

January 13, 2015

Office of the Center Director
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave, Bldg. 66
Silver Spring MD, 20993

Re: Comments to Docket: FDA-2011-D-0360-0001, Framework for Regulatory Oversight of Laboratory Developed Tests

On behalf of the Association of Public Health Laboratories (APHL), please accept the following comments concerning the Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), Docket FDA-2011-D-0360-0001.

APHL strongly believes in accurate and quality testing; however, the unintended consequences of the proposed LDT regulatory framework will put undue burden on the public health system, which includes laboratory testing for diagnosis, screening, outbreak investigation and surveillance. As currently written, this regulation has the potential to greatly reduce or eliminate testing that provides important public health benefits. As FDA considers modifying its regulations, it is critical that public health laboratories continue to operate and fulfill their unique mission under the final LDT Regulatory Framework.

APHL has several grave concerns that in its present form, the framework will have a significant negative impact on public health laboratories.

General Concerns

1. One size does not fit all

The rationale for increased FDA oversight of LDTs stands on attributes identified by FDA as having changed the landscape of LDTs over the years, rendering FDA's current overall enforcement discretion inappropriate for the modern world. Many of these attributes, such as offering LDTs beyond local populations, manufacturing LDTs in high volumes, the evolving business models of laboratories, and using LDTs to screen for common diseases instead of rare diseases, are not characteristics of public health laboratories. Public health laboratories do not mass manufacture LDTs and instead continue to use and develop LDTs to inform public health needs in their local or state jurisdictions. Public health laboratories do not profit from developing LDTs nor is this their intent—at best, they break even by offering a test in a fee-for-

service model. APHL is deeply concerned that FDA has written a comprehensive regulatory framework to address certain, specific aspects of laboratories in the LDT landscape, but has not recognized the reach of the draft regulation and may not fully understand the detrimental implications for public health laboratories. *We understand from FDA that this regulation is not intended to harm the public's health or the public health system; however, the way the proposed regulation is written, it does little to protect it. FDA must recognize that the proposed regulatory framework does not accommodate public health laboratories or the greater public health system, and FDA must build in greater flexibility for public health services.*

2. *FDA must be responsible for a timely premarket review process*

APHL believes that there will be a significant burden on FDA to review LDT premarket review applications in a timely manner. Through anecdotal conversations with public health laboratories, it is apparent that there is a wide range in the number of LDTs utilized in each laboratory. One public health laboratory estimates utilizing nearly 200 LDTs on a regular basis, while others numbers range from 96 to 34 LDTs. The majority of the LDTs are used for infectious disease testing or for newborn screening. All of these tests are validated according to the Clinical Laboratory Improvement Amendments' (CLIA) guidelines and regulations and only put to use after review and approval by the laboratory director. In addition, it is the laboratory director's responsibility to determine the suitability of the test before it is developed and validated. The testing services provided by public health laboratories are critical and cannot be delayed due to a redundant, inefficient and slow review process. FDA needs to be aware of the large number of LDTs that will be affected by the proposed regulation and the critical public health needs that rely on these test results. *The work of public health laboratories cannot be delayed by a burdensome FDA review process. It is the responsibility of FDA to ensure a timely and efficient review process that reduces the need for multiple review cycles.*

3. *Ensuring the public health response to non-emergency use authorization (EUA) outbreaks*

Public health laboratories operate as a first line of defense to protect the public against disease and other health hazards. FDA is familiar with the need to be flexible when responding to large outbreaks of public health significance as shown through their EUA process. However, EUAs are only issued when a Secretary declares a public health emergency or significant potential for a domestic emergency. While EUAs are helping in the current Ebola outbreak and have helped with the recent threats of MERS Co-V and H7N9, there are and will be a number of outbreaks that will never elevate to the level of a public health emergency. Outbreaks of vaccine preventable diseases such as measles and pertussis are occurring in the United States with higher frequency and ferocity. Other emerging diseases such as enterovirus D68 and chikungunya have caused significant public health impact over this past summer. While these outbreaks will never be declared public health emergencies, they are no less significant or deserving of critically important testing. In order to respond to these types of emerging

outbreaks, public health laboratories often rely on LDTs developed in their own laboratories, or on standardized protocols deployed from the Centers for Disease Control and Prevention (CDC). *Public health laboratories receive specific training in emergency response for preparedness, which includes laboratory testing of emerging pathogens and biothreat agents. Because of this, they are responsive and adaptive to outbreaks often outside of the scope of an EUA and in reliance of LDTs. It is critical for FDA to recognize the limitations of EUAs and develop a system for expedited review or enforcement discretion for the use of LDTs in outbreaks of public health significance.*

