



July 5, 2024

Office of the Center Director  
Center for Devices and Radiological Health  
Food and Drug Administration  
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**Re: Comments to Dockets:** FDA-2024-D-0083 and FDA-2023-D-5365.

The Association of Public Health Laboratories (APHL) appreciates the opportunity to respond to the Food and Drug Administration (FDA) requests for input on the "Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration Under Section 564; Draft Guidance for Laboratory Manufacturers and Food and Drug Administration Staff; Availability" (Docket No. FDA-2024-D-0083) and "Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency; Draft Guidance for Industry and Food and Drug Administration Staff; Availability" (Docket No. FDA-2023-D-5365) guidance documents.

APHL represents state and local public health, environmental, and agricultural laboratories in the United States (US) and works to strengthen laboratory systems in the US and globally. APHL supports FDA's efforts toward sensitive and specific laboratory tests and appreciates FDA's understanding that the important and unique work of public health laboratories (PHLs) must continue in the changing regulatory environment. PHLs must be able to develop and implement new tests when needs arise: before, during, and after public health emergencies; for outbreaks of any size; for genetic disorders in newborns and infants; for chemical, biological, radiological, and nuclear agents of concern; and to quickly respond to specific concerns that have an impact on local, state, tribal, or territorial communities due to their unique populations, geography, and exposures.

The draft guidances provide important clarity on the steps that are necessary for responding to public health threats and APHL commends FDA for creating a pathway for laboratories to quickly respond. However, FDA must assure the guidances do not limit testing and exposure mitigation efforts; not all threats have been addressed by the policies and PHLs need clarification on FDA requirements to effectively respond.

APHL recommends FDA revise the draft guidances with the following considerations:

Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564

**1. Laboratories need additional information on validation requirements.**

PHLs need more information on acceptable validation criteria and emergency use authorization submission packages as soon as possible so they can build these requirements into their operating plans. APHL also encourages FDA to work with the Centers for Medicare and Medicaid Services (CMS) to assure validation criteria that are met for FDA will also be acceptable under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) so laboratories can quickly respond to emergent situations and use their limited resources efficiently. Additional information is also needed on the summary validation and performance information that must be made publicly available and some flexibility should be given to PHLs for displaying that information on their websites as governmental laboratories must submit formal requests to their information technology programs to make such edits. Website revisions are often not quick for PHLs, and testing should not be delayed because of this.

Additionally, APHL agrees that it is not generally unreasonable to validate a test with 30 positives and 30 negatives and appreciates the flexibility to do so with contrived specimens; however, it becomes significantly more difficult when the test requires uncommon and/or difficult specimen types such as conjunctival swabs. As with other laboratories, PHLs have difficulty obtaining positive material for new agents and rare diseases or conditions, thus making rolling validations necessary. APHL appreciates FDA's recognition of this as well as the difficulty of supply chain issues as highlighted during the COVID-19 pandemic, both of which can lead to lengthy validations.

Finally, FDA needs to better define validation terms and crosswalk them with the CMS terms laboratories are more familiar with (i.e., specificity instead of cross-reactivity) and share recommendations for how the limit of detection, sensitivity, and specificity should be determined.

**2. Include laboratory developed tests (LDTs) for genetic diseases and disorders in newborns as immediate health response tests covered by this policy.**

Newborn disorders are serious and life-threatening. PHLs often develop and offer testing for these rare diseases and hereditary disorders because they cause devastating morbidity and mortality if left

untreated. The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) recommends conditions to the Recommended Uniform Screening Panel (RUSP) based on the benefit of testing, the ability to test for the disorder, and the availability of treatment. State governments regularly review the RUSP and add testing for those disorders to their NBS panels within a limited timeframe of their addition to the RUSP (often 18 to 36 months). An immediate public health response is needed once these conditions are added to the RUSP because testing options and treatments have been identified and newborns and children will suffer devastating health outcomes if not tested and appropriately referred for care. A pathway for PHLs utilizing LDTs for assessing newborns should be included in this guidance.

APHL has learned many PHLs are ceasing development of NBS assays since the LDT final rule was released because they are not currently capable of developing and submitting a 510(k) or De Novo package to the FDA. Florida, Connecticut, and California PHLs were ready to release testing for mucopolysaccharidosis type II (MPS II) on July 1, 2024 with Arizona following closely (August 1, 2024) and Texas early next year (February 2025). Test development for guanidinoacetate methyltransferase (GAMT) deficiency was to start soon (January 2025) for Arizona, Florida, and California and in January 2026 for Arkansas and North Carolina. These higher tier tests are more sensitive and specific than many first-tier and FDA-approved assays and are necessary to respond to the immediate needs of the most vulnerable population. The time from addition of a condition to the RUSP to marketing of an FDA-approved assay by a commercial manufacturer is regularly 3-5 years; this is too long for disorders that need an immediate health response.

Additionally, NBS is more than a test, it is a system with active engagement between the PHL, clinicians, and the healthcare community. Healthcare providers in the NBS system work in conjunction with laboratorians, analyzing test results and quickly identifying and referring at-risk infants to the follow-up care that is critical to their survival. The close partnership between providers and the laboratory mitigates the risk of inaccurate results from NBS LDTs.

Genetic diseases and disorders in newborns are serious and life-threatening conditions, and FDA should expand the categories of LDTs acceptable for immediate health responses to include testing for these conditions. Furthermore, there should be dialogue between FDA, the ACHDNC, and the US Secretary of Health and Human Services on disorders under consideration for addition to the RUSP to ensure test development will progress unencumbered once conditions are added to the panel.

- 3. Expand the definition of emergent situation to include chemical agents that are not newly identified but for which there is a new concern for exposure, such as from a clinician, community group, legislature, or advisory board.**

Serious public health threats such as those posed by chronic chemical exposures must also be taken into consideration with this guidance and the final policy must assure that testing and exposure mitigation are not limited. PHLs develop test methods as they learn about potential exposures. The scope describing “immediate response” tests as those “...intended to detect or diagnose...a newly identified, previously unknown, or unusual CBRN agent...” or those presenting “...in a newly identified or unusual presentation...” is problematic as many environmental contaminants are known but the exposure to the population may change and suddenly become concerning. More is learned about environmental chemical exposures every day and PHLs must be able to respond to both acute and chronic exposures. The body of knowledge for some, like per- and polyfluoroalkyl substances (PFAS), is rapidly expanding. Over the past ten years it has been discovered that acute exposure to PFAS can have chronic health effects. As written, this guidance would not allow for a nimble response to a community PFAS exposure; PHLs must remain response-ready for all types of public health events, including these evolving emergencies, and not just those agents that are “previously unknown”.

Additionally, every state has different priorities and a different focus on environmental threats to health based on exposures unique to their geography or population. PHLs need the flexibility to be responsive to community and clinician concerns. For example, the California Department of Public Health Biomonitoring Laboratory is in the process of adding nickel to their panel of twelve metals assessed in urine because a community group is concerned about industrial exposure. Similarly, the Minnesota Department of Health Public Health Laboratory regularly adds novel psychoactive substances to their test panel because the landscape of drugs of abuse is rapidly changing. Once confirmatory test reagents are available, the Minnesota PHL purchases them and updates their assay to account for what may be circulating in their community. The definition of emergent situation must be expanded to account for these important public health initiatives.

**4. Expand the definition of emergent situation to make clear that the health threat may be outside of the United States.**

FDA should provide clarity to the definition of emergent situation such that the scope of immediate response tests applies to life-threatening diseases or conditions that may not be present yet in the US, but for which test development and surveillance is needed. PHLs must prepare for those health threats and implement testing to identify when the health threat is in the US so they can work with partners for a coordinated public health response that involves laboratory testing, healthcare, and vaccination/treatment/follow-up.

Although there is an [FDA policy](#) in place for enforcement discretion for mpox LDTs, this public health threat is a great example of how laboratories need to rapidly implement LDTs for assessing emergent

threats circulating outside the US. The mpox public health emergency began in 2022 in West Africa with mpox clade II and the introduction of the virus into the US was first detected by the Massachusetts State Public Health Laboratory using a Laboratory Response Network (LRN)-developed assay. The first US laboratory to offer a specific test for mpox clade II, an LDT, was the San Diego Public Health Laboratory. The test proved invaluable to the US public health emergency response. PHLs now need to develop LDTs for mpox clade I, which is endemic to Central Africa. International cases are on the rise and given global mobility, it is only a matter of time before this threat enters the US. PHLs must be able to respond with a sensitive and specific assay to identify the new clade and it is needed now so they can begin surveillance for this more virulent virus. A proactive response is needed to save lives and APHL encourages FDA to make this pathway clear in the guidance.

