion draft:

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- **Review Standard—**The premarket review standard should be clearly defined for diagnostics, which is analytical and clinical validity (AV and CV). We are pleased to see this concept reflected in the review standard for tests that supports accurate and high quality diagnostic innovation.

- **Timeliness of Review Process and Transition**—We have a shared public health goal for innovation diagnostics to reach patients and healthcare professionals in a timely fashion to aid in decision-making. To this end, it is essential to have an efficient and modernized regulatory process for diagnostics. We appreciate FDA's inclusion of provisions aimed to support overall timeliness in the review process (e.g., priority review) and incorporation of flexible efficient pathways. We would encourage additional discussion on how we might foster further efficient premarket review requirements, including leveraging of summary reporting, to support the review process. We also propose inclusion of a "least burdensome" approach as part of the review process and as a core principle of the framework.

  We would also like to better understand how FDA will work to implement the broader framework in a clear, timely, and equitable manner and encourage further discussions to support these goals. We remain support of a transition period that requires all developers to come under promulgated regulations in a timely fashion, which is important from a public health and safety perspective.

- **Ensuring Flexibility in Diagnostic Updates (or Modifications)**—As a AdvaMedDx key policy priority fundamental to diagnostic reform, we wholeheartedly agree that regulatory policy must be sufficiently flexible to enable diagnostic innovators to make modifications in a timely fashion and keep the pace of science while supporting access to high quality diagnostic tests. AdvaMedDx has long supported use of a pre-approved protocol to allow for certain updates, where otherwise would be part of a premarket submission, to support diagnostic innovation. This would include the ability to allow for updates to support the public health and accommodate specimen needs or addition of analytes among others. We are pleased with FDA implementation of use of change protocols in recent flexible efficient reviews (e.g., next generation sequencing, tumor profiling), and explicit incorporation of this approach in the FDA TA demonstrates a wide Agency commitment to supporting diagnostic innovation. Furthermore, we recommend FDA expeditiously move with administrative policy to support recognition of use of change protocols, including validation methods and acceptance criteria, as a flexible approach that can be readily implemented to support diagnostic innovators while working to implement wider legislation reform with respect to a streamlined process for diagnostic technology updates.

  While we appreciate FDA efforts to incorporate provisions related to modifications of diagnostic tests in the TA, we have concerns with the use of new, overly broad terminology such as "test groups" and proposed notification procedures that may have unintended consequences as drafted. Further discussion is necessary on a flexible, efficient approach to enabling modifications that can best leverage Agency and developer resources as well as the role of quality systems in changes to in vitro clinical tests (IVCTs). AdvaMedDx believes it is important to include a risk-based analysis for modifications as part of expanded thinking regarding modifications.

- **Diagnostic Instrument Innovation**—We have long supported reform to ensure continued innovation in modern diagnostic instruments (otherwise referred to as "platforms"). As part of a risk-based approach, we must better incentivize the development of new platforms as well as improvements to existing platforms. Platforms themselves do not carry the risk, it is the test and test application software that carries both the clinical claims and the risk. FDA has recognized this with its exemption of a number of platforms.

  As drafted, the TA does not reflect historical treatment of platforms and imposes duplicative regulation on both tests and platforms. While we appreciate FDA TA's provision that platforms demonstrate only analytical validity, platforms should continue to be exempt as low risk. This issue can be further addressed via integration of Agency policies that reflect consistent risk-based treatment of platforms, such as ongoing application of exemption for such well-established technologies, ease of updates through clear and predictable replacement reagent and instrument policy, and wider application of flexible approaches for platform technologies beyond next generation sequencing.

- **Clear Definition of IVCT, Including Treatment of Accessories**—While all IVCTs would be encompassed under the proposal, we note the TA appears to set forth a duplicative process for some products as proposed in the definition of in vitro clinical test (IVCT). The TA defines parts, components and accessories as one concept, when those concepts are actually quite different. Parts and components should be grouped together and assessed under the quality system in place by developers. Accessories, on the other hand, are finished goods, and should be classified independently based on their own risk and intended use, as recognized recently under the 21st Century Cures Act. These changes ensure continued innovation in lab automation that improves patient care and has potential to lower health care costs. We suggest further discussion to support appropriate treatment of components, parts, and accessories as part of a modern, risk-based framework.

- **Point of Care Diagnostic Innovation**—As part of efforts to support a modernized framework, point of care diagnostics are critical to the future of healthcare. Specifically, CLIA waived tests (i.e., physician offices, clinics) play a vital role to support the public health. FDA has been working to support advances in the field, including commitment as part of 21st Cures Act. With the increasing need for timely point of care diagnostics from emerging infectious disease to antibiotic resistance, such technologies are integral to support access and timely care for patients. We are unclear how FDA intends to address point of care technologies, and we encourage incorporation of reforms to ensure advances in these important products. In addition to implementation of CLIA waiver reform, the categorical limitation on exemptions for point of care tests should be removed as it no longer makes sense in today's healthcare system since the regulation was established over 20 years ago.

- **Grandfathering**—AdvaMedDx continues to agree the reform framework should include some form of grandfathering of LDTs. We also agree no new tests introduced after 90 days prior to legislative enactment should be grandfathered. We relayed that grandfathering considerations might also include, for example, clinical conditions associated with the test, whether an FDA-approved or cleared test is available for the same intended use, and the level of risk associated with the test. This section will require further substantive review and input from our members in the future, including in the context of the proposed

transition period.

- **Precertification for Diagnostics**—AdvaMedDx strongly supports the concept of precertification for diagnostics and is pleased with FDA's prioritization of such a pathway for all interested diagnostic developers to help promote excellence in quality and ensure patient benefit from a regulatory apparatus that keeps pace with scientific advancement. We look forward to further discussion on this concept and sharing of our perspective on how a well-designed, appropriately implemented program can help advance a least burdensome approach to diagnostics and promote high quality diagnostic innovation.

  It is important to carefully consider how best to maximize the benefits of such a groundbreaking program for FDA, developers, and other stakeholders. We believe more discussion is needed in how to meaningfully design and implement such an innovative, yet complex, program in order to fully realize its potential. AdvaMedDx would welcome and anticipate further dialogue on our thinking to help support a successful program for innovators.

- **Risk-Based Classification Provisions**—While we agree that many diagnostics are low risk and focus should be on tests that pose the greatest risk to patients as part of the framework, we will need to better understand the two-tier classification approach, how it might work, and its potential impact for current and future tests, i.e., moderate risk tests.

- **Notice and Comment Rulemaking**—With the need for promulgation of regulation post-enactment to support implementation, we do not support a proposed exception to the Administrative Procedures Act (APA) for the framework. We note our appreciation for the incorporation of due process measures with respect to some of the classification and review provisions as reflected in the TA, but we do not support a broad exception to APA for purposes of implementation. While we remain interested to hear more about FDA's interest in using orders in conjunction with IVCT approvals, we continue to assess whether orders may raise issues in the context of classification/regulatory system as well as appropriate application of mitigating measures in terms of opportunity for stakeholder feedback, overall transparency, and potential impact on multiple products or across IVCT areas. For example, a first-of-a-kind test would be approved and requirements could, as stated in the TA, be imposed for the test group without the opportunity for other developers to comment on such an approach.

- **Exemptions for Lower Risk and Well-Established Diagnostics**—We are pleased with incorporation of expanded exemptions for diagnostics as a critical part of a risk-based framework for diagnostics. We seek further clarity on FDA's consideration of a "manual IVCT."

In additional to the general comments provided above, we provide more specific comments based on our initial review of the TA that we believe merit further consideration as part of a risk-based, least burdensome approach. We look forward to providing further, specific comments as dialogue on the discussion draft continues.

AdvaMedDx Specific Comments

Topic/Section	Specific Page(s)	General Comment
Definition-Analytical and Clinical Validity	3, 4	• Appreciate clarification on reference of "adequately." At present, the review standard is clearly defined as "analytical and clinical validity. • Appreciate clarification on specific insertion of "articles taking or deriving specimens from the human body."
Definitions – Clinical Use	3	• Appreciate clarification on this term. Is it meant to differentiate use of an IVCT for a "clinical" purpose as opposed to a different purpose, such as for law enforcement? • Recommend "clinical use as intended by the developer."
Cross-Referenced Test	4	• We are not clear as to this specific test category. Is this intended reference companion test and complimentary tests or only tests that are co-labeled?
Definition-Relevant Standard	5	• While we support the concepts, would suggest definition for probable clinical validity. Previous definition had been included.
Developer	4	• Is an importer a developer?
First-of-A-Kind	6	• Add "and real world data (RWD)" to (14)(E). • Would like to better understand this term and associated regulatory treatment.
Applicability Special Rule	8	• Further discussion is needed to ensure appropriated tailored provisions. For example, we believe the standard of "insufficient valid scientific evidence" is ill defined. Suggest striking as already captured by provisions related to use of "valid scientific definition."
Supplier Controls	11	• Would appreciate clarification on why "supplier controls" are specifically called out rather than referring to broader concepts of QSR or CLIA.
Limitations on Exemption	13	• Consistent with previous general comments, we do not support blanket carry over of limitations of exemptions put in place over 20 years ago. Not all are appropriate or relevant in today's modern healthcare system (e.g., limitation on exemption for "near patient testing" or otherwise referred to as point of care testing).
Premarket Review	16	• Appreciate clarification on whether cited provisions in 21 CFR 814.20 will apply to all developers of IVCTs – both IVD manufacturers and labs – until new IVCT regulations are developed.

Topic/Section	Specific Page(s)	General Comment
Premarket Review	16-17, 19	• Ensure appropriate incorporation of summary reports of valid scientific evidence in most cases unless higher risk IVCTs raise specific question related to assurance of analytical validity and clinical validity for the IVCT for its intended use. • First of a kind could include low risk tests. Suggest improved risk treatment. • 21 CFR 58 [referenced in 587B (b)(2)(E)(i)] applies to animal studies. Recommend removal. It is not appropriate to simply incorporate it into statute to apply to IVCT validation studies when it was designed for animal studies and thereafter cite noncompliance as with 21 CFR 58 to deny application approval.
Clinical Investigations	17 and 19	• Calling for compliance with 21 CFR 56 and 21 CFR 50 without recognition of how studies are currently completed will bring approvals to a halt. Recommend removal. To deny an application for noncompliance with such regulations is also not appropriate in all circumstances for IVCTs (e.g., reflected in TA recognition of critically important deidentified specimen policy to support diagnostic research and development) and creates an inoperable system.
Provisional Approval	20 and 24-26	• Support the concept, but recommend a definition and better understanding of application to support consistency and predictability.
Mitigating Measures and Risk Redesignation (Due Process)	33-34, 45	• Per previous general comments, we request further discussion on processes and related due process (e.g., appeals placeholder). However, we appreciate that FDA intends to publish a proposed order for establishment, changes, or withdrawals of mitigating measures. A similar process was also incorporated into risk redesignation.
Request for Informal Feedback	34	• Strongly support continued access to and use of presubmission meetings for IVCT developers.
Notification	35-37	• We note the TA importantly incorporates use of notification as a transparency measure for public availability of IVCTs. For existing IVCTs with a marketing approval prior to enactment, however, this is already captured and is redundant and unnecessary. • Labeling submission is inefficient and costly regulation for both the Agency and for affected stakeholders.
Labels	40	• Permit use of a website in place of street address in current age. • Allow for IVCT developer use of electronic labeling and use of symbols consistent with current modern, efficient approaches.

Topic/Section	Specific Page(s)	General Comment
Accredited Persons	45	• Promote global harmonization via leveraging of Medical Device Single Audit program (MDSAP) or recognition of Australia, Canada, EU or Japan as a path to market. This is consistent with current provisions related to MDSAP in existing statute.
Investigational Use	51-52	• We appreciate the incorporation of longstanding policy on the use of deidentified samples
Collaborative Communities	54	• We would like to better understand how collaborative communities will be used and how they differ from advisory committees and other expert panels utilized by FDA. • Should not replace notice and comment rulemaking, classifications, and mitigation measures.
Combination Products	58-59	• Consider incorporating IVCT combination products as within the framework. This could be accomplished by exclusion under current statute for "combination products constituted of a device and IVCT" along with conforming amendments.