4. *LDT regulatory framework must not burden public health by limiting use of research use only components*

Public health laboratories play a pivotal role in the first line of defense against new disease threats and an effective response to emergencies requires the use of the best tools available. APHL has been informed by FDA that reagents, platforms or databases that are “not legally marketed” for diagnostic use will require the assay go through the premarket review process. As explained above, the premarket review process is overly burdensome and costly for public health laboratories and will result in loss of diagnostic capability and capacity. One way for FDA to relieve the burden on public health laboratories is to allow assays afforded enforcement discretion to include research use only (RUO) components. This will allow public health laboratories to continue to keep pace with emerging technologies that often have RUO components.

An example is matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), which rapidly identifies bacterial pathogens in a cost-effective manner and requires a reference database for comparison to the unknown sample. While the MALDI-TOF MS technology is FDA approved, some manufactures offer RUO reference databases to keep pace with emerging pathogens that are unknown and not originally included in the FDA approved database. These databases enable public health laboratories to be on the frontline of disease response as new diseases emerge. However, according to the proposed LDT Regulatory Framework, laboratories using the RUO database would need to seek premarket review every time a new organism is added to the database, rendering MALDI-TOF MS impractical for public health response. It is simply unreasonable and untenable for FDA to expect public health laboratories to seek premarket review every time a new organism is validated for MALDI-TOF MS. *For additional flexibility, APHL asks FDA to allow LDTs that fall within an enforcement discretion category (low risk, rare disease, unmet needs or traditional) to be comprised of non-FDA cleared reagents and instrument platforms. FDA should consider utilizing special controls for non-cleared reagents and platforms to assess reagent quality, similar to the Clinical Laboratory Improvement Act (CLIA) requirements.*

5. *FDA regulatory activities must preserve public health surveillance*

Disease surveillance is an essential pillar of the public health system. Continuous and systematic collection of data allows public health professionals to accurately understand health problems and subsequently design and conduct appropriate health interventions. Several national surveillance systems such as weekly virologic surveillance for influenza, PulseNet, and the National Antimicrobial Resistance Monitoring System rely on many of the same LDTs that will fall under FDA's proposed regulation. Often, LDTs have a dual purpose of informing surveillance programs and providing clinical information to providers. *As FDA continues to modify and shape the LDT regulatory framework, it is necessary to understand that the proposed regulation will negatively impact national surveillance programs. A cumbersome premarket review process for LDTs will limit and halt critical surveillance activities, and modifications must be made to protect public health.*

Additionally, there is a subset of tests that public health laboratories conduct that are solely intended for surveillance purposes. In these cases, public health laboratories do not provide results from surveillance tests to inform clinical decisions but instead report to the health department for epidemiology purposes. For example, biomonitoring is a process that measures environmental chemicals and toxic substances in people's blood, urine and other fluids. The testing provides a unique laboratory-based tool for conducting reliable, hypothesis-driven research. Such research is necessary to obtain quality data required to identify linkages between environmental exposures and disease. Biomonitoring data is intended to be used to set research priorities, inform effective public health interventions, develop public policy and evaluate the impact of policy changes and programs. While public health laboratories follow strict procedures outlined by institutional review boards and have appropriate practices in place to ensure the proper handling of test specimens, occasionally—beyond the control of the public health laboratory—biomonitoring test results may be reported as clinical information to a physician from the health department. APHL is concerned that LDTs with an intended use for surveillance purposes that occasionally end up in medical records, but do not inform a medical decision, will be considered diagnostic by FDA and therefore be inadvertently and inappropriately subject to the LDT regulatory framework. *It is critical that FDA preserve the functionality of LDTs that have a sole intended use of surveillance by excluding them from the regulatory framework. APHL suggests that FDA clearly outline their definition and interpretation of surveillance in order to ensure this.*

6. *FDA must include experts from governmental public health laboratories in risk-based prioritization of LDTs*

Public health laboratorians can provide expert input to FDA's public process of risk-based prioritization for LDTs, and should be included in this process for LDTs used for public health needs, including:

- Newborn screening

- Infectious diseases
- Biomonitoring for harmful chemicals and toxins
- Food safety
- Public health preparedness
 - Biothreats
 - Chemical threats

APHL is willing to facilitate FDA’s connection with public health laboratorians who can provide input on this panel.