- 5. Public health laboratories should be able to provide evidence of their ability to develop sensitive and specific diagnostic tests using approaches other than demonstrating a history of FDA cleared, approved, or authorized tests.**

APHL and its member laboratories agree that tests should be designed, developed, and used within a CLIA-certified high-complexity laboratory; however, most PHLs do not have a history of test submission and review by FDA. The FDA should allow other approaches by which PHLs could demonstrate a history of developing highly accurate and sensitive tests, such as by adopting the policy used by the [New York State Clinical Laboratory Evaluation Program \(CLEP\)](#) for test approval. The FDA could require PHLs to share a summary of the validation performed, complete a risk assessment of all analytical stages of the test, and document all aspects of the test materials and methods as described (for example) in Section 3.3 of the CLEP [Genetic Testing Molecular Checklist](#). FDA could also request documentation of the number of LDTs developed by the PHL over the past “n” years and to indicate the number of false positive and false negative results that resulted from the use of that test. These records can serve as evidence that PHLs are able to develop sensitive and specific tests.

- 6. Laboratories may need more than 21 days to submit an emergency use authorization (EUA) application after a public health emergency (PHE) is declared; this timeframe should be flexible.**

APHL members have noted there will be difficulty with submitting an EUA to the FDA within 21 days of a public health emergency declaration. PHLs operate within a governmental structure with significant oversight; regulatory paperwork must be reviewed by their internal chain of command and legal program which can take weeks to months. Additionally, PHLs need EUA submission criteria as soon as possible so they can revise their internal validation policies to meet FDA requirements thereby limiting duplicative efforts once a PHE is declared (see #1 above on validation clarification

needs). PHLs will face lengthy delays when submitting EUA packages if they are not informed of FDA requirements before the onset of the public health threat, including a process accounting for rolling validations due to limited positive (non-contrived) specimens. For these reasons, laboratories may need more than 21 days to submit their EUA application after a PHE is declared and they should be able to continue performing the LDT during that timeframe. Jurisdictional public health responses should not stop because PHLs must follow governmental chain of command and legal processes nor because they did not have all the necessary resources from FDA to successfully comply with regulations.

**7. FDA consultation with CDC should not impede PHLs from offering tests for emergent situations in their own jurisdictions.**

There should be a simple, direct pathway for CDC and FDA to communicate with each other regarding enforcement discretion for LDTs during emergent situations and PHLs should be able to implement LDTs in their jurisdictions, prior to and without CDC and FDA consultation, should their populations require an immediate and effective public health response. FDA should not impede the ability of PHLs to respond to local public health issues.

**8. FDA should allow enforcement discretion for immediate response tests when designed, manufactured, and distributed by PHLs participating in the CDC LRN.**

All PHLs are CLIA-certified high complexity laboratories, and many participate in the CDC LRN for biological and chemical threats. Standardization of testing is important when responding to emergent situations that cross jurisdictions, and sharing LDTs among government operated PHLs may be necessary. The LRN is overseen by the CDC; however, it may not always be efficient or practical for CDC to be the sole manufacturer and distributor of LRN tests for PHLs. PHLs need to retain the flexibility to add redundancy to CDC efforts at manufacturing and distributing LRN LDTs for immediate health threats and emergent situations.

**9. More clarity is needed on the steps required after a test has been marketed for 12 months or after a PHE has been declared.**

The guidance requires laboratories submit the LDT for FDA review after it has been marketed for 12 months or after a PHE has been declared or laboratories must stop offering the test. The guidance is clear on these steps but does not describe how laboratories should proceed if they choose to stop offering the LDT but then the health threat reemerges, making the test necessary again. FDA

should allow use of the LDT, without submission to FDA for an EUA or similar application, if the public health threat reemerges during the absence of a PHE. Related, if during the threat reemergence there is an FDA-approved test, but the LDT is unique and preferable (based on factors such as sensitivity, specificity, specimen type, acceptable population range, specimen storage conditions, etc.), then the LDT should be an allowable option.

### Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency

1. **FDA should include consultation with CDC and APHL when considering LDT enforcement discretion policies.**

CDC, APHL, and PHLs are on the front lines of public health responses. APHL member laboratories are the tripwires that alert the rest of the public health and healthcare community to health threats; they and the CDC are the foundation of the National Laboratory System. APHL appreciates the guidance describes the factors that will be considered when FDA evaluates whether enforcement discretion should be allowed during a PHE; however, FDA should include that they will consult with CDC and APHL when gathering this information. The agency and APHL, informed by its PHL members, are experts on public health threats and test processes. They will be able to advise FDA on the public health response and bring the laboratory perspective on the need for accelerated testing, test risk potential, availability of appropriate alternative tests, and the availability of sufficient mitigations to address risks of false results.

