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December 4, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-N-2177 Medical Devices; Laboratory Developed Tests

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Technology Association (“AdvaMed”), and its members, we provide these comments in response to the Food and Drug Administration’s (FDA’s) Proposed Rule: Medical Devices; Laboratory Developed Tests (“Proposed Rule”).

AdvaMedDx member companies produce *in vitro* diagnostic (IVD) tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Operating as an association within AdvaMed, AdvaMedDx is the only policy organization exclusively addressing issues facing the *in vitro* diagnostic industry in the United States and abroad. Diagnostic tests are a cornerstone of the healthcare industry: The Centers for Disease Control and Prevention estimates that 70 percent of all health care decisions rely on laboratory testing.

Our members develop and manufacture innovative diagnostic technologies that support and advance public health and play an integral role in the work of clinical laboratories, as the tests laboratories run, including tests considered to be Laboratory Developed Tests (“LDTs”), often rely on instruments and equipment made by our members, or even utilize a test kit made by our members. In addition, our membership includes test developers that have pursued, and successfully obtained, FDA authorization of their own LDTs.

I. AdvaMedDx Continues to Support Comprehensive Diagnostics Legislative Reform

AdvaMedDx has consistently maintained that FDA possesses statutory authority to regulate LDTs as medical devices. Consequently, we believe FDA is fully within its purview to clarify the regulatory definition of *in vitro* diagnostics to encompass tests manufactured within a laboratory setting. While FDA, diagnostic test manufacturers, and the public would benefit significantly from comprehensive diagnostics regulatory reform, we acknowledge that such a transformation of the FDA’s regulatory environment likely necessitates an act of Congress.



It is for this reason that we have supported, and continue to steadfastly support, the bipartisan Verifying, Accurate, Leading-Edge IVCT Development (“VALID”) Act. In late 2022, the VALID Act was on the verge of congressional passage. Had it been enacted, VALID would have ushered in a long-awaited modernization of the regulatory framework governing all diagnostic tests, regardless of their development or performance location. VALID or similar legislation could optimize FDA’s ability to establish a comprehensive, unified, modernized, diagnostics-specific, risk-based regulatory framework for all IVDs, including those manufactured by a laboratory, regardless of where they are developed, separate from medical devices. This framework, we firmly believe, must be risk-based to ensure that IVD regulation aligns with individual risk levels rather than the test’s developer. Adopting a modernized, risk-based framework would yield significant benefits to public health, expanding the reach of cutting-edge diagnostics, thereby enabling patients to reap the benefits more swiftly and widely, while simultaneously bolstering the confidence of patients and healthcare providers in the latest diagnostic technologies.

II. The IVD Industry Has a Long, Proven Record of Innovation Within a Regulated Environment

AdvaMedDx’s members are among the world's most innovative companies, and they have successfully brought to market, nationwide and accessible to patients of all backgrounds, exceptionally sophisticated, groundbreaking, and technologically advanced diagnostic products, all while operating within the existing FDA medical device framework. While the current FDA regulatory framework may not be as well-tailored for modern diagnostics as, for instance, the structure proposed by the VALID Act, the current statutory program incorporates pre-market review pathways that have proven to be effective.

Our members have also leveraged the breakthrough devices program and the pre-submission process to support their efforts to obtain marketing authorization for their innovative diagnostic products. Additionally, FDA recently obtained legislative authorization to grant predetermined change control plans (“PCCPs”), enabling diagnostic test manufacturers (and other device manufacturers) to expeditiously iterate and update existing products. When properly utilized by both industry and FDA, these regulatory tools help support a regulatory environment that fosters patient access to safe, effective, and cutting-edge, diagnostics.

There are countless examples of innovative IVDs that FDA has authorized in 2022-2023 alone, including:

- *de novo* authorizations for the first:
 - Preeclampsia risk assessment test¹

¹ <https://www.fda.gov/news-events/press-announcements/fda-roundup-may-19-2023>.