APHL’s Recommendations for Modifying the LDT Regulatory Framework

APHL strongly urges FDA to: 1) utilize an alternate definition for a rare disease as defined by the Orphan Drug Act of 1983; 2) provide an efficient review process for established rare diseases; 3) reframe LDT regulation for public health laboratories that is not based on the 510(k) or PMA paradigm; and 4) include governmental public health laboratories as part of FDA’s definition of a “healthcare system.”

Recommendation 1: FDA will redefine a rare disease based on a disease or condition’s prevalence estimate rather than a national device usage estimate.

REDEFINING RARE DISEASES BASED ON PREVALENCE

APHL would like to see the Center for Devices and Radiological Health’s (CDRH) definition of a rare disease apply to LDTs with the following proposed language:

“The definition of a rare disease for the purpose of FDA continuing to provide enforcement discretion with respect to premarket review requirements for LDTs used for rare diseases shall be defined as:

Any disease or condition which affects less than 200,000 persons in the United States”

Rationale: As the draft regulation is currently written, the definition of a rare disease is based on the number of patients per year that would be subjected to diagnosis by the device. APHL believes that this is not an effective definition of a rare disease because the ability to accurately document that fewer than 4,000 persons may be tested with the device is so complex that it would be nearly impossible. There is no current database that provides a national estimate of this measure. It is also incongruent that FDA would base the definition of a rare disease on a national usage measure when the LDT, as outlined by FDA’s definition of its purpose, will be used in a single laboratory. If FDA believes it is essential to define a rare disease based on the

number of times the device is used, a more appropriate, specific and population-based measure that reflects the device usage in a community should be considered. Laboratories are more likely to be able to provide documentation reflecting an accurate jurisdictional estimate of device usage rather than a national estimate. However, APHL urges FDA to consider the national prevalence of the disease or condition in defining a rare disease and to unify and standardize its approach to defining rare diseases across its agency.

Currently, FDA's Center for Drug Evaluation and Research's (CDER) Rare Disease Program¹ and FDA's Office of Orphan Product Development² uses the rare disease definition established by the Orphaned Drug Act of 1983 (Public Law 97-414)³. In this definition, a rare disease or condition is defined as "*any disease or condition which*

1. *affects less than 200,000 persons in the United States or*
2. *affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.*"

If CDRH were to adopt the recommended definition, not only does this standardize FDA's approach to a rare disease and sets the same precedent for diagnostics as it does for treatments, it also avoids the proposed draft guidance definition based on national device usage, which, again, is very difficult to ascertain.

Recommendation 2: *FDA will provide a streamlined and efficient review process of LDTs for rare diseases by allowing laboratories who utilize an LDT with an intended use listed on NIH's Office of Rare Diseases Research list to be relieved of needing to provide documentation and evidence that their LDT falls within the definition of a rare disease.*

FDA WILL WAIVE THE DOCUMENTATION REQUIREMENT FOR ESTABLISHED RARE DISEASES

The definition of a rare disease affecting less than 200,000 has set the precedent for the activities of the [Office of Rare Diseases Research](#) (ORDR) at the National Institutes of Health, which has a list of ~6,800 rare diseases. APHL recommends that FDA CDRH utilize ORDR's list as a baseline for establishing what rare disease LDTs should be automatically entitled to rare disease enforcement discretion. Documentation by the public health laboratory will not be required if the LDT has a diagnostic intended use for a rare diseases on ORDR's list.

¹ <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm221248.htm>

² <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143563.htm>

³ <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdca/significantamendments/tothefdcact/orphandrugact/default.htm>

Rationale: By utilizing this list,⁴ the LDT regulatory process will be effectively streamlined by eliminating requests and documentation for humanitarian use device designation, and will remove the step of FDA's review of those submissions.

If laboratories seek enforcement discretion for rare disease LDT that is NOT on the ORDR's list, they should be expected to provide full documentation to FDA establishing that the LDT was developed to diagnose or to help diagnose a disease or condition that affects less than 200,000 persons in the United States.

Rare diseases of public health importance can be found at the following links:

1. Viral Infections: <http://rarediseases.info.nih.gov/gard/diseases-by-category/25/viral-infections>
2. Bacterial Infections: <http://rarediseases.info.nih.gov/gard/diseases-by-category/2/bacterial-infections>
3. Newborn Screening: <http://rarediseases.info.nih.gov/gard/diseases-by-category/37/newborn-screening>
4. Parasitic Diseases: <http://rarediseases.info.nih.gov/gard/diseases-by-category/20/parasitic-diseases>
5. Fungal Infections: <http://rarediseases.info.nih.gov/gard/diseases-by-category/11/fungal-infections>
6. Congenital and Genetic Diseases: <http://rarediseases.info.nih.gov/gard/categories>

Recommendation 3: FDA will create a new regulatory framework for governmental public health laboratories to preserve and protect the public health system.

REFRAME REGULATION FOR GOVERNMENTAL PUBLIC HEALTH LABORATORIES

The 510(k) and premarket approval paradigm that has effectively regulated device manufacturers **DOES NOT** translate to an effective regulatory scheme for LDTs used in the public health system. It instead threatens the daily work of public health laboratories, because they cannot surmount the burden of premarket review requirements. FDA must reframe LDT regulation to allow a functional public health laboratory system, while at the same time ensuring accurate and high quality testing.

Rationale: Part of FDA's rationale for increased oversight of LDTs is that business models for laboratories have changed and LDT manufacturers are now large corporations that nationally market complex, high-risk devices. *This is an instance where FDA has written the regulatory framework directed towards a specific entity to address a specific problem, yet the implications are broad, cross cutting, inappropriate and unfounded for the wider audience that will ultimately*

⁴ <http://rarediseases.info.nih.gov/gard/categories>

be affected by the regulation. There will be severe and unintended consequences to public health if FDA does not give governmental public health laboratories flexibility under the framework. Unlike diagnostic manufacturers or commercial laboratories, state and local public health laboratories do not manufacture LDTs for sale or profit; this is outside the scope of their mission. Instead, they rely on federal and state funding sources. Public health laboratories are concerned with diseases and conditions of public health importance that impact the overall health of populations and are not founded or driven by the business models that have rationalized the need for increased oversight. Many times these diseases are emerging and manufacturers have not developed a marketed assay to detect the disease, or the disease has such a low incidence such that manufacturers will not recover through sales the cost of developing the test, conducting studies to collect clinical validity data, and the cost of a 510(k) or PMA application with FDA. This often leaves a gap between what is needed for public health and what is profitable for manufacturers. For example, gonorrhea and chlamydia tests are cleared by FDA for a subset of specimens, but not for extragenital specimens such as rectal and oropharyngeal swabs. Device manufacturers have not attempted to seek FDA clearance for these specimens because there is a small commercial market for these specimens. However, a limited commercial market does not equate insignificance in public health. As drug resistance may initially emerge in extragenital sites,⁵ it is critical that rectal and oropharyngeal specimens be tested for treatment and surveillance purposes. Due to the lack of FDA cleared tests for extragenital specimens, public health laboratories fill a necessary testing gap by validating the tests in compliance with Clinical Laboratory Improvement Amendments (CLIA).

It is unreasonable to believe that public health laboratories will be able to pursue LDT premarket review with their limited resources if for-profit manufacturers do not have the means to clear extragenital specimens through the 510(k) process. Additionally, the Unmet Needs enforcement discretion category will not provide flexibility to public health laboratories, because FDA's proposed definition of a healthcare system excludes governmental laboratories.

FDA's willingness to reframe LDT regulation for public health laboratories would indicate that FDA: 1) understands and values the fundamental difference between governmental public health laboratories and LDT manufacturers/commercial laboratories that market products for profit and 2) respects that governmental public health laboratories need a unique and more flexible regulatory approach.

APHL believes in high quality and accurate testing and is willing to work with FDA to define an appropriate framework for governmental public health laboratories. APHL envisions a framework with the following components:

- Notification to FDA of all LDTs performed within the specified timeline;

⁵ Unemo, M., & Nicholas, R. (2012). Emergence of multi-drug resistant, extensively drug-resistant and untreatable gonorrhea. *Future Microbiol.*, 7(12), 1404-1422.

- Establishment of an adverse event reporting system;
- Adherence to special controls for Class II LDTs to provide reasonable assurance of the safety and effectiveness of LDTs conducted in public health laboratories;
- Submission of analytical and clinical validation and verification data that is conducted for other regulatory bodies such as CLIA or CAP.

Recommendation 4: *FDA must consider public health laboratories as part of the “healthcare system.”*

PUBLIC HEALTH LABORATORIES ARE AN ESSENTIAL COMPONENT OF THE HEALTHCARE SYSTEM

FDA needs to recognize that the scope of a healthcare system goes beyond that of a hospital system. Public health laboratories serve as reference laboratories to hospitals and clinical laboratories within their jurisdictions. Additionally, some public health laboratories support and assist in testing for other states and territories. Public health laboratories perform specialized, high quality testing for diseases of public health importance that hospital or clinical laboratories do not have the capability or capacity to perform. Excluding public health laboratories from the healthcare system will compromise patient care and the public health system.

Rationale: FDA’s rationale that limiting the definition of healthcare facility laboratories to those located in a hospital or a clinic will mitigate the risk associated with LDTs is speculative. There is no basis to suspect that hospital laboratories have a higher level of personnel or expertise simply because they are located within the same facility as the patient. In fact, many hospitals and clinical laboratories rely on the specialized expertise provided by public health laboratories to perform and interpret assays that they cannot perform in their own laboratories. Examples where hospital and clinical laboratories rely on the expertise of public health laboratories include molecular drug susceptibility testing for TB, pyrosequencing to detect anti-viral drug resistance influenza, and identifying organisms involved in novel outbreaks such as fungal meningitis. Public health laboratories are often the first to receive assays deployed from the Laboratory Response Network for public health emergencies like anthrax, Ebola or MERS. Hospital laboratories rely on using public health laboratories as reference laboratories to perform or confirm testing so that clinical decisions can be made. This flow of information and division of work does not indicate a lack of quality or accuracy and all parties share a responsibility for patient and public health outcomes.

Moreover, public health laboratories, as part of their core functions, foster a culture of quality. They continually strive to improve operations at their facilities and at clinical laboratories within their jurisdiction. They sponsor specialized training, send updates concerning health threats and

share information on best practices. In many states, public health laboratories regulate private clinical and environmental laboratories.

FDA must redefine their concept of a healthcare system to include governmental public health laboratories. Neglecting to do so will not only inhibit public health functions, but also diminish a critical reference resource for hospital and clinical laboratories, and thereby adversely impact patient outcomes.

Factors that Mitigate Risk of LDTs Utilized in Governmental Public Health Laboratories

Discretionary Advisory Committee on Heritable Disorders in Newborns and Children

Newborn screening screens for rare genetic disorders in infants and children and is a core component of all state public health departments. In most states, newborns are screened for 31 core conditions that are listed on the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of disorders that are screened at birth and recommended by the Secretary of the Department of Health and Human Services (HHS). The Secretary of HHS is advised by the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) as established under the Public Health Service Act 42 U.S.C. 217a. The advisory committee uses an explicit approach to make recommendations, and disorders on the RUSP are selected based on evidence that supports the net benefit of screening, including but not limited to the availability of: a valid and reliable screening test, a system to ensure quality implementation of the screening test, quality control and proficiency-testing samples, a centralized quality assurance program and an effective treatment.⁶ APHL believes that the expert panel review provided by DACHDNC and subsequent recommendation by the Secretary of HHS provides significant risk mitigation for those LDTs that are used in the newborn screening field. We ask that FDA take this into consideration when reviewing and assigning risk to newborn screening LDTs.

Areas Requiring Further Clarification and Interpretation from FDA

1. Adverse Events Reporting
 - a. Are incorrect test results or interpretation required to be reported as adverse events?
 - b. Are delays in reporting test results considered adverse events?
 - c. Are software related malfunctions in LIMS that cause delays in testing or incorrect results considered adverse events?
2. Definition and Interpretation of Surveillance

⁶ Kemper, A., Green, N., Calonge, N., Lam, W., Comeau, A., Goldenberg, A., ... Bocchini Jr, J. (2013). Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: Statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genetics in Medicine*, 16(2), 183-187.

- a. How does FDA distinguish between LDTs used for clinical purposes and those used for surveillance?
 - b. Can FDA provide a clear definition and interpretation of surveillance so it is clear which LDTs will be subject to the regulatory framework?
 - c. Will LDTs with a surveillance intended use be outside the scope of the regulatory framework?
3. Rationale for Premarket Review if Alternative Specimens are Used on Previously Cleared Assays
 - a. Can FDA provide rationale for requiring premarket review for FDA-cleared assays if specimen types change?
 - b. Can public health laboratories provide equivalency data that shows sample types perform the same on previously cleared assays?
4. Definition of Screening Assays
 - a. Screening assays are not used for diagnosis and rely on outside laboratories or other methods to confirm results. Can FDA carve out a definition for screening assays?

APHL appreciates the opportunity to provide recommendations to FDA to help shape the LDT regulatory framework. For more information, please contact Celia Hagan, APHL's Senior Specialist of Public Policy at celia.hagan@aphl.org or 240-485-2758. APHL looks forward to continue conversations with FDA as modifications are made to the regulatory framework for LDTs.

Sincerely,

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