2. **FDA should expand the list of acceptable mitigation measures that reduce the risk of false results.**

These could include PHL participation in programs such as the National Institutes of Health Independent Test Assessment Program (ITAP) or mechanisms to monitor adverse or unexpected test performance at PHLs.

3. **FDA should develop a pathway for PHL multi-site test validations for the collection of reproducibility data that does not require one laboratory to hold the authority to distribute the test.**

PHLs are governmental labs, and there is low likelihood that their overseeing bodies will allow them to be under the administration of an entity outside their government. This will restrict the ability of

PHLs to quickly bring on new assays during a PHE or imminent PHE due to the lack of specimens and resources necessary to complete validations. APHL is currently observing this as PHLs try to validate conjunctival swabs for highly pathogenic avian influenza (HPAI) testing. Few laboratories have positive specimens or material that can be used to contrive positives; a less restrictive pathway for PHL multi-site validations would allow more laboratories to add the HPAI assay to their test panels and prepare states for response to this imminent public health threat.

**4. FDA should allow modifications to LDTs and cleared/approved/authorized tests so laboratories can meet the needs of their unique jurisdictions.**

As described in the [September 2022 FDA Policy for Monkeypox Tests to Address the Public Health Emergency](#), FDA should not object to the modification and implementation of a cleared or authorized test as long as the modifications do not change the indication for use as described in the original 510(k) or EUA, and where the validation demonstrates the modifications do not adversely affect test performance. This explanation should be included in the guidance along with examples of acceptable modifications. These should include kits and instruments that operate utilizing the same or similar chemistry and software and do not change the overall indication for use. Examples may include replacing the ABI 7500 Fast Dx real-time polymerase chain reaction (PCR) operating system with the QuantStudio PCR system or replacing a sample preparation step from manual to a liquid handler to improve test throughput. Furthermore, chemistry assays need to be continuously optimized with changes and adjustments such as voltage and retention time based on the unique characteristics of the instrument (such as age), laboratory (environmental conditions), and column (integrity). These optimization modifications are necessary to maintain test sensitivity and specificity and should be included as allowable modifications.

Finally, an important lesson learned from the COVID-19 pandemic was the impact of the supply chain on testing. Laboratories need to be able to quickly pivot to different, but similar products, instruments, and kits when bottlenecks form. The ability to quickly change course is pivotal to an effective public health response and saving lives and FDA should be clear about allowable modifications to LDTs and FDA cleared/approved/authorized tests to allow for a coordinated and efficient response.

In addition to the above improvements to the draft policies, laboratories need additional resources to comply with these guidances and other FDA LDT regulations. Guidelines, templates, checklists, webinars and other resources are needed for LDT submission packages, medical device reporting, device kit labeling, soliciting

and tracking LDT complaints, and other quality system requirements as well as the mechanisms for communicating with FDA. Related, PHLs are resource-constrained and have been operating at a deficit; they are not funded to pay FDA fees associated with LDT reporting requirements or medical device applications nor do they have staff dedicated to those tasks. FDA should make it clear that PHLs will not be charged a fee as long as they are not commercially gaining from the test as stated in [21 USC Chapter 9, Subchapter VII, Part C, subpart 3: fees relating to devices](#), where no fee will be charged to state or federal government entities. This description should be expanded to include all levels of government (i.e., include local, tribal, and territorial PHLs).

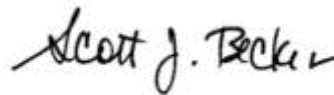
APHL appreciates that FDA does not want to stop the important work being done in PHLs. APHL member laboratories are the first line of defense in public health emergencies, threats, and outbreaks and their testing and assessment of health threats is what often leads to the mobilization of the rest of the laboratory system (commercial laboratories, hospital laboratories, academic medical centers, etc.). PHLs need to be able to quickly add tests when warranted, not only for chemical, biological, radiological, and nuclear agents but also for heritable disorders in newborns and known contaminants with evolving exposures. Expanding the scope of these guidances to address PHL needs will help ensure the government's coordinated and effective public health response to all types of immediate health threats.

APHL appreciates the opportunity to provide recommendations to the FDA to help shape the draft guidances on enforcement discretion during and in the absence of a public health emergency. For more information, please contact Amanda Cosser, APHL Manager of Regulatory and Public Policy, at [amanda.cosser@aphl.org](mailto:amanda.cosser@aphl.org). APHL looks forward to continued conversations with FDA as modifications are made to the proposed guidances.

Sincerely,



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