AMERICAN CLINICAL LABORATORY ASSOCIATION

April 3, 2024

Ranking Member Bill Cassidy, M.D.
Senate Health, Education, Labor, and Pensions (HELP) Committee
332 Dirksen Senate Office Building
Washington, DC, 20510

By Email: *diagnostics@help.senate.gov*

Re: Comments on the Diagnostics Reform Request for Information

Dear Ranking Member Cassidy:

The American Clinical Laboratory Association (ACLA) appreciates the opportunity to provide these comments in response to the request for information (RFI) regarding the regulation of clinical tests. Laboratory developed testing services are an indispensable pillar of our health care system, providing patients and physicians with diagnostic information to inform clinical care, power precision medicine, contribute to the discovery of novel therapeutics, and lead the fight against emerging pathogens.

ACLA is the national trade association representing leading clinical laboratories that deliver essential diagnostic health information to patients and providers by advocating for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized care. ACLA member laboratories are at the forefront of developing tests to respond to emerging health issues, and they frequently innovate new areas of science. Laboratory developed testing services offered by ACLA members play an indispensable role in delivering healthcare to patients.

Our comments below are organized according to the sections of the RFI. Section I provides comments on specific changes Congress could make to advance a modern, comprehensive regulatory framework for diagnostics under the jurisdiction of the Food and Drug Administration (FDA). Section II provides comments on improving the robust framework governing laboratory operations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), under the jurisdiction of the Centers for Medicare and Medicaid Services (CMS).

I. FDA Regulatory Framework for Diagnostics

1. How well is FDA's medical device framework working for the regulation of diagnostic products? Are there improvements that should be made?

a. Of these specific changes, which would require Congressional action, and which can be effectuated by FDA alone?

FDA's medical device framework does not fit laboratory developed testing services, which are not devices. Laboratory developed testing services are not tangible medical device products, like pacemakers, stents or even *in vitro* diagnostic (IVD) test kits. They are services whereby laboratory professionals leverage methods of using tools to provide diagnostic information to patients and providers, and many of the concepts underlying medical device regulation make no sense when applied to laboratory developed testing services. For example:

- FDA regulation of devices governs the manufacture, labeling, and packaging of devices, but (1) laboratory developed testing services are not "manufactured"—they are validated under the quality requirements of CLIA and performed in high-complexity clinical laboratories at the request of an authorized person, generally a healthcare professional; and (2) laboratory developed testing services cannot be "labeled" or "packaged"—just like other medical procedures cannot be labeled or packaged.
- Moreover, the applicable standard for medical devices—safety and effectiveness—is wrong for laboratory developed testing services. A better standard would be a reasonable assurance of analytical and clinical validity, i.e., the ability of the service to provide accurate and precise information that is relevant to the disease or condition for which the service is being provided.

Congressional action is necessary to grant FDA authority to regulate laboratory developed testing services. Just as there are specific regulatory paradigms for food, devices, biologics, and drugs, diagnostics—including laboratory developed testing services—should have their own regulatory framework suited to their unique characteristics. In 2022, ACLA worked closely with FDA, Congress, and other stakeholders to refine and improve proposed legislation (called the Verifying Accurate Leading-edge IVCT Development Act, or VALID Act) that would have provided FDA with statutory authority and direction on how to regulate all diagnostics, including laboratory developed testing services. This legislation would have provided a regulatory framework tailored to diagnostics, rather than retrofitting existing but inappropriate regulatory frameworks designed for device products. This bill was not enacted by Congress in 2022 and has been re-introduced in the House of Representatives in 2023. ACLA remains committed to working constructively with Congress on diagnostics-specific legislation.

2. Does the current device regulatory framework support the review of diagnostics that are developed using AI or that incorporate AI?

FDA has various tools under the device framework that it is using to try to address artificial intelligence (AI) such as predetermined change control plans (PCCPs), which aims to facilitate approval of specific, planned changes to devices, during the review process. However, at a fundamental level, FDA lacks authority to regulate laboratory developed testing services, which can also leverage AI, and which are offered by clinical laboratories. As noted above, Congressional action is necessary to grant FDA authority to regulate laboratory developed testing services.

A modern regulatory framework for diagnostics, including laboratory developed testing services, could include diagnostic-specific tools for FDA to support the review of diagnostics that are developed using AI or that incorporate AI, such as provisions that allow FDA to approve change protocols—submitted with premarket applications for tests—that would be similar to, yet more robust than, current PCCPs. Additionally, legislation could include provisions that would authorize FDA to certify test developers that have demonstrated expertise in a particular technology to introduce new tests and modifications to tests without additional premarket review. Finally, legislation could also establish a flexible modification policy so that non-significant changes to tests—such as incremental improvements that may be incorporated with AI—do not require additional premarket review.

3. What, if anything, makes diagnostics distinct among FDA-regulated medical products to warrant specific attention to how AI may be used in the review of product submissions?

Diagnostic tests—and laboratory developed testing services in particular—have driven innovation in medical care at an extraordinary pace. As the sensitivity of diagnostic instruments improves, and as AI algorithms become more powerful, the pace of innovation in diagnostics is only expected to accelerate. For example, as additional data is gathered about a particular analyte or its connection to a disease or condition, the analytical and clinical validity of a diagnostic test can become more refined. Accordingly, there is a distinct opportunity for AI to be leveraged for the continuous improvement of diagnostics and the advancement of personalized medicine.

However, as noted above, FDA currently has no authority to regulate laboratory developed testing services—including those that leverage AI. Under a new legislative framework for all diagnostics, Congress could establish tools—such as the technology certification program, change protocols, and a flexible modifications policy—that can be leveraged to address unique aspects of AI in diagnostics.

4. Are the regulatory pathways intended to evaluate diagnostics for special populations (i.e., rare diseases or genetic disorders) working?

a. How could they be enhanced to accelerate and authorize products for special populations, for example, certain companion diagnostics for rare biomarkers?

Given the economics of commercial test development, rare diseases frequently lack a commercialized FDA-cleared or -approved test. Laboratories have filled this gap by offering laboratory developed testing services for very small patient populations, thereby meeting unmet clinical needs. For example, the only tests available to help diagnose Rett Syndrome—one of the most common genetic causes of developmental and intellectual impairment in girls, Fabry Disease—a rare and progressive lysosomal storage disorder, and UBE3A mutation in patients with Angelman's Syndrome—a rare neuro-genetic disorder that causes development delays are available as laboratory developed testing services. There are no FDA-cleared or -approved alternatives for these patients.

Likewise, laboratory developed testing services continue to be important for detecting rare and infectious pathogens where there is no FDA-cleared or -approved diagnostic available. For example, no FDA-approved tests were available to detect avian influenza virus,

chikungunya virus, Ebola virus, Middle Eastern respiratory syndrome virus, severe acute respiratory syndrome virus, or Zika virus when those pathogens first emerged. In the absence of FDA-cleared or -approved diagnostics, clinical laboratories developed, validated, and implemented laboratory developed testing services that facilitated the rapid treatment and appropriate isolation of patients, thereby slowing the spread of potentially deadly infections. Additionally, to this day, laboratory developed testing services remain the only available diagnostics to detect the pathogen that causes high-risk human papilloma virus in oropharyngeal cancers and the genetic mutations that cause Huntington's Disease and epidermolysis bullosa.

As noted above, FDA currently has no authority to regulate laboratory developed testing services—including those for rare diseases. If FDA's proposed rule to regulate laboratory developed testing services as devices were to go into effect, however, it would have significant negative impacts on the availability of tests for rare diseases. Tests for rare diseases typically do not generate sufficient revenue to bring such products through the FDA clearance/approval process. And although FDA has authority to grant a humanitarian device exemption (HDE) for devices for rare diseases and conditions, such authority is not well-suited for diagnostics for rare diseases. First, the HDE prohibits test developers from selling the test for a profit, removing significant incentives for developing such test. Second, under FDA's regulations, such exemption is limited to diagnostic tests where "not more than 8,000 patients per year would be subjected to diagnosis by the device in the United States." 21 CFR § 814.102(5). Although a diagnostic may be intended to identify patients with a disease that affects no more than 8,000 patients, screening more than 8,000 patients would almost always be necessary. Indeed, even if a disease affects only 100 people in the United States, it may be necessary to test more than 8,000 patients per year to identify them. Third, the process of developing data and obtaining HDE approval from FDA is still burdensome and time-consuming, thereby making it infeasible for developers to commercialize such tests.

Under a new legislative framework for FDA regulation of diagnostics, Congress could establish the appropriate tools to support the availability of diagnostic tests for rare diseases. For example, diagnostic-specific legislation could include appropriate thresholds for tests intended for rare diseases or conditions, under which the test would be exempted from FDA premarket review. Importantly, the cutoff points for such an exemption could be based on the number of people affected by the disease, rather than the number of people tested for the disease (as is the case under the current device HDE program). Additionally, legislation could include exemptions for custom and low-volume laboratory developed testing services. ACLA believes the exemption for low-volume testing should be expanded beyond the threshold included in the latest version of VALID (5 patients) to distinguish it from the custom test exemption, but we otherwise support such an exemption which affords laboratories the necessary flexibility to accommodate individual patients with special health concerns. Finally, legislation could preserve existing laboratory developed testing services for rare diseases through grandfathering provisions, and a flexible modifications policy.

5. Are there regulatory hurdles to expanding the settings in which diagnostics are performed, i.e. point-of-care (POC) tests performed in patients' homes?

a. In what ways could/should FDA leverage regulatory flexibilities to reduce testing barriers?

ACLA supports expanding access to testing services, which may include expanding the settings in which diagnostics are performed. In particular, ACLA supports expanding access to

testing that involves self-collection of specimens, which may be sent to a high-complexity clinical laboratory for performance of laboratory developed testing services. This has the potential to greatly expand access to testing for patients unable to physically visit a clinical laboratory, phlebotomist, or other healthcare professional for specimen collection. However, it is important that such self-collection maintains specimen adequacy and integrity to support the accuracy and validity of test results. Under a modern regulatory framework for diagnostics, established via legislation, there could be flexibility to modify a test to incorporate self-collection of specimens without additional premarket review, conditioned on the use of a specimen collection article that is authorized for such use, and as long as the modification otherwise meets certain requirements for exemption (e.g., no significant and adverse changes to performance).

6. What are your views on FDA's implementation of predetermined change control plans; is FDA's approach in its recent guidance readily applicable to IVDs and other diagnostic products?

PCCPs have begun to be used successfully to allow for greater flexibility in incorporating changes to medical devices. However, the need for PCCPs underscores the inherent inflexibility of the device framework, which further highlights the need for a modern regulatory framework for innovative diagnostics. A modern regulatory framework for diagnostics could leverage approved change protocols—like PCCPs—but also could establish a flexible policy for modifications to diagnostics. PCCPs only apply to changes pre-specified by the developer of the device. However, laboratory diagnostics are often refined over time as clinical information evolves – and these refinements cannot always be predicted. Accordingly, a flexible modifications policy would be essential to supporting continued innovation in diagnostics. For example, diagnostic-specific legislation could permit developers to modify their own approved tests—and could permit high-complexity clinical laboratories to modify any lawfully offered test—without additional FDA review if those modifications do not: (1) significantly change certain essential test elements; (2) cause the test to no longer comply with mitigating measures or restrictions; (3) significantly change performance claims or significantly and adversely change performance; or (4) adversely change the safety for individuals who come in contact with the test.

Thus, although PCCPs are a welcome area of change to the device regulatory system, they do not cure the ill-fit of device law to laboratory developed testing services.

7. Does FDA's current risk classification framework properly measure risk versus regulatory controls for diagnostics products?

a. If not, how can FDA's risk-based regulatory approach to diagnostics be improved to better align the degree of regulatory oversight with patient risk and benefit?

It is appropriate to classify tests according to their risk, rather than applying a one-size-fits-all approach. However, FDA's current risk classification system is based on the regulatory controls needed to provide a reasonable assurance of safety and effectiveness of a device, and "safety and effectiveness" is the wrong standard for diagnostics. Accordingly, FDA's device risk classification framework is necessarily also wrong for diagnostics. Moreover, application of device law to laboratory developed testing services would add rigid and burdensome validation and testing requirements that are not deemed necessary by existing regulatory frameworks (such as CLIA, New York State's clinical laboratory law, and accreditation organization

standards), and would lead to less innovation and slower development timelines, often without corresponding benefit to patients. The end result would be that important and innovative tests would not make their way through FDA's cumbersome device regulatory framework, and patients and providers would not receive important diagnostic information.

Instead, the appropriate standard for diagnostics should be based on analytical and clinical validity, i.e., the test's ability to identify or measure a target and the test's ability to achieve its intended purpose with such measurement. Then, the risk classification for diagnostics should be defined based upon the risks associated with an undetected inaccurate result, i.e., what happens if the test does not accurately identify or measure its target, considering the test's intended purpose. Under a new legislative framework for diagnostics, an appropriate risk-classification framework could be established for all diagnostics, including laboratory developed testing services.

For example, a diagnostics-specific framework established via legislation could classify tests as low-risk, moderate-risk, or high-risk, based on the risk associated with an undetected inaccurate result, and the level of risk would determine the premarket pathways and other regulatory controls that apply to a test. Under the VALID Act, these tests would have been classified as follows:

- Low-risk tests would include tests for which an undetected inaccurate result "would cause only minimal or immediately reversible harm, and would lead to only a remote risk of adverse patient impact or adverse public health impact." Low-risk tests would be exempt from premarket review.
- Moderate-risk tests would include tests that are neither low-risk nor high-risk. Moderate-risk tests could be offered according one of two premarket pathways: "abbreviated premarket review" for individual tests, or "technology certification" for developers of eligible tests.
- High-risk tests would include tests for which an undetected inaccurate result "is reasonably likely to result in serious or irreversible harm or death to a patient or patients, or would otherwise cause serious harm to the public health," or "is reasonably likely to result in the absence, significant delay, or discontinuation of life-supporting or life-sustaining medical treatment." High-risk tests would be required to undergo standard premarket review.

An appropriate risk-based approach based on the risks associated with an undetected inaccurate result would continue to incentivize development of innovative tests, while preserving patient access to existing laboratory developed testing services.

8. In considering reforms to FDA's risk classification framework for diagnostics, what types of IVDs should be exempt from premarket review?

a. What factors related to risk management should be applied to risk classification of IVDs?

As described above, FDA's device risk classification framework is inappropriate for diagnostics, and FDA does not have authority to regulate laboratory developed testing services. However, under a new statutory framework for diagnostics, a new risk classification scheme could be developed that appropriately classifies tests based on the likelihood of harm from an

undetected inaccurate result, including consideration of the seriousness of such harm, whether it is reversible, its potential effect on treatment, and whether there are measures that can be applied to mitigate the risk.

Under a modern risk classification, low-risk tests should be exempt from premarket review. This is appropriate because premarket review is not necessary to protect the public health when other regulatory controls are applied to low-risk tests, such as labeling, quality, and adverse event reporting.

Other categories of tests should be exempt from premarket review to further availability of tests needed to satisfy clinical and public health needs, even if those tests are not low-risk. For example:

- Tests currently on the market should be grandfathered, subject to review only if there is credible information indicating that the test is not analytically or clinically valid; that it is being marketed with false or misleading claims; or that it is probable that use of the test as intended will cause serious adverse health consequences.
- Custom or low-volume tests, intended to meet the unique needs of individual patients, should be exempted from premarket review to ensure these patients have access to the care they need (see our response to question 4, above).
- Humanitarian tests should also be exempted from premarket review (see our response to question 4, above).
- Tests intended for public health surveillance and forensic use should be exempted, as they are not intended for clinical care.
- Manual tests, as well as general laboratory equipment, also should be exempted so as not to interfere with laboratory operations.

Additionally, certain modifications to lawfully offered tests should be exempt from premarket review where those modifications are made by either a high-complexity lab or a developer that obtained premarket approval for the unmodified test (see our response to Question 6, above).

9. Is the "safety and effectiveness" standard against which diagnostics are reviewed the most appropriate review standard to assign risk management for clinical tests?

No, as discussed above, the safety and effectiveness standard is inappropriate for evaluating and classifying risk in diagnostics. Under a new regulatory framework for diagnostics, including laboratory developed testing services, an appropriate standard would be based on a reasonable assurance of analytical and clinical validity.

10. Do the proposed reforms to FDA's device framework warrant the establishment of a new regulatory pathway specific to diagnostics? If yes, what are the principles that should guide such a new framework, as it would be applied to diagnostics currently subject to FDA premarket review?

As stated above, FDA lacks authority to regulate laboratory developed testing services, and a new, diagnostics-specific regulatory framework, established via legislation, would be

necessary for FDA to have a role in regulating laboratory developed testing services. Such a new framework should reflect several key principles.

1. The new framework must not interfere with continued access to existing testing. If the new framework retroactively applies extensive, burdensome premarket review requirements, patients and providers will lose access to critical diagnostic information.
2. The new framework must facilitate patient access to cutting-edge, high quality, reliable and accurate diagnostics by incentivizing the development of novel tests, considering the time and resources required for the research, development, and commercialization of diagnostics.
3. There must be a reasonable and transparent transition to the new framework. Implementation should not be rushed, and substantive requirements should be implemented through rulemaking, rather than FDA guidance documents.
4. Boundaries of jurisdiction must be clearly drawn between FDA and CMS. Laboratory operations must continue to be governed by CLIA, and duplicative and overlapping requirements between CLIA and a new framework must be harmonized.

Over the past several years, ACLA worked collaboratively with Congress, as well as FDA and other stakeholders, on legislation that could have established a role for FDA in an appropriate regulatory system for all diagnostics. ACLA steadfastly maintains that legislation is the right—and only—approach for FDA to regulate laboratory develop testing services. We would be pleased to again work with Congress to advance appropriate legislation that preserves the critical role of laboratory diagnostics and ensures that patients continue to have access to lifesaving tests.

II. CLIA Regulatory Framework for LDTs

1. What updates to the clinical laboratory regulatory structure under CLIA should Congress consider to reflect the latest scientific practices and safety standards?

CLIA should be updated to accommodate remote testing activities and the use of software in laboratory examinations. We believe these updates can be accomplished through revisions to the regulations, however, and Congressional action likely is not necessary. Indeed, last year, ACLA submitted detailed comments and a redline to CLIAC proposing updates to the CLIA regulations to accommodate remote testing activities and the use of software in laboratory examinations. ACLA's recommendations are attached, for your reference.

First, the CLIA regulations should be updated to accommodate remote testing activities. Under CLIA, each laboratory site requires its own certificate, and this has been interpreted to include home offices where remote review of digital laboratory information occurs. During the COVID-19 pandemic, significant flexibilities were offered that enabled pathologists to conduct remote testing activities by reviewing digital laboratory information at home offices. Since the pandemic, CMS has announced that it will continue to exercise enforcement discretion that allows pathologists to examine digital images and laboratory data at remote locations. However, we believe this practice should be expressly allowed, and that this could be accomplished by amending the CLIA regulations. Under such practice, the activities at the remote location would remain subject to CLIA, but they would be understood to be conducted

under the oversight of a non-residential laboratory that holds a primary CLIA certificate.

Second, the CLIA regulations should be updated to accommodate the use of software in laboratory examinations. Advancements in laboratory technologies and non-traditional workflow models warrant this modernization of CLIA. In particular, CLIA should apply to patient-specific "digital laboratory information," which would be defined to include digital information derived from a human specimen (e.g., digital images from glass slides or genetic expression, array and sequencing data). This could be accomplished by amending the definition of "laboratory" in the CLIA regulations as described in the attached redline. Alternatively, if Congressional action were required to amend the statutory definition of "laboratory" (42 U.S.C. § 263a(a)), the CLIA regulations instead could be revised to add a definition for "materials derived from the human body" (part of the definition of "laboratory") that includes patient-specific "digital laboratory information." Additionally, the definition of "test system" could be revised in regulation to include "software algorithms" and "data exchange and analysis procedures." These changes would extend the high standards of CLIA testing to software aspects of clinical laboratory operations.

2. What are your views on the effectiveness and use of the Clinical Laboratory Improvement Advisory Committee (CLIAC) in providing scientific and technical guidance to inform potential updates to CLIA standards?

CLIAC is an important advisory body to inform potential updates to the CLIA standards. However, it has been difficult to engage substantively with CLIAC and, more generally, with CMS. We see opportunities for improvement.

First, because CLIAC votes on recommendations at the same meetings in which topics are initially raised for discussion, there is little opportunity for substantive public comment prior to a CLIAC vote. For example, at the CLIAC meeting on April 12, 2023, CLIAC adopted 29 recommendations related to updating the quality requirements under CLIA. However, the Federal Register notice announcing the meeting on March 15 described the relevant "Matters to be Considered" only as a report from the CLIA Regulations Assessment Workgroup. Accordingly, there was no meaningful opportunity to provide comment on the recommendations. Instead, ACLA submitted written and verbal comments on the recommendations adopted at the *prior* CLIAC meeting in November 2022, based on the materials posted following that meeting.

To support better engagement with the committee, we would appreciate if CLIAC presentation materials could be posted further in advance of future meetings. Alternatively, public comment could be accepted after the CLIAC meeting has concluded, and CLIAC could defer voting on recommendations until the subsequent CLIAC meeting.

Second, we strongly recommend significant enhancements to the clinical laboratory community's avenues to engage with CMS officials responsible for CLIA. Clinical laboratories would appreciate better mechanisms, such as laboratory "open door forums," as exists for hospitals and other providers, for meeting with CMS officials to discuss issues related to CLIA and laboratory operations more generally. While we would appreciate better engagement with CLIAC, we note that CLIAC is not a regulatory body, and such improved engagement would not be a substitute for direct engagement with CMS.

3. Do the proficiency testing programs currently approved by the Department of Health and Human Services (HHS) reflect the latest clinical standards of laboratory medicine? Are there specialties, subspecialties, or analytes that should receive greater consideration for HHS approval?

Currently approved proficiency testing programs are appropriate. However, there are many specialties, subspecialties, and analytes for which no approved proficiency testing programs are available, and for which a laboratory must arrange for alternative proficiency testing. HHS approval of additional programs is needed.

4. How well does the existing enforcement structure under CLIA work in ensuring compliance with regulatory requirements and taking action against noncompliance? What should be improved, if anything at all?

CLIA inspection and enforcement procedures are described under 42 CFR Part 493, subparts Q and R, respectively. Under subpart Q, laboratories are subject to inspection (called "surveys") prior to initial certification and on a biennial basis. CMS may also conduct an inspection based on receipt of a complaint about a laboratory. During an inspection, CMS may require the laboratory to test samples or perform procedures, permit the interview of personnel, permit laboratory personnel to be observed performing all phases of the total testing process, and be granted access to all areas encompassed under the certificate and to all records and data.

Under subpart R, if a laboratory is found to be out of compliance, then CMS can impose principal or alternative sanctions on laboratories. Principal sanctions include suspending, limiting, or revoking a CLIA certificate. Alternative sanctions include a directed plan of correction, state onsite monitoring, and civil money penalties. CMS may also enjoin continuation of any activity of any laboratory if it has reason to believe that continuation of the activity would constitute a significant hazard to public health, and individuals convicted of intentionally violating CLIA may be imprisoned or fined. An index of CLIA-related hearing decisions, from 1994 to 2022 can be found here. We generally find these enforcement authorities to be appropriate.

5. Should legislative reforms address CLIA's quality system requirements? If yes, which of those changes would require Congressional action, and which could be effectuated by CMS alone?

If laboratory developed testing services become subject to device regulation by FDA, then there would be overlapping, duplicative, and conflicting quality system requirements under CLIA and the FDCA. For example, as noted above, CLIA laboratories already are subject to inspection and enforcement procedures. If FDA can regulate laboratories as manufacturers, then these laboratories become subject to duplicative inspections and twice the enforcement risk. Accordingly, if FDA regulates laboratory developed testing services, Congress should – at a very minimum – clarify that FDA regulation does not apply to clinical laboratory operations. Likewise, existing quality requirements under CLIA would need to be harmonized to avoid overlap, duplication, and conflict with FDA quality requirements. As stated above, however, rather than clarifying these discrete issues, we believe that Congress should enact comprehensive and diagnostic-specific legislation that would address these issues and otherwise modernize and optimize the regulatory system for diagnostics.

6. Where does redundancy exist, if at all, within the current CLIA regulatory structure with respect accreditation standards under federal and state licensure programs, as well as through CMS-approved accreditation organizations?

CLIA is appropriately harmonized with accreditation standards and state licensure

programs. Under CLIA, a laboratory may receive a certificate of compliance by demonstrating compliance with the CLIA regulations as written, or a laboratory may receive a certificate of accreditation by demonstrating compliance with the standards of an accreditation organization, which has been recognized by CMS to be require standards as stringent or more stringent than CLIA. Additionally, state licensure programs apply requirements that are additional to, but may not replace, requirements under CLIA, unless the state has been "exempted" by CMS. Only two such states have been exempted under CLIA: New York and Washington. In those states, compliance with state licensure programs exempts the laboratories from having to comply with CLIA, such that there is no inherent redundancy.

7. In considering legislative reforms to CLIA, should LDTs be defined in statute? What aspects of test development would characterize such a definition?

Laboratory developed testing services are currently described in the CLIA regulations as tests "not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures)." 42 CFR § 493.1253. This is an appropriate and sufficient definition under the current regulatory framework because laboratory developed testing services are not devices and, therefore, not subject to FDA clearance or approval. If legislative reforms to CLIA are enacted, no changes to this definition are needed.

However, if Congress were to enact a new regulatory framework for all diagnostics that includes a role for FDA regulation of laboratory developed testing services, then it would be appropriate to describe laboratory developed testing services in order to distinguish them from diagnostic test kits that are distributed by manufacturers. This was the approach taken in the VALID Act, which described laboratory developed testing services as a diagnostic test that is—

- (i) developed by a laboratory certified by the Secretary under section 353 of the Public Health Service Act that meets the requirements to perform tests of high-complexity; and
- (ii) performed in—
    - (I) the same laboratory in which such test was developed; or
    - (II) by a another laboratory certified by the Secretary under section 353 of the Public Health Service Act that—
        - (aa) meets the requirements to perform tests of high complexity; and
        - (bb) is under common ownership and control as the laboratory that developed the test.

8. How should Congress consider issues relating to the practice of medicine and its relationship with labeling for LDTs? Should there be additional oversight of the information conveyed to patients serviced by LDTs?

Under CLIA, laboratory directors and clinical consultants—most of whom are licensed physicians—provide important interpretive and consultative services to ordering providers in connection with laboratory developed testing services. Ordering health care providers rely on these candid conversations with the laboratory to inform the care of their patients. FDA regulation of laboratory developed testing services offered by clinical laboratories must not disrupt this.

Specifically, under CLIA, high-complexity laboratories that develop and perform laboratory developed testing services are overseen by a laboratory director, the majority of whom are licensed physicians in the state, and the rest of whom hold an earned doctoral degree in chemical, physical, biological or clinical laboratory science and a certification by an HHS-approved board. *See* 42 CFR § 493.1443. Moreover, CLIA requires that a laboratory may also require support from a clinical consultant qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care. *Id.* at § 493.1455. The clinical consultant must either meet qualifications equivalent to a laboratory director, or otherwise be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice in the state.

The responsibilities of the laboratory director and clinical consultant underscore the value of the services provided by clinical laboratories. In addition to overseeing the operation and administration of the laboratory, the laboratory director is responsible for ensuring that selected test methodologies "have the capability of providing the quality of results required for patient care," "reports of test results include pertinent information required for interpretation," and "consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific conditions." *Id.* at § 493.1445(e)(3)(i), (e)(8)-(e)(9). The clinical consultant is expressly responsible for "provid[ing] consultation regarding the appropriateness of the testing ordered and interpretation of test results." *Id.* at § 493.1457.

These activities of the laboratory director, clinical consultants, and other professionals employed by laboratories, such as accredited genetic counselors, all may fall within the practice of medicine, and are recognized under state laws as such. *See, e.g.*, Utah Code Ann. §§ 58-67-102(19)(a) ("Practice of medicine" means "(i) to diagnose ... by any means or instrumentality") & 58-67-102(12)(a) ("Diagnose" means "to examine in any manner another person, parts of a person's body, substances, fluids, or materials excreted, taken, or removed form a person's body, or produced by a person's body, to determine the source, nature, kind, or extent of a disease or other physical or mental condition"). These activities are core to the professional services provided by laboratories that enable ordering providers to provide the highest quality clinical care for their patients.

To the extent FDA seeks to regulate laboratory developed testing services as medical devices, there would be significant conflicts between the ability of laboratory directors and clinical consultants to fulfill their responsibilities under CLIA and to practice medicine within the scope of their licenses. In particular, FDA could restrict appropriate labeling for a laboratory developed testing service, which in turn would limit what a laboratory director or clinical consultant could share with an ordering provider as part of results interpretation or clinical consultation.

Under a new diagnostics framework, established via legislation, that encompasses laboratory developed testing services, the ability of laboratory directors and clinical consultants to provide important interpretive and consultative services must be preserved. This could be accomplished by clarifying that any new FDA authority does not extend to laboratory operations already regulated under CLIA, which include the interpretive and consultative services of laboratory directors and clinical consultants.

Additionally, any new diagnostic framework must protect the ability of health care providers to order tests, including laboratory developed testing services, for any purpose the ordering provider believes is medical appropriate. This could be accomplished in legislation

with a provision expressly stating that nothing in the new law should be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any lawfully offered in vitro clinical test for any condition or disease within a legitimate health care practitioner-patient relationship pursuant to applicable Federal or State law.

9. Should certain CLIA regulations be updated, would it necessitate a reevaluation of the CLIA fee schedule?

Last year, ACLA submitted detailed comments and a redline to CLIAC proposing updates to the CLIA regulations to accommodate the use of software in laboratory examinations and remote testing activities. For the reasons discussed in response to question 2 above, however, those comments could not be considered by CLIAC prior to their adoption of recommendations to CMS to revise the CLIA regulations. We are reattaching those recommendations here, for your reference.

10. What compliance challenges would legislative reforms to CLIA create? How should new regulatory requirements apply to tests currently available to patients?

To the extent that CLIA is reformed, any new requirements should be prospective with a reasonable transition period for implementation. For example, any legislative reforms would necessitate updates to laboratory policies and procedures, training on such revised policies and procedures, and potential changes to staffing. The length of the transition period would necessarily depend on the extent of the reforms.

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ACLA appreciates the opportunity to respond to the RFI on the regulation of clinical tests. ACLA and ACLA member laboratories remain committed to serving patients and providers, and to serving as a resource in your efforts to bolster our nation's preparedness response. As noted above, ACLA worked collaboratively with Congress over the last several years, as well as FDA and other stakeholders, on legislation that could have established a role for FDA in an appropriate regulatory system for all diagnostics. ACLA steadfastly maintains that legislation is the right—and only—approach for FDA to regulate laboratory develop testing services. We would be pleased to again work with Congress to advance appropriate legislation that preserves the critical role of laboratory diagnostics and ensures that patients continue to have access to lifesaving tests.

If you have follow-up questions, please reach out to Mary Lee Watts, Vice President of Government Affairs and Policy, at mlwatts@acla.com.

Sincerely,

Susan Van Meter
President
American Clinical Laboratory Association

AMERICAN CLINICAL LABORATORY ASSOCIATION

April 5, 2023

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Dear Ms. Stang,

The American Clinical Laboratory Association (ACLA), representing the nation's leading clinical laboratories, is pleased to provide these comments on CLIAC's Recommendations 1 through 5 from the November 2022 meeting of the Committee. These CLIAC recommendations had been made regarding modernization of the CLIA regulations, based on the Interim Report of the CLIA Regulations Assessment Workgroup ("CRA Workgroup"). Also attached as Appendix 1, please find a redline of select CLIA regulations with proposed edits to effect the policies described in our comments.

ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers. ACLA members are at the forefront of driving diagnostic innovation to meet the country's evolving healthcare needs and provide vital clinical laboratory tests that help identify and prevent infectious, acute, and chronic disease. ACLA works to advance the next generation of healthcare delivery through policies that expand access to testing services that improve and save lives. Accordingly, our members are uniquely qualified to provide feedback on both the need for, and the practical impacts of, modernizing the CLIA regulations.

ACLA appreciates the proactive steps that CLIAC has taken to evaluate and make recommendations on modernizing the CLIA regulations to reflect the technologies and workflows of the 21st century. We applaud CLIAC for establishing the CRA Workgroup, and we appreciate the substantive evaluation and assessment of the CLIA regulations that such group has undertaken. ACLA agrees that advancements in laboratory technologies and non-traditional workflow models warrant modernization of the CLIA regulations. As such, ACLA generally agrees with the spirit of CLIAC recommendations 2, 3 and 5, which accommodate the use of software in laboratory examinations, remote testing activities, and home specimen collection, respectively, though we have some recommendations for improving these recommendations in implementation, as discussed further below and as proposed in the CLIA redlines in Appendix 1. However, also as explained below, ACLA does not agree with recommendations 1 and 4, which would expand the scope of CLIA to apply to any data analysis supporting laboratory examinations and create a new certificate type for entities analyzing such data. We believe that the CLIA regulations can be modernized without such a broad expansion of jurisdiction.

I. Recommendation 1: "Materials derived from the human body" should not include all data derived therefrom. Rather, it should include only patient-specific digital laboratory information.

As noted above, ACLA agrees that advancements in laboratory technologies and non-traditional workflow models warrant modernization of the CLIA regulations. However, we disagree that this modernization requires broadening the scope of CLIA to apply to any data analysis that is conducted in furtherance of an examination. As such, we disagree with elements of Recommendation 1.[1]

Recommendation 1 would broaden CLIA to apply to any examination of "data derived from a human specimen such as images, genetic and protein sequence(s), -omics data, **and other data that is used for the purpose of providing information for**" a traditional CLIA examination (emphasis added). This expansion of jurisdiction is too broad, however, and could have unforeseen consequences, particularly for analysis of deidentified (i.e., not patient-specific) information, such as annotations for genetic variants, blood type, or raw measurements of analytes in accordance with medical literature.

Instead of the broad definition proposed in Recommendation 1, ACLA has proposed a more limited definition of "digital laboratory information," which may be considered "materials derived from the human body" only when it is patient-specific, i.e., tied to a particular patient specimen. This definition is more consistent with the concept of a patient specimen, which is necessarily linked to the identity of the patient from which it was derived.

For clarity, ACLA also has proposed a new exception from CLIA for entities analyzing only deidentified information for the purpose of supporting a clinical laboratory's examination of a patient specimen. Entities that would fall under this exception include, for example, third parties that receive deidentified genetic variant information from a clinical laboratory that has examined a patient specimen, annotate such deidentified information based on medical literature, and provide such annotations back to the clinical laboratory for consideration and potential inclusion in the patient test report. Although standalone entities performing such services would not be directly subject to CLIA under this proposal (as they analyze only deidentified information), the clinical laboratory procuring their services *is* subject to CLIA, and as such, is responsible for the quality of the services as they relate to the laboratory's test system, especially if "test system" is revised as recommended in CLIAC Recommendation 2, discussed below.

In the attached redlines, please refer to the proposed changes to the following regulations:

- 42 CFR § 493.2 Definitions
- 42 CFR § 493.3 Applicability

[1] Recommendation 1: The term "materials derived from the human body," as stated in [CLIA], should be defined ... as the patient specimen, including data derived from a human specimen such as images, genetic and protein sequence(s), -omics data, and other data that is used for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings.

II. Recommendation 2: "Test system" should be defined to reflect the use of software.

ACLA largely agrees with CLIAC recommendation 2[2], except that "test system" should not be defined to include all such components needed to generate a "report," which could have unintended consequences, such as imposing postanalytic requirements to generic software used to generate and communicate test reports. In the attached redlines, please refer to the proposed change to the following regulation:

- 42 CFR § 493.2 Definitions

III. Recommendation 3: A primary site's CLIA certificate should extend to remote testing activities under certain circumstances.

ACLA largely agrees with CLIAC recommendation 3 and we have proposed redlines to existing CLIA regulations to facilitate implementation.[3] In particular, we propose that remote review of digital laboratory information may be performed under a primary site's CLIA certificate, and therefore, does not require a separate CLIA certificate.[4] Such practices remain subject to CLIA, but they are understood to be conducted under the oversite of a non-residential laboratory that holds a primary CLIA certificate.[5] In the attached redlines, please refer to the proposed changes to the following regulations:

- 42 CFR § 493.43 Application for registration certificate, certificate for provider-performed microscopy (PPM) procedures, and certificate of compliance
- 42 CFR § 493.55 Application for registration certificate and certificate of accreditation
- 42 CFR § 493.1274 Standard: Cytology[6]
- 42 CFR § 493.1291 Standard: Test report[7]

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[2] Recommendation 2: The definition of a "test system" should be modified in CLIA to include all of the instructions, instrumentation, equipment, reagents, supplies, software algorithms, data exchange and analysis procedures, and other components needed to perform an assay or examination and generate test results and report.

[3] Recommendation 3: CLIAC recommends that the following guidelines be used when assessing the applicability of a site's CLIA certificate when evaluating whether remote testing requires an additional CLIA certificate for staff working at a remote location:

1. The CLIA regulations should be revised to allow remote analysis for any CLIA specialty or subspecialty.
2. If a laboratory employee works out of their home or at another remote location performing duties such as data analysis and interpretation associated with that laboratory, then those activities would be covered through an extension of that laboratory's CLIA certificate and do not require disclosure of the address of the remote location.
3. A laboratory's CLIA certificate covers the qualified laboratory personnel when using a secured connection authorized and/or managed by that laboratory to review and report data for test processing remotely.

[4] Note that conducting remote review activities for multiple laboratories from a single residential site could present tensions with CMS's 2018 memo on the operation of multiple laboratories at the same location. *See* CMS Memo, Ref: QSO-18-20-CLIA, Clarification of the Operation of Multiple Laboratories at the Same Location and the Discontinued Use of the Term "Shared Laboratory" (July 20, 2018) ("Multiple laboratories with separate CLIA numbers may operate at one location as long as it can be demonstrated that each laboratory is operating as a separate and distinct entity."). Updates to this guidance may be needed to accommodate situations where an individual conducts remote review activities on behalf of multiple primary site laboratories.

[5] Note also that CMS guidance may be necessary to clarify that use of this "remote access" exception shall not preclude a laboratory from availing itself of another exception (*e.g.*, temporary testing site).

[6] This is a conforming amendment to enable remote review of digital laboratory information.

[7] ACLA has proposed that the home office location does not need to appear on a test report when the designated primary site is the certificate holder. Certifying bodies may allow a home office location to be identified in a way other than its physical address.

- 42 CFR § 493.1777 Standard: Inspection of laboratories that have requested or have been issued a certificate of compliance.[8]
- 42 CFR § 493.1780 Standard: Inspection of CLIA-exempt laboratories or laboratories requesting or issued a certificate of accreditation.[9]

ACLA also has proposed revisions to accommodate remote review activities by directors of laboratories that do not have the resources to digitize slides, and therefore cannot avail themselves of a proposed exception that would allow remote review of digital laboratory information under a primary site's CLIA certificate. For directors of these laboratories, remote review necessarily entails the transport and analysis of physical slides, which presents different risks (compared to review of digital laboratory information) and requires more direct control by a CLIA-certified laboratory than is generally afforded when a remote site conducts the examination of digital laboratory information under a primary site certificate. Therefore, ACLA's position is that home laboratories where physical slides are held and reviewed are (and should continue to be) required to be certified as separate laboratories under CLIA, i.e., they should continue to require their own CLIA certificate and not operate under the oversite of a primary site CLIA certificate.

However, this discrepancy between an exception for remote review of digital laboratory information and no exception for remote review of physical slides could place directors of such laboratories at a disadvantage because their home laboratory would count against the 5-laboratory limit specified in the CLIA regulations.[10] Therefore, ACLA has proposed an exception to this five-laboratory limit to avoid this disadvantage under the following circumstances: (1) the additional laboratories are located at the laboratory director's residence; and (2) activities at such additional laboratories are limited to the examination of slides that were prepared at a non-residential laboratory. This maintains the level of oversight required for transport and analysis of physical specimens and provides flexibility for remote review of slides for laboratories without the ability for digitization.

In the attached redlines, please refer to the proposed changes to the following regulations:

- 42 CFR § 493.1359 Standard; PPM laboratory director responsibilities
- 42 CFR § 493.1407 Standard; Laboratory director responsibilities
- 42 CFR § 493.1445 Standard; Laboratory director responsibilities

IV. Recommendation 4: A new certificate type is not necessary for entities analyzing patient-specific digital laboratory information.

Although ACLA agrees that analysis of patient-specific digital laboratory information may come within the purview of CLIA, and that "test systems" should include "software algorithms, data exchange and analysis procedures," we do not agree that a new certificate type needs to be established, as recommended by CLIAC Recommendation 4, for entities manipulating information received from and returned to clinical laboratories for inclusion in the patient report

[8] ACLA has recommended changes to reflect that inspectors must acknowledge the different circumstances of a home office operating under the CLIA certificate of the designated primary site, and inspections of home office laboratories should not be unannounced.
[9] *See* note 7, *infra*.
[10] *See* 42 CFR §§ 493.1359(a) (The laboratory director must "[d]irect no more than five laboratories"), 493.1407(d) ("Each individual [laboratory director] may direct no more than five laboratories."), 493.1445(d) ("Each individual [laboratory director] may direct no more than five laboratories.").

or for patient care.[11]

These types of entities would be reference laboratories, and would be subject to existing provisions of CLIA.[12] Likewise, when a clinical laboratory generates patient-specific digital laboratory information and analyzes such information within the same laboratory, those activities remain subject to CLIA. Indeed, CLIA's quality requirements already apply to the entire test system.[13] If "patient-specific digital laboratory information" is considered "material derived from the human body," and "test system" includes data analysis, then these existing quality requirements would govern analysis of patient-specific digital laboratory information.

A separate certificate type is not necessary for analysis of patient-specific digital laboratory information for the same reason that a separate certificate type is not required for microscopy activities: there are not separate *certificate types* for different laboratory methodologies. However, there are different *specialties* with different applicable quality standards. It may be the case, therefore, that new specialties need to be added to CLIA to account for advances in laboratory technologies, e.g., next generation sequencing (NGS).

V. Recommendation 5: FDA should include, whenever possible, controls for specimen adequacy, integrity, and human origin for authorization of self-collection devices.

ACLA generally agrees with this recommendation, although we note that it is not a recommendation for modernizing CLIA, and therefore should not result in any changes to the CLIA regulations.

VI. Other CRA Workgroup Agreements

Finally, ACLA offers the following comments on additional CRA Workgroup Agreements that did not result in CLIAC Recommendations at the prior CLIAC meeting in November 2022.[14]

A. Personnel

The CRA Workgroup agreed that CLIA should define new personnel roles and categories for variant scientists and personnel that perform digital pathology and digital image analysis. The rationale for this recommendation is not clear, and ACLA requests additional information regarding this proposal.

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[11] Recommendation 4: CLIAC recommends a new certificate type for an entity manipulating information received from and returned to the clinical laboratory for inclusion in the patient report or for patient care.

[12] In contrast, entities analyzing de-identified digital laboratory information—such as third party services providing annotations of anonymized genetic variants based on the latest medical literature for consideration by a clinical laboratory—would not be subject to CLIA under ACLA's proposed redlines. As discussed in our comments on CLIAC Recommendation 1, CLIA's jurisdiction should not be so broadly expanded.

[13] *See, e.g.*, 42 CFR § 493.1200(a) ("Each laboratory that performs nonwaived testing must establish and maintain written policies and procedures that implement and monitor a quality system for **all phases of the total testing process** (that is, preanalytic, analytic, and postanalytic) as well as general laboratory systems.") (emphasis added); 42 CFR § 493.1445(e) ("The laboratory director must . . . (3) Ensure that – (i) The test methodologies selected have the capability of providing the quality of results required for patient care; (ii) Verification procedures used are adequate to determine the accuracy, precision, and other pertinent performance characteristics of the method; and (iii) Laboratory personnel are performing the test methods as required for accurate and reliable results' . . . . (5) Ensure that the quality control and quality assessment programs are established and maintained to assure the quality of laboratory services provided and to identify failures in quality as they occur; (6) Ensure the establishment and maintenance of acceptable levels of analytical performance for each test system . . . ."). *See also* State Operations Manual, Appendix C – Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services at 300 (Rev. 166, 02-03-17) ("QA of the Analytic System includes assessing: Test procedures; Accurate and reliable test systems....").

[14] CLIA Regulations Assessment Workgroup Interim Report at 11-12 (Nov. 9-10, 2022).

The CRA Workgroup also agreed that a new specialty is needed to accommodate the post-analytic analysis of laboratory data or results for practice areas such as NGS. ACLA disagrees with this proposal, which would treat as its own specialty a portion of a test system that is already regulated under several other specialties. Moreover, as described in section IV above, CLIA's quality requirements already apply to the entire test system, and this would include any "post-analytic analysis" that is conducted in support of generating a test result.[15] However, also as noted above, it may be the case that new specialties need to be added to CLIA, such as a specialty for next generation sequencing (NGS).

B. Other Areas

The CRA Workgroup also made statements regarding robotics, digital data and specimen integrity, data identifiers, and the HIPAA Final Security Rule. It is unclear what several of these agreements are referring to, and ACLA requests additional information and consideration before they are considered for CLIAC Recommendations.

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Thank you for your consideration of these comments. Please do not hesitate to reach out to me with any questions at aborden@acla.com.

Sincerely,

Adam Borden
Senior Vice President, Policy & Strategy
American Clinical Laboratory Association

Enclosure

[15] *See* note 12, *supra*. We further note that it is unclear what "post-analytic analysis" means, but we presume it is a reference to analysis of digital laboratory information.

Appendix 1: American Clinical Laboratory Association (ACLA) redline of CLIA regulations to accommodate remote reading

§ 493.2 Definitions.

…

Digital laboratory information:

(1) means any of the following:
   a. A digital image derived from a glass slide.
   b. Data including, but not limited to, flow cytometry plots, cytogenetic karyograms; chromatographic, mass spectrometric, clinical chemistry, immunological, and hematologic data; electropherograms; gel images; and genetic expression, array and sequencing data; and

(2) Is patient-specific when it is accompanied by information that can be used to identify the individual from whose specimen the information was derived.

…

Laboratory means a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body, including patient-specific digital laboratory information, for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. These examinations also include procