September 14, 2026

Dr. Mehmet Oz
Administrator, Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dr. Erica Schwartz
Director, Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 03029

Re: APHL comments in response to file code CMS-3485-NC.

Dear Administrator Oz and Director Schwartz,

As you evaluate which areas of the CLIA regulations may need to be updated to better reflect current knowledge and advancements in laboratory testing, the Association of Public Health Laboratories (APHL) would like to offer the enclosed response to the Request for Information (RFI); Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations.

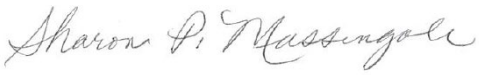
APHL envisions a healthier world through quality laboratory systems. The membership-based organization strengthens the impact of state and local public health, environmental, and agriculture laboratories nationally by providing connection to federal, programmatic, and academic partners, analytical training, and technical assistance. APHL shapes national outcomes by promoting the value and contributions of public health laboratories (PHLs) and continuously improving PHL systems and practices.

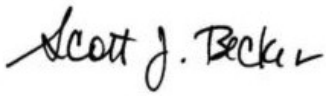
APHL is uniquely positioned to assemble a team of stakeholders to continue the important progress made by the Clinical Laboratory Improvement Advisory Committee (CLIAC) and resume the dialogue about CLIA modernization. The partners gathered would not replace the federal advisory committee but rather create a forum for discussion with representatives from relevant areas of laboratory practice, as well as the Centers for Medicare & Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA). APHL's strong relationships with these federal agencies, combined with the strategic partnerships the association has developed with academic, public health, clinical, and commercial laboratories, uniquely position APHL to be a convening body for laboratory peers. As you review the enclosed response to the RFI, APHL also encourages you to consider establishing a platform for APHL-facilitated conversations about CLIA regulatory updates.

Additionally, APHL supports CMS and CDC efforts to improve laboratory data quality and similarly strives for data quality improvement through standardization. APHL maintains critical national public health data exchange infrastructure through the APHL Informatics Messaging Services (AIMS) Platform. Operating since 2008, AIMS serves as a secure, cloud-based hub that enables the exchange of more than 50 million public health and laboratory test result messages each month among PHLs, healthcare organizations, federal agencies, and commercial laboratories. CMS and CDC are encouraged to leverage this standardized, shared infrastructure that provides validated and secure processes for electronic test orders and results. Including AIMS in CLIA guidance as a model for laboratory test ordering and reporting will improve laboratory data standardization and quality.

APHL appreciates the opportunity to suggest improvements to the CLIA regulations. We look forward to continuing our valued relationship and strengthening the laboratory system together.

Sincerely,





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Enclosure: APHL Response to CMS and CDC CLIA RFI

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Section A. Breath Testing

No comment; PHLs do not offer breath testing.

Section B. Laboratory Processes and Procedures

Subsection 1. Pathology Specimen Block Retention

No comment; PHLs do not offer pathology specimen block testing.

Subsection 2. Specimen Preparation Activities and Personnel

Question 1. What activities does the laboratory consider to be part of specimen preparation (for example, centrifuging, aliquoting, loading on analyzers, adding chemicals for preparation, tissue processing, slide staining, inoculating culture plates, DNA/RNA extraction)?

Public health laboratories (PHLs) generally classify specimen preparation as preanalytic work that may affect a specimen's identity, integrity, concentration, recovery, or suitability before testing. This includes activities that do not produce a qualitative or quantitative result, such as specimen receipt and accessioning, acceptability checks, labeling, centrifuging, aliquoting, vortexing, dilution, slide preparation, reagent or preservative addition, digestion, decontamination, inoculation (i.e. streaking microbiological culture plates), concentration, reconstitution, and transport-related handling. There is variation in how PHLs classify steps such as nucleic acid extraction, chemical extraction, slide staining, instrument loading, and specimen manipulation after a container is opened. Some PHLs treat these steps as analytic because they are integral to the testing workflow and may affect downstream results.

The Centers for Medicare & Medicaid Services (CMS) and Centers for Disease Control and Prevention (CDC) should more clearly define the boundary between preanalytic specimen preparation and analytic testing in the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations while recognizing that public health testing often spans multiple linked processes in different laboratory programs. Providing clear, risk-based guidance that includes validation requirements for specimen preparation platforms (such as the King Fisher nucleic acid extraction instrument) along with personnel qualifications and competency requirements would improve and standardize the current regulation.

Question 2. What is the education and experience of the personnel who perform specimen preparation activities for your laboratory?

Personnel qualifications for specimen preparation activities at PHLs align with the complexity and risk of the work. Staff perform the activities under supervision using documented procedures after successful training and competency assessment.

Routine preanalytic functions such as sample receiving, labeling and test order verification, data entry, container and volume checks, and transport condition review are generally performed by personnel with at least a high school diploma or equivalent, although associate and bachelor degrees are preferred. More complex activities, particularly those involving sample handling or manipulation after a container is opened,

typically require higher education and experience. All applicable CLIA personnel qualification requirements are followed.

Question 3. What types of training does the laboratory provide for the personnel who perform specimen preparation activities?

PHL personnel performing specimen preparation must complete documented training before working independently, typically within the first 30 to 90 days. Training commonly includes reading standard operating procedures (SOPs) and job aids; completing biosafety, bloodborne pathogen, chemical safety, Health Insurance Portability and Accountability Act (HIPAA), and CLIA-related training; and learning proper use of personal protective equipment (PPE), safety protocols, specialized equipment, and the Laboratory Information Management System (LIMS) for accurate data entry, patient identification, specimen tracking, and testing.

Training is generally hands-on and process-specific, using checklists and a progression of reading the procedure, observing the task, performing it under supervision, and then performing it independently. Online training from CDC OneLAB REACH is also used for topics such as biological safety cabinets (BSCs), chemical fume hoods (CFHs), and centrifuges. Personnel must demonstrate competency before independently performing accessioning or specimen preparation activities, and competency assessments often include the six CLIA elements (direct observation, record review, quality control review, instrument-related tasks, and problem-solving) along with a seventh related to safety.

Question 4. How does the laboratory ensure that personnel who perform specimen preparation activities remain competent?

Competency for personnel performing specimen preparation is documented through initial, semi-annual, and annual evaluations that align with their job description and the procedures they are qualified to perform. Assessments typically include the six CLIA-required competency elements. Some PHLs also add a safety-focused assessment to evaluate appropriate PPE use, safe laboratory practices, and proper work in BSCs or CFHs.

Subsection 3. Suboptimal Specimens

Question 1. What are the circumstances under which the laboratory tests suboptimal specimens?

PHLs test suboptimal specimens when the sample cannot be replaced or retrieved, and generally only with approval from the laboratory director. This applies to specimens collected from a patient who has since died, one obtained through a highly invasive procedure like a biopsy, or one that is inherently difficult to obtain again, such as pediatric cerebral spinal fluid or a specimen from an incarcerated individual. Suboptimal specimens may also be tested during circumstances of high public health consequence, such as public health emergencies and outbreaks. For example, cases involving bioterrorism agents, highly pathogenic avian influenza, Ebola, Marburg virus, or botulism, as well as broader pandemic or emerging disease responses. In these situations, the suboptimal specimen may be the first specimen received or one of only a few received and the potential information obtained from the result is extremely valuable to informing next steps and preventing additional exposures and disease. Newborn screening (NBS) represents a special case because these samples capture a biological timepoint that cannot be recreated. Analyte levels in a newborn can change significantly within just a few days, so a specimen collected too early or too late may appear falsely normal or only be abnormal within a narrow window. This makes testing the suboptimal specimen more important than waiting for an ideal sample.

Question 2. How often does your laboratory test suboptimal specimens annually?

PHLs rarely test suboptimal specimens due to regulatory requirements and because they are infrequent events.

Question 3. How does the laboratory document and report results from suboptimal specimens?

PHLs document and report results from suboptimal specimens by including reportable comments or disclaimers on the test report that note compromised sample integrity. This language is typically approved by the laboratory director. If the suboptimal specimen is rejected for testing, the report states the specimen was unsatisfactory and that a new specimen should be collected and submitted to the lab. PHLs monitor suboptimal specimen submission, testing, and rejection rates, and some document them in corrective action plans that include activities to reduce their submission. **CMS and CDC should more clearly define reporting requirements related to comments and disclaimers for suboptimal specimens in the CLIA regulations and guidance.**

Question 4. How does the laboratory communicate with ordering providers regarding suboptimal specimens?

PHLs communicate with ordering providers about suboptimal specimens through a combination of phone, fax, mail, and automated electronic systems. The communication method is based on how urgently the test result is needed and the communication is documented. A phone call is often the preferred approach; these conversations also give the provider an opportunity to raise questions or concerns and allow the laboratory to offer guidance on how to improve submission conditions for future specimens. If a specimen is rejected, a LIMS report is generated that includes language noting why the specimen could not be tested. If a suboptimal specimen is tested, the report will include a comment describing the specimen's suboptimal condition and may include a disclaimer that a negative result may not reflect a true negative given the compromised quality of the specimen. Many PHLs also track rejection rates, and when a provider shows a higher-than-usual rejection rate, that pattern is discussed directly with the provider to help reduce future issues.

Question 5. What quality assurance measures does the laboratory apply to the testing of suboptimal specimens?

PHLs apply quality assurance measures to suboptimal specimens largely by maintaining the same standards used for optimal samples, beginning with specimen acceptability criteria defined in SOPs for each test method. Preanalytical staff perform an initial review of specimen acceptability, and analytical staff may conduct a final review to confirm whether a specimen is suitable for testing. For critical or urgent situations, a team lead or manager may contact the laboratory director to request an SOP exception allowing an unsuitable specimen to be tested. Throughout this process, staff aim to follow the SOP as closely as possible including verification that quality controls pass. For example, confirming that a human nucleic acid marker in a suboptimal specimen shows a detected result (i.e. a detectable RnaseP marker) provides evidence that human cells were in the specimen and the molecular test was successful. Any deviations are noted in the LIMS and accompanied by a disclaimer on the test report, and rejection rate tracking along with corrective and preventive actions are maintained as part of this quality framework.

Additional specialized measures are applied depending on the specimen type and test. For samples undergoing chemical extraction, an internal standard is added, and quality control samples are included for reassurance of successful extraction. In some cases, the PHL will recreate the suboptimal condition on a

contrived specimen to test its stability under that condition, generating data that supports testing the actual specimen.

Question 6. What challenges does the laboratory face in managing suboptimal specimens while ensuring test result quality?

Testing suboptimal specimens is challenging to PHLs because the process requires a significant time commitment. This is due to the amount of internal and external communication needed to decide whether the specimen should be tested, communicating the results with the appropriate disclaimer or comment, and educating the submitter on why the specimen was suboptimal and how to prevent the issue from recurring. Test result quality is preserved by the quality assurance processes previously described; all other steps of the SOP are followed and results are not reported if controls and other quality assurance measures do not pass. Disclaimers are included on the test report; for example, a negative result often includes a disclaimer that the result may not be reliable due to the suboptimal nature of the specimen and that another specimen should be recollected and tested. Positive results often include comments that note the specimen was suboptimal and include proper specimen conditions for that test such as, "specimens for xxx test should be collected and tested within 48 hours".

Subsection 4. Establishment and Verification of Performance Specifications

Question 1. For tests that are not FDA-cleared or approved, including modifications of FDA-cleared or approved tests, what challenges does the laboratory encounter when establishing adequate performance specifications and appropriate acceptance criteria? Specify the relevant test or procedure associated with such challenges.

PHLs overcome many challenges when validating laboratory developed tests (LDTs) and modifying FDA-cleared/approved tests, particularly for rare, emerging, or emergency-response threats. This is because clinical specimens, reference materials, and established acceptance criteria may be limited or unavailable (e.g., validation of conjunctiva swabs for avian influenza, reference materials for viral hemorrhagic fever viruses, and validation of Middle Eastern Respiratory Syndrome coronavirus [MERS-CoV] testing). Common challenges to test validation include difficultly obtaining positive specimens, those in the correct matrix, or collected in the correct timeframe; determining the acceptable sample volume; limited availability of control material; lack of reference methods for test development; and lack of reference ranges for result reporting. Quickly evolving pathogens or those with multiple circulating variants create another challenge for PHLs as the test target must be updated and the test revalidated. These challenges are especially pronounced for highly complex methods such as sequencing assays, where laboratories must determine scientifically defensible thresholds for performance. For example, determining when sequence data are of sufficient quality to accept or when results are no longer reliable.

Additionally, establishing limits of detection can be resource-intensive and costly, requiring many replicates, additional performance measures, and substantial personnel time spent on validation efforts. The financial burden of this process is challenging for PHLs which are governmental/not-for-profit laboratories.

Because PHLs may need to implement testing before large clinical datasets exist, validation approaches often rely on scientifically justified alternatives. **CMS and CDC should allow scientifically justified validation designs that use contrived or simulated specimens, spiked controls, characterized reference materials, different instrumentation, in silico evidence (computer modeling), and post-implementation test monitoring, especially for novel or emerging pathogens. These approaches should be documented clearly and include any limitations.**

Question 2a. What testing methods (for example, toxicology and next-generation sequencing (NGS)), and/or specific applications of those methods (for example, use of NGS to test for somatic or germline variants, minimal residual disease, methylation, bacterial resistance mutations, viral identification, or HLA matching), have unique performance characteristics that need to be established and are not already addressed in the CLIA regulations or guidance?

Whole genome and next generation sequencing along with related molecular technologies have unique performance characteristics that are not well addressed by current CLIA categories or guidance. These tests are inherently different from other microbiological tests and should have their own specialty under CLIA requirements. Any CLIA oversight expectations should also include when raw analytical data are interpreted outside the laboratory, such as by epidemiologists or health professionals that may not hold a CLIA certificate. **Additionally, CMS and CDC should provide guidance for toxicological methods, especially those utilizing high resolution mass spectrometry.** Any specifications should include test validation and quality control parameters.

Question 2b. What are those performance characteristics (for example, stability studies, carry-over, internal standards, ionization, and clinical validity)?

PHLs need additional guidance on key performance specifications such the differences between sequencing coverage and Q score, and what internal standards, stability studies, and QC criteria are most appropriate based on the various testing situations. The distinction between sequencer performance for quality control measures such as error rates versus assay performance for specific pathogens should be included in any guidance.

Clearer guidance on acceptable thresholds for read quality, variant allele fraction, on-target rate, duplication rate, insert size distribution, mapping rate, platform-specific error profiles, contamination, host read depletion, and taxonomic classification accuracy is also needed. Although published examples exist, there is limited consensus on when sequence data are sufficiently reliable versus when resequencing is needed.

PHLs also need guidance on bioinformatics pipeline validation, including how to compare pipelines, determine whether a platform is adequate and trustworthy, ensure pipeline reproducibility, manage version control, and test pipeline updates.

Whole genome sequencing (WGS) is still relatively new, and many analytical pipelines have not been fully developed, evaluated, or standardized across microorganisms. This limits the microbiological characteristics laboratories can confidently report (e.g., antimicrobial resistance, toxin production, pathogen identification, and other genomic characteristics). These and other tests need clearer performance expectations from CLIA, including next generation sequencing (NGS) for *Mycobacterium tuberculosis* complex and detection and sequencing of viral pathogens (including differentiation between rhinoviruses and enteroviruses). Overall, sequencing and molecular assays require distinct quality and performance criteria rather than being grouped under broad existing specialty categories and PHLs would greatly benefit from additional guidance from CLIA.

Question 3. How does the laboratory currently design, develop, and prepare reagents for tests developed in-house?

For reagents and tests developed in-house, PHLs rely on peer-reviewed literature, CDC reference methods, and assays developed by other PHLs, while consulting with subject matter experts from those laboratories, CDC, the Association of Public Health Laboratories (APHL), and the Food and Drug Administration (FDA). Most reagents are sourced externally; however, any prepared in-house are subjected to quality checks throughout the testing process. This includes sample preparation, extraction, and instrument analysis to confirm

acceptability and all CLIA requirements for LDTs. Written protocols and procedures document the method, reagent preparation, optimization steps, and performance checks. Quality control officers and technical supervisors review results, determine pass/fail status, and provide final approval before reagents or methods are released for use.

Question 4. What types of modifications does the laboratory commonly make to FDA- cleared or approved test systems?

PHLs may modify and validate FDA-cleared or approved tests in accordance with CLIA regulations to better meet public health testing needs. Common modifications include extending specimen hold times between collection and testing, broadening acceptable storage or shipping temperature ranges, changing incubation times, adding specimen types or matrices, adjusting specimen volume or quantity requirements, expanding specimen acceptability criteria for sex or age, and using different extraction methods or PCR instruments.

These modifications are often driven by operational and public health realities, such as broad geographic service areas resulting in longer transport times, rare or difficult-to-obtain specimens (such as sputum for *Mycobacterium tuberculosis* rifampicin resistance testing), the need to complete critical testing as soon as possible (such as decreasing NBS test incubation times to quickly identify affected infants), and governmental laboratory weekend or holiday workflows due to business hours. PHLs need more flexibility than clinical laboratories because specimens often come from a wider range of providers and locations; however, modifications are supported by validation studies, temperature or stability studies, CDC guidance, peer-reviewed literature, and documented evidence showing that test performance remains acceptable.

Subsection 5. Calibration Verification

Question 1. What technical and operational challenges does the laboratory face when performing calibration verification on FDA-cleared or approved manufacturer-calibrated devices?

Calibration verification can be challenging when laboratories have limited visibility or control over instrument calibration systems. Barriers include proprietary calibration algorithms, inaccessible calibration parameters, limited availability of materials across the reportable range, and difficulty determining whether problems are due to calibration, reagents, software, hardware, environmental conditions, or other system issues. For sealed or non-adjustable systems, repeating a standard calibration-verification exercise may offer limited value, especially when the laboratory cannot directly modify calibration settings.

Time and resources are needed but are generally manageable when performing calibration verification on these devices; however, when instruments are out of calibration and cannot be adjusted by the laboratory, delays impacting public health responses may occur when manufacturer service must be scheduled to repair the instrument.

CMS and CDC should allow an alternative approach where performance is verified using manufacturer controls, independent materials, comparison testing, maintenance records, quality-control trends, and checks across the analytical measurement range, with manufacturer escalation when results fall outside acceptance criteria.

Subsection 6. Postanalytic Interpretation and Use of Artificial Intelligence (AI)

Question 1. How does the laboratory use software algorithms or AI tools in the postanalytic process?

PHLs generally do not use AI tools in the postanalytic process; however, validated and tested software algorithms are often utilized. These algorithms identify where test results fall regarding cutoffs (such as a value indicating a negative, positive, or indeterminate result) and determine next steps for the specimen and reporting (such as additional testing or finalizing the result). PHLs use software algorithms that are programmed on instruments with FDA-approved tests (such as the BioFire which provides result interpretation) or program algorithms in their LIMS that trigger additional testing or reporting based on a result. A few laboratories use AI for genomics-based epidemiological clustering.

Question 2. Under what circumstances are software functions, including certain AI tools, used for the interpretation of the results of a test? For example, NGS, histocompatibility, and pharmacogenomics testing.

PHLs do not use AI tools for analytical processes or test result interpretation; however, they are implemented when using bioinformatics pipelines to process large quantities of sequencing data for species identification, antibiotic resistance gene identification, genomic epidemiology interpretation, and tree creation.

Software functions may be used when interpretation requires multivariable algorithms, comparison to reference libraries or databases, or decision rules. For NGS and other complex methods, software may convert instrument output into reportable results, but qualified laboratory personnel remain responsible for reviewing quality criteria and the final report. The degree of human review should be based on risk and maturity of the validated workflow.

For NBS, software algorithms are programmed to identify where values lie regarding cutoffs and determine next steps for the specimen and reporting statements. For example, based on a screen assay, the software determines which specimens would need additional testing and then ultimately determines the reporting statement for the specimen based on result value and full algorithm programmed into the software.

Question 3. What roles do software functions, including certain AI tools, currently play in the interpretation of histopathology slides or results?

No comment; PHLs do not interpret histopathology slides or results.

Question 4. What methods do laboratories use to verify the performance of the software functions (including image resolution accuracy and quality, and AI tools as well as the performance of computers and monitors) used with a test system?

PHLs verify the performance of software functions used with a test system by evaluating the algorithm and calculations via a second process, such as comparing the software calculations with Excel calculations. This is completed during the test development and validation phase, which must be reviewed and approved by the CLIA laboratory director. Additionally, controls and stock specimens with known results are tested on the platform to ensure that the software does not generate unexpected results; laboratories may also do this after software and hardware updates. Software is often version-controlled with documentation of the version used with each test. Finally, bioinformatics tools are validated in conjunction with traditional wet lab methods to verify an analytical pipeline is functioning correctly.

Question 5. Are there additional technology considerations for high complexity tests, including but not limited to laboratory use of automation, laboratory use of cloud analytics, and laboratory use of artificial intelligence, that CMS and the CDC should consider incorporating into the CLIA regulations?

CMS and CDC should address cloud services, AI beyond postanalytic interpretation, and maintaining human oversight of high complexity technology. For example, bioinformatics depends on cloud tools and pipelines for evaluating genomics data which have largely been developed by industry best practices without guidance from CLIA. The use of AI in the laboratory is increasingly being explored, and regulatory oversight to standardize practices and create quality control assurances is needed. PHLs are also concerned about the potential for AI to come integrated into instrument and evaluation software without appropriate oversight from CLIA. This leads to apprehension about privacy considerations and AI-aided quality control and result evaluation by instrument software that may not be explicitly known to the laboratory analyst.

CMS and CDC should consider different use cases for cloud services; utilizing it in PHLs for NGS analysis is different than how a hospital or commercial laboratory may utilize it for evaluating cancer markers and making treatment decisions. As such, any CLIA guidance should be specific to how the technology is used.

Subsection 7. Data-Only Facilities

What activities do data-only facilities perform to generate, or help to generate, test results and interpretations?

PHLs do not function as data-only facilities currently; however, some PHLs are discussing whether to offer genomic sequencing services in the future. This would be assessment of the sequencing output data from an outside entity, such as analyzing a FASTQ file utilizing the PHL genomic pipelines for pathogen identification and characterization. Minimum thresholds for acceptable files and data quality would need to be established.

Subsection 8. Remote Direct Observation Competency Assessment

Question 1. How does the laboratory currently use remote direct observation for competency assessment?

Generally, remote direct observation for competency assessment is not used at PHLs. If they were to implement remote direct observation, the devices would likely need to be camera and video systems that work with virtual meeting platforms. One PHL reported utilizing a telehealth video system for remote competency assessments for county health department staff. The process has been found to be both efficient and acceptable to their CLIA auditors.

Section C. Emergency Preparedness, Biosafety and Biosecurity, and Cybersecurity

Subsection 1. Emergency Preparedness

Question 1. What are the best practices for laboratory emergency preparedness? Indicate the type of laboratory, for example, hospital-based or independent laboratory.

Strong PHL emergency preparedness relies on a robust continuity of operations plan (COOP) that includes emergency contacts, referral and alternate testing arrangements, mutual-aid agreements, supply and reagent continuity, data and reporting workflows, communication plans, after-action review, and regular updates. COOPs should address both laboratory-wide hazards such as power outages as well as test-specific dependencies such as high-throughput extraction for a large-scale infectious disease threat.

Key best practices include maintaining relationships with CDC, Laboratory Response Network (LRN) partners, clinical and sentinel laboratories, internal incident command system (ICS) teams, and other laboratory system partners; participating in drills and exercises; utilizing alerts, newsletters, email, and regular outreach to keep partners informed; and having memorandums of understand (MOUs) or other agreements in place for alternate testing and referral arrangements. PHLs should also plan for rapid test implementation, access to supplies, and conducting equipment and test risk assessments before bringing on new methods. Best practices for emergency preparedness for PHLs include the above considerations for all scales of emergency (e.g., local, state, national, or global).

Operational readiness requires scalable equipment, flexible laboratory space, inventory, instrument redundancy, and staffing plans that support surge testing. PHLs train backup staff, aim to have multiple scientists competent in each test method, and consider flexible staffing models such as shifts, contracted staff, or reassignment of nonclinical staff to support specimen receipt, accessioning, and storage. Staffing plans also include LIMS data support and other response functions such as waste management. Additional emergency preparedness actions address developing test workflows and LIMS reporting, security needs if staff are working outside of normal hours, and test considerations such as anticipating whether high-throughput testing may be needed.

Overall, emergency response best practices include not only testing capability, but also advanced planning, partner coordination, workforce flexibility, scalable infrastructure, and routine exercises. It also includes regular participation in drills to test the limits of the COOP and staff; this is essential for identifying gaps in current procedures and strengthening networks.

Question 2. What challenges does the laboratory face in maintaining operations during emergencies such as natural and human-caused disasters, facility emergencies, and emerging infectious diseases?

PHLs face infrastructure, workforce, logistical, technological, and coordination challenges during emergencies. Laboratories may struggle to recruit, license, train, and credential staff quickly during surge events or when staff are also affected by the emergency. Maintaining competency for new tests, sustaining extended or 7-day operations, utilizing shifts, and keeping staff engaged can be difficult, especially when PHLs are already facing workforce shortages and have limited funding to hire new staff.

Operational bottlenecks often occur outside the analytical testing stage, particularly in specimen receipt, accessioning, and patient identifier quality checks, as well as due to LIMS updates for new testing workflows, creating new submitter profiles, and where applicable, submitter onboarding to the LIMS for electronic test ordering and reporting (ETOR). PHLs need broad investment in data modernization to create more adaptable LIMS to reduce these test ordering and reporting challenges. Additional issues include physically getting specimens to the laboratory, especially from rural areas or during severe weather, while maintaining required transport conditions.

For the analytical stage, availability of supplies can be a challenge in maintaining operations. If many laboratories rely on the same testing platforms or emergency use authorization (EUA)-specific materials, supply shortages can intensify and testing is impacted. PHLs also face limitations in high-throughput capacity/automation, flexible laboratory space, and scalable equipment. An investment in PHL infrastructure that allows for space and equipment flexibility and scalability is needed.

Preparedness is further complicated by decentralized response structures, inconsistent continuity plans across agencies, unclear expectations for partner laboratories, and limited time and funding to drill COOPs and systems like the ICS. Sustained funding is needed for continuity planning, LIMS and ETOR data modernization,

LRN testing supplies, equipment maintenance, trained personnel, surge capacity, and laboratory infrastructure.

Question 3. What elements does the laboratory include in its current emergency preparedness plans and protocols?

PHL emergency preparedness plans and protocols center on a core set of elements: emergency contacts, alternate testing and referral arrangements, mutual-aid agreements, supply and reagent information (including vendor contacts), information and data flow processes, communication with submitters and public health partners, records protection, event after-action review, and periodic plan updates. Plans address both lab-wide hazards such as power outages and test-specific dependencies like high-throughput automation. They identify common types of operational interruptions and provide generalized guidance to address them. These protocols extend to natural and manmade disasters that could delay testing or destabilize facilities, with attention to staff safety, equipment and facility considerations, and strategies to avoid or manage testing delays.

PHLs preparedness plans include executing an ICS during events. Although ICS was not originally designed with labs in mind, PHLs value the ICS structure for the communication and standardization it provides. Plans also address scalability (how to shift from routine daily testing to an emergency response posture), which requires specimen transport plans, a LIMS plan for specimen accessioning and building out new testing and reporting workflows, and supply backup plans.

Additional components include efforts by biothreat and chemical threat staff to meet LRN surge testing requirements; maintaining accreditation for emergency response test methods; regularly exercising those methods; biosafety and chemical risk assessments; collaboration with epidemiologists for disease investigation; and clinical laboratory education and outreach. Plans also typically document staffing details, such as employee names, phone numbers, and skill sets beyond typical job duties, as well as define operational teams and their leaders.

Question 4. What lessons has the laboratory learned from recent emergency situations (for example, natural disasters, pandemics, and power outages)?

Lessons learned from emergency situations, including natural disasters, pandemics, infrastructure failures, and power outages, underscore the need for PHLs to have practical, tested COOPs in place before a crisis occurs. The most consistent lesson is that collaboration before disaster is essential: laboratories, public health partners, providers, couriers, emergency management, and support staff all need clear roles, communication channels, and memorandums of understanding or mutual aid agreements established in advance. Key lessons learned include:

- **Develop workable backup testing plans.** PHLs need predefined options for referring specimens to other laboratories when normal testing operations are interrupted, including agreements with partner laboratories and clear criteria for when referral testing will be activated.
- **Build data-transfer solutions before they are needed.** Manual transfer of test results on specimens referred to another laboratory during an emergency is difficult and time-consuming. Interfaces and electronic data exchange processes like the APHL Informatics Messaging Services (AIMS) Platform make result transfer faster, reduce errors, and support timely reporting of critical results.
- **Formalize collaboration before disaster.** Relationships with other laboratories, couriers, emergency management, finance/logistics staff, providers, and public health partners should be established before emergencies occur.

- **Prepare annually for predictable hazards.** For events such as hurricanes and major storms, laboratories should have seasonal readiness plans, including facility "hardening" (readying the facility for a potential weather event), provider notification procedures, staff communication plans, and well-stocked test supplies by the start of the risk season.
- **Strengthen communication systems.** Laboratories need efficient ways to notify staff, providers, partners, and customers about closures, delays, process changes, and resolution of problems. A single information number and frequently asked questions document can help reduce confusion and repetitive inquiries.
- **Plan for disrupted infrastructure.** Emergency plans should account for power outages, generator failures, cell tower disruptions, transportation barriers, and staff inability to travel. Uninterrupted power systems, generators, alternate communication methods, and courier surge plans are important safeguards.
- **Maintain workforce flexibility.** Cross-training is critical for all stages of testing and supportive workflows, such as specimen accessioning, surge response testing, result reporting, and packaging and shipping. Laboratories should identify just-in-time training needs and clarify how these activities intersect with CLIA requirements and competency assessment.
- **Ensure operational redundancy and surge capacity.** Laboratories should maintain critical supplies, reagents, PPE, instrument and extraction-method redundancy, defined testing capacities, documented surge plans, and ETOR capabilities.

Emergency preparedness should focus on realistic, operationally workable solutions: backup testing agreements, electronic data transfer, clear communications, trained and cross-trained staff, redundant instruments and tests, courier surge capacity, and documented surge testing plans. These components are difficult to create during a crisis, so they should be established, tested, and updated before emergencies occur.

Subsection 2. Biosafety and Biosecurity

Question 1. What challenges does the laboratory face in biosafety and biosecurity?

PHLs face a wide range of biosafety and biosecurity challenges, beginning with a lack of standardized, comprehensive risk assessment practices. A consistent definition of biosafety risk assessment that addresses hazard identification, mitigation, ongoing risk management, and performance monitoring should be formally incorporated into 42 CFR 493.2. Assessing biosafety risks associated with existing and new instrumentation and equipment is difficult and is often compounded by insufficient manufacturer information on instrument hazards, disinfection, and decontamination. Greater collaboration among manufacturers, laboratories, and regulators could help close this gap.

Specimen submission and handling remain an ongoing concern, with issues like leaking or broken containers, missing seals, and specimens placed in direct contact with test requisition forms. Quality assurance activities are constrained by limited availability of some proficiency testing panels and quality control materials, and the lack of laboratory space for BSCs presents an issue for some PHLs with outdated infrastructure.

Personnel-related biosecurity concerns present another layer of difficulty, particularly around insider threats, where limited regulatory guidance and legal precedent make it hard to terminate staff for cause. Clearer requirements would help laboratories respond more effectively.

Surge events strain personnel, resources, and established biosafety and biosecurity processes. PHLs are experiencing significant staff shortages and inadequate funding, so they are unable to keep additional

personnel at the laboratory during off-hours testing when heightened biosafety and biosecurity measures should be in place. Additionally, ensuring biosafety and biosecurity practices activities are coordinated, documented, consistently implemented, and evaluated can be challenging. Effective biorisk management requires clear leadership roles, accountability, and organizational commitment. It also requires monitoring whether biorisk controls such as safe specimen handling procedures, laboratory access controls, decontamination practices, and exposure/near-miss incident response procedures work by identifying deficiencies and making improvements. These efforts are frequently hampered by inadequate funding for safety supplies, training, and continuing education, as well as outdated guidance and a lack of time to drill staff on plans and protocols.

Question 2. What elements or best practices does the laboratory include in its current biosafety and biosecurity plans and protocols?

PHL best practices for biosafety and biosecurity plans and protocols integrate risk assessment, staff training and competency, and continuous monitoring and improvement. Assessments identify equipment and test hazards and mitigation measures. These are reviewed annually and additional biosafety risks are considered when introducing new equipment and tests. PHLs strive to obtain manufacturer-provided disinfection and decontamination instructions before purchasing new equipment to aid in biosafety assessments of new processes.

Staff training and competency assessment are central to biosafety and biosecurity, with competencies specific to the laboratory program. These are designed to include assurances that personnel develop necessary skills before performing increasingly complex work. PHL staff are provided with annual refresher trainings and in-person training whenever possible. These trainings include the following: working safely in a biosafety level 3 laboratory, proper usage of PPE including powered-air purifying respirators, Select Agent requirements, bloodborne pathogen safety, and others that support ethical reporting, whistleblower protections, and near-miss documentation to capture and improve related safety vulnerabilities in test processes.

PHLs maintain comprehensive safety manuals that cover biosafety and chemical hygiene and require annual staff review with competency assessment. Where applicable, they provide Select Agent-registered staff with additional annual trainings on biosafety, biosecurity, and incident response plans. PHLs also utilize audits and safety inspections, and review incident trends, competency results, and risk assessments as part of their biosafety and biosecurity best practices. These laboratories follow all federal and state guidelines, consult with public health partners and APHL on safe and secure practices (especially for emerging pathogens), and some PHLs are considering implementation of the International Organization for Standardization 35001:2019, “Biorisk management for laboratories and other related organisations” guidance document.

Question 3. How does the laboratory train personnel on biosafety and biosecurity plans and protocols?

PHLs use a blended and competency-based training approach that combines initial in-person instruction, online learning, standardized observations, and recurring competency assessments. New employees typically begin with in-person orientation that emphasizes biosafety, chemical hygiene, security, emergency response, and ethics trainings, often including direct instruction from the laboratory safety officer, Safety Committee representative, or their supervisor. Training progresses as staff advance, and are given laboratory program-, equipment-, and test-specific competencies. These are reinforced through annual safety manual review and refresher training. Laboratories assess training effectiveness through competency evaluations, direct observation, exercises, proficiency demonstrations, internal audits, and safety inspections to ensure personnel can apply biosafety and biosecurity practices correctly. Additional training is provided when new hazards, equipment, test procedures, regulatory requirements, or operational changes are introduced, and risk

assessments are used to help staff understand potential hazards and the engineering controls in place. PHLs also rely on external partners such as APHL and CDC to support standardization and need more in-person training opportunities to strengthen practical application of biosafety and biosecurity fundamentals and build a broader community of trained biosafety professionals and laboratorians.

Subsection 3. Cybersecurity

Question 1. What cybersecurity protocols/policies does the laboratory have in place to protect patient data and laboratory operations?

Many PHLs rely on centralized state, agency, or enterprise information technology (IT)/security divisions for core cybersecurity functions, including network controls, incident response planning, access governance, cybersecurity training administration, and security monitoring through software like CrowdStrike. Laboratorians are trained that cybersecurity is the responsibility of everyone and that they must remain vigilant and report suspicious activity.

Laboratories commonly use role-based permissions with least-privilege access, multifactor authentication where available, firewalls, virtual private network (VPN) or application-based access, and other network controls to protect systems that contain protected health information or personally identifiable information. Examples of network controls include restrictions based on approved internet protocol (IP) addresses and permissions tied to authorized devices, users, or roles.

Policies and security controls such as Acceptable Use Policy, Information Security Incident Response Process, Cybersecurity, and AI Policy are often aligned with state or organizational requirements. Many agencies implement widely used frameworks or standards such as from the National Institute of Standards and Technology (NIST), as well as HIPAA, CMS, and applicable state information security standards. Access is typically documented through access request or tracking systems that are approved by system owners or data stewards and reviewed on a recurring basis.

Question 1a. What is the frequency and process you follow to verify new or existing user identity and access requirements?

PHLs perform background checks during the hiring process and confirm staff identity at that time. Access to shared computer drives and laboratory-specific data systems is established at the time of hiring based on their job responsibilities, reevaluated each time they change positions, and terminated when they leave the organization. Agency IT departments grant and manage access to shared drives, and access to laboratory-specific systems like the LIMS requires leadership approval and execution by the LIMS administrator. User identity and access to these systems is recorded with periodic activity audits.

Question 1b. Are individuals, entities, or both outside the U.S. and its Territories ever allowed to access your lab systems that contain personal information? If so, when and under what conditions?

Access to laboratory systems that contain personal information from outside the U.S. and its territories is generally prohibited or tightly controlled, with exceptions requiring prior authorization, defined security review, temporary IP address allowances, secure U.S.-based VPN connections, or geofencing.

Question 1c. How does your laboratory system(s) restrict ports and/or internet protocol (IP) addresses used to access the environment?

Ports, IP addresses, cloud access and external traffic are typically restricted and routed through centralized IT or security review processes. The laboratory subnet (a laboratory-specific computer network) is often required to connect instruments and equipment for data transfer to the LIMS and is also restricted with permission-based access where formal requests must be made to the agency IT department and undergo a security review. The LIMS runs on a protected internal network behind multiple firewalls.

Question 1d. What elements are included in your cybersecurity incident response plan?

Cybersecurity incident response planning is handled at the agency level and generally follows NIST standards and includes the purpose, audience, process, and documentation for incident response. The response phases include preparation, detection and analysis, containment, eradication and recovery, and post-incident evaluation. Roles are identified and assigned, and workflow, communication, documentation, and retention processes are established in the plans.

Question 2. What challenges or experiences has the laboratory faced in maintaining cybersecurity?

PHLs face several cybersecurity and operational challenges related to balancing IT security requirements with laboratory needs. In some cases, IT controls may be too restrictive, requiring discussions with IT teams to explain laboratory use cases to ensure essential testing can continue. For example, many challenges relate to outdated computer operating systems on older instruments that are cost-prohibitive to replace. Some IT departments prohibit connecting the secure network to computer operating systems older than Windows 11 because the systems are not maintained. Many laboratory instruments function with Windows 10 systems, creating difficulty with transmitting test data from the instrument to the LIMS. PHLs have compensated by installing these instruments on secure subnetworks (vLAN) that allows the computer to connect to a shared file folder for subsequent data transfer to the LIMS. PHLs also utilize secure flash drives for data transfer to newer computers connected to the secure network; however, flash drives can still be affected by malware.

Laboratories have an increasing need to connect externally for activities like cloud-based NGS analysis and vendor library updates for matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) instruments. An investment in PHL data modernization and laboratory infrastructure is needed.

Question 3. Which laboratory job position(s) is responsible for cybersecurity in the laboratory?

All PHL positions are responsible for cybersecurity to the level of their authority. Users are responsible for safeguarding their credentials, maintaining situational awareness and physical security, and reporting issues. PHL LIMS teams are responsible for complying with agency and state cybersecurity requirements.

Question 4. How does the laboratory train personnel on cybersecurity?

Agency IT departments require cybersecurity training for all PHL staff, typically beginning during new employee orientation and continuing through annual and often more frequent refreshers (monthly in several cases) with non-completion reported to supervisors. A common practice is the use of simulated phishing emails to test employee awareness, with those who "fail" required to complete additional training. Some organizations rely on established platforms, such as the KnowBe4 for annual cybersecurity awareness training, alongside required annual security policy reviews maintained through a learning management system. Several PHLs also require

staff to review and sign an Acceptable Use Agreement each year, documenting their individual role and responsibility in maintaining security and privacy.

Section D. Specialty Testing Areas

Subsection 1. General

Question 1. What specific challenges or limitations, if any, does your laboratory currently experience with the test specialty and subspecialty categories in the CLIA regulations? For example, are there areas where existing CLIA test specialty and subspecialty categories could be revised to better reflect current laboratory testing practices?

Current CLIA specialty and subspecialty categories do not consistently reflect modern PHL workflows, which often integrate molecular biology, sequencing, mass spectrometry, microbiology, genetics, bioinformatics, informatics, and clinical or algorithmic interpretation within a single testing process. Examples include NGS for infectious disease surveillance or pathogen characterization and tandem mass spectrometry for NBS, both of which cross multiple traditional categories.

CMS and CDC should modernize and clarify specialty and category definitions, particularly for molecular and NGS-based testing. Molecular infectious disease testing does not fit neatly into existing microbiology subspecialties, and NGS may require either a distinct category or substantial updates to molecular standards and checklists. Clarification is also needed for reporting test volumes on forms such as CMS-116, including where to count PCR tests; multiplex molecular tests that test for bacteria, viruses, and parasites; and other molecular assays.

Finally, PHLs should not be required to maintain separate quality systems, validations, or oversight structures for each category when the testing is performed using a single, integrated process. The CLIA framework should focus on method complexity, specimen type, interpretation, personnel expertise, and workflow risk rather than historical departmental labels.

Question 2. Are there additional specialties or subspecialties that CMS and the CDC should consider incorporating into the CLIA regulations to ensure comprehensive oversight of laboratory testing as specialties evolve? Provide evidence-based rationale supporting their inclusion, including considerations related to patient safety, testing complexity, and public health impact.

CMS and CDC should recognize molecular infectious disease testing as its own subspecialty or category rather than being forced into traditional areas such as virology or bacteriology, since PCR and related methods can apply across organism types. Additionally, PHLs need clearer and more flexible CLIA guidance for emerging pathogens and emergency response testing, real-time PCR for infectious disease diagnosis, multiplex molecular assays, metagenomics, biomonitoring for environmental chemicals, and surveillance-focused drug testing that does not fit neatly into forensic or clinical categories. When new or re-emerging threats arise, PHLs are asked to rapidly validate and implement testing, often before clinical or commercial laboratories are ready to participate. This was evident during COVID-19 and remains relevant for vaccine-preventable diseases such as measles, mumps, and rubella, where some laboratories may still rely on older technology or non-scalable methods. Clearer CLIA requirements in these areas would support faster, more agile public health responses while maintaining appropriate quality standards.

Subsection 2. Clinical Cytogenetics

No comment; PHLs do not offer cytogenetic testing.

Subsection 3. Immunohematology

No comment; PHLs do not offer immunohematology testing.

Subsection 4. Microbiology

No comment; PHLs do not offer blood culture testing. PHLs test the bacterial isolates grown from the blood culture bottles.