- Test intended to aid in the assessment of risk of progressive kidney function decline in adult patients with Type 2 diabetes and existing chronic kidney disease,² and
- COVID-19 molecular test for at-home, over-the-counter (“OTC”) use;³
- companion diagnostics tests, including:
 - A companion diagnostic, developed as, and meeting the criteria for, an LDT, that detects mutations in multiple genes and can direct use of a novel combination therapy for many people with metastatic breast cancer⁴,
 - An adeno-associated virus (AAV) companion diagnostic test to detect pre-existing antibodies to help health care providers identify patients who may benefit from receiving gene therapy to treat severe hemophilia A,⁵ and
 - The first companion diagnostic for HER2-low Breast Cancer to identify breast cancer patients belonging to the new classification of HER2-low who are now eligible for targeted treatment.
- The first commercially available rapid Traumatic Brain Injury biomarker laboratory-based blood test to evaluate concussions,⁶
- A newborn screening test for Spinal Muscular Atrophy,⁷
- The first IVD test for early detection of amyloid plaques associated with Alzheimer’s disease,⁸
- The first point-of-care diagnostic test for pulmonary anthrax, as an aid in the diagnosis of inhalation anthrax,⁹ and
- A multiplex test for bacterial and yeast detection in synovial fluid to aid in the diagnosis of bone and joint infections.¹⁰

² <https://renalytix.com/fda-grants-de-novo-marketing-authorization-for-kidneyintelx-dkd-to-assess-risk-of-progressive-kidney-function-decline-in-adults-with-diabetes-and-early-stage-kidney-disease/>.

³ <https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-covid-19-home-test-using-traditional-premarket-review-process>.

⁴ <https://www.foundationmedicine.com/press-release/us-fda-approves-foundationonercdx-companion-diagnostic-astrazenecas-truqapm-0>

⁵ <https://www.fda.gov/medical-devices/recently-approved-devices/aav5-detectcdx-p190033>.

⁶ <https://abbott.mediaroom.com/2023-03-07-Abbott-Receives-FDA-Clearance-for-First-Commercially-Available-Lab-based-Blood-Test-to-Help-Evaluate-Concussion>.

⁷ https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200044.pdf.

⁸ <https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-new-test-improve-diagnosis-alzheimers-disease>.

⁹ https://www.accessdata.fda.gov/cdrh_docs/pdf22/DEN220044.pdf.

¹⁰ https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200066.pdf.



FDA has also, in recent years, cleared or approved innovative LDTs, including cutting-edge, advanced diagnostics relating to tumor profiling and cancer detection. These LDTs were developed and brought through FDA by both private companies and academic medical centers.

There are certainly additional enhancements to the FDA review program that could further support innovation, such as some of the reforms offered in the VALID Act. It is also the case, however, that the current fragmented regulatory approach based on the developer of the test hinders investment in, and deployment of, IVDs nationwide due to the market dynamics it fosters. The investment community has stated that to the Proposed Rule is unlikely to impede innovation. Indeed, numerous financial analysts and even some LDT developers have indicated that regulatory clarity and certainty is likely to encourage further investment in novel diagnostic tests and that the Proposed Rule will not significantly impede the ability of LDTs to reach the market.

III. FDA Should Prioritize a Smooth Implementation and Minimize Disruptions

We agree that the Food, Drug, and Cosmetic Act does not distinguish between types of manufacturers when regulating *in vitro* diagnostics as devices. FDA's implementation of the rule should nevertheless aim to minimize disruptions and ensure effective workload management. We support FDA's proposal for an appropriate phased-in transition period that minimizes disruption, including issues with test accessibility, availability, and prolonged review times.

We provide below two illustrative, but not exhaustive, areas that FDA should prioritize during the transition period to ensure minimal disruptions to patient care:

1. *Specimen Collection Systems*: Given the significant volume of specimen receptacles used annually in the U.S., approximately 3 billion, FDA should carefully consider the approach for submissions related to specimen collection devices. Although these devices are not covered by the Proposed Rule, FDA should consider whether these devices may benefit from validation for a broader range of tests under a regulatory framework that is actively applied to LDTs.
2. *Ongoing Clinical Studies*: FDA should anticipate the potential impact to ongoing clinical studies involving investigational tests during the transition period. As noted in the preamble to the Proposed Rule, many investigational IVDs under the current regulatory scheme may not require an Investigational Device Exemption (IDE). Clear and early communication regarding the current framework and expectations for investigational tests would be highly beneficial to developers. We commend the FDA's commitment to education as part of the transition, including the October 31 public webinar, and future Town Hall meetings, Frequently Asked Questions documents, and implementing guidance. We believe that FDA expectations regarding

investigational requirements should be specifically addressed in these educational efforts.

IV. FDA Utilizes Multiple Pathways for Novel Tests, which Our Members Have Successfully Leveraged to Bring Innovative Products to Market

The FDA uses multiple regulatory tools to assist developers in bringing innovative tests to market, such as pre-submission, breakthrough designation, the Humanitarian Device Exemption (HDE), and the *de novo* pathways. These tools were the outgrowth of experiences of the diagnostics industry, and our members have been early and frequent adopters of these regulatory tools, and successfully collaborated with FDA for improvements to them over the years. Importantly, these same mechanisms are available for LDTs now, and would be under the Proposed Rule.

- *De novo* pathway: The *de novo* pathway provides a streamlined mechanism for novel low-to-moderate risk IVDs to reach the market. IVD developers were among the first to utilize this pathway, recognizing its efficiency and effectiveness in bringing novel diagnostic technologies to patients.
- *Breakthrough designation*: The breakthrough designation program expedites the development and review of innovative IVDs (and other devices) that address unmet medical needs or offers significant advantages over available alternatives. IVDs have been at the forefront of this program, with FDA granting 169 breakthrough designations to IVDs as of October 18, 2023. Of the 81 devices that received authorization after receiving breakthrough designations, 18 were IVDs, representing 22% of the total. These 18 FDA-authorized devices with breakthrough designation include six FDA approved PMAs, four 510(k)s cleared, and eight authorized *de novos*, spanning multiple risk levels. These data highlight the success of IVDs in the breakthrough designation program.
- *Total Product Life Cycle Advisory Program (TAP)*: FDA recently established TAP to provide early and ongoing regulatory guidance and support to industry throughout the entire lifecycle of a medical device. The program began with OHT2 and has been expanded to OHT5. While the program is still in its infancy and success has yet to be determined, FDA should consider expanding it to OHT7 to help IVD developers.
- *Predetermined Change Control Plans (PCCPs)*: FDA has, for a number of years, deployed tools in certain instances to allow diagnostic manufacturers to quickly update or iterate tests previously reviewed by the Agency, including in the context of LDTs.¹¹ This approach was codified in 2022 when Congress authorized FDA to use PCCPs, which will help ensure that patients have timely access to accurate and reliable diagnostic tests. Recently, FDA published guidance recognizing the long-standing use of PCCPs for updating breakpoints for Antimicrobial Susceptibility

¹¹ https://www.accessdata.fda.gov/cdrh_docs/reviews/den170058.pdf



Testing Systems (ASTs).¹² Broad use of PCCP authority will be beneficial for all types of IVD developers.

Broad and timely use of this PCCP authority for IVDs will be essential in managing workload and the increased volume of solutions and ensuring access to accurate and reliable tests, and facilitating continuous product improvement. For this reason, we are pleased to see that FDA has included in its Guidance Development list for the upcoming fiscal year that it intends to issue a draft of how it interprets to implement the broad legislative authority.

- *FDA Recognized Databases:* FDA has adopted an innovative approach that allows developers to rely on FDA-recognized databases to demonstrate clinical validity. Examples of such databases include MSK Oncology Knowledge Base (OncoKB), Clinical Genome Resource (ClinGen), and Merck Study for Monitoring Antimicrobial Resistance Trends (SMART) database. This approach further streamlines the regulatory process and enables quicker access to innovative IVDs. *See also* FDA Guidance for Stakeholders and FDA Staff: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based IVDs (April 2018).
- *Enforcement Policy for Certain Supplements:* FDA has also issued guidance that outlines a policy of enforcement discretion to expedite certain changes needed for PMA/HDE (premarket approval/humanitarian device exemption) devices to address possible shortages or supply issues (e.g., a need to change a component).¹³ Instead of having to submit a supplement and wait for FDA review and approval, the developer can make the change and report the change in the next annual report. While only a small percentage of IVDs go through the PMA process, for those that do, this is a very welcome development from FDA.

We also encourage FDA to explore opportunities to enhance the regulatory pathways and environment for diagnostics within the scope of its existing authorities. With newly established and upcoming technologies such as next-generation sequencing, digital PCR, mini mass spectrometry, and personalized medicine, the Agency has demonstrated its adaptability on numerous occasions, adjusting its policies to align with industry advancements. Now is the opportune time for FDA to engage in international harmonization pilots for IVDs (e.g., expanding the pilot with Health Canada), adopt a streamlined approach to low-risk modifications (outside of PCCPs), encourage the utilization of real-world evidence, clarify the review standard as a combination of analytical and clinical validity in

¹² Guidance for Industry and FDA Staff: Antimicrobial Susceptibility Test System Devices – Updating Breakpoints in Device Labeling, available at <https://www.fda.gov/media/172463/download>.

¹³ <https://www.fda.gov/media/138265/download>.



the context of IVDs, and effectively leverage scientific literature. These policies, in our view, can be implemented under FDA's current statutory authority.

Finally, it is worth noting that diagnostic tools are increasingly powered by AI/ML (artificial intelligence/machine learning) and other advanced software algorithms. The above-referenced regulatory pathways are currently being employed to accommodate the unique nature of these technologies. In many cases, these algorithms already fall outside of the LDT framework, and thus this significant source of innovation are already subject to regulation as medical devices (except to the extent such software falls within the device exemptions in the 21st Century Cures Act).

V. We Support FDA's Plan for Educational Efforts and Guidance to Help Laboratories Better Understand the FDA Regulatory Framework

The Proposed Rule has raised concerns among some laboratory personnel regarding the process of determining an LDT's risk classification, including whether a submission is required and the specific type of submission expected by the FDA. During the October 31, 2023 public webinar, FDA estimated that only about 5% of LDTs would undergo review through the PMA pathway. Additionally, FDA stated that most LDTs subject to premarket review requirements would be eligible for either the 510(k) or *de novo* pathways.¹⁴ These estimates are consistent with our general experience regarding the overall breakdown of IVDs among the risk classification levels, with relatively few IVDs being classified as high-risk.

FDA already has many resources available to help new and small IVD developers understand the FDA regulatory framework. For instance, FDA has multiple databases that a developer can use to research the risk classification of their test, and those databases provide summaries of relevant FDA authorizations and FDA expectations for that particular test.¹⁵ Moreover, the CDRH Learn series of web videos provides helpful instruction on a variety of topics, including ones related to submissions.¹⁶

We were pleased to hear during the October 31, 2023 public webinar that FDA is considering ways to help laboratories during the proposed transition. For instance, FDA held a series of Town Hall meetings during the COVID-19 Public Health Emergency to outline expectations for developers of COVID-19 tests. FDA also developed and posted on its website Frequently Asked Questions ("FAQs"). The Town Hall meetings and FAQs were an effective education tool, and we believe FDA's plans to leverage these tools to help LDT developers transition

¹⁴ <https://www.fda.gov/media/173623/download?attachment>.

¹⁵ <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/medical-device-databases>.

¹⁶ <https://www.fda.gov/training-and-continuing-education/cdrh-learn>.



will be helpful. We also appreciate that FDA plans to issue implementing guidances with appropriate opportunity for notice and comment.

VI. Response to Questions Posed in the Proposed Rule Preamble

Enforcement Discretion: We support the areas in which FDA proposed continued enforcement discretion in the preamble to the Proposed Rule, including HLA (human leukocyte antigens) for transplant, public health surveillance as defined in the rule, “1976-type tests” and tests intended for forensic use (law enforcement purposes). *See, e.g.*, 21 CFR 864.3260¹⁷ and 66 Fed. Reg. 1823018 (exempting from premarket review OTC collection systems for drugs of abuse testing for forensic use). Similarly, we recommend FDA apply to LDTs its existing enforcement discretion for tests for drugs of abuse used in employment and insurance testing as described on FDA website except for requiring specific labeling, which generally would not apply to LDTs.

Unmet Needs: We agree with FDA about the importance of maintaining, and encouraging development of, tests for unmet needs. We understand tests for unmet needs to be those tests generally intended for rare disorders and for which no FDA authorized test is available. As mentioned above, we support a regulatory approach based on the test, not on the manufacturer of the test. As FDA considers comments to the Proposed Rule, we support careful consideration of its impact on unmet needs during the transition period and how to facilitate the review and authorization of such tests.

Third-Party Programs: In response to FDA’s request for input regarding whether the New York State Clinical Laboratory Evaluation Program (“CLEP”) at the Wadsworth Center should be utilized, we do not recommend that New York State approval replace FDA regulation. However, we do believe it may be in the interest of public health to leverage New York State CLEP and other trusted third-party programs to provide tests certified under such regimes with more time to fulfill FDA premarket submission requirements or otherwise streamline their review. Such an approach may be an appropriate tool for managing FDA’s transition workload in a risk-based manner.

Academic Medical Centers (“AMCs”) and Small Laboratories: With respect to FDA’s question asking whether a carve-out should be offered for AMCs and small laboratories, we believe such a categorical exception based on entity is inconsistent with a risk-based approach. The FDCA statutory framework is grounded in the risk classification of the individual device type. In this instance, we are not aware of any public health reason to provide a carve-out for tests offered by these entities. It would be more consistent with the statutory framework and in the interest of public health for the Agency instead to prioritize its

¹⁷ [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=864.3260#:~:text=An%20over-the-counter%20\(sports%2C%20or%20workplace%20setting\)%3B](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=864.3260#:~:text=An%20over-the-counter%20(sports%2C%20or%20workplace%20setting)%3B).

¹⁸ [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=864.3260#:~:text=An%20over-the-counter%20\(sports%2C%20or%20workplace%20setting\)%3B](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=864.3260#:~:text=An%20over-the-counter%20(sports%2C%20or%20workplace%20setting)%3B).



resources on specific tests for unmet needs, to the extent FDA is concerned about their availability. However, FDA would continue to have the authority to transparently make benefit-risk decisions about a test, not an entity, recognizing public health needs. Regarding AMCs in particular, we also are not aware of a clear definition of what constitutes an AMC. Nor are we aware of any risk-based characteristics that are unique to AMCs and different from other regulated entities. In fact, a supporting memorandum to this docket reports that the deficiencies FDA found in design, validation, and performance of COVID-19 tests were similar across all types of laboratories, including AMCs.

Grandfathering: We believe any use of grandfathering should be based on a strong public health need and be directly linked to both ensuring access to accurate and reliable tests and facilitating a smooth transition for the FDA in managing its workload. If FDA were to allow certain tests to be grandfathered, it would be critical that the labeling for such tests clearly disclose that the test has not been cleared or approved by FDA, and that other appropriate risk-based safeguards are included.

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AdvaMedDx appreciates the opportunity to provide these comments. Should you have any questions, please do not hesitate to contact Jamie Wolszon at jwolszon@advamed.org.

Respectfully submitted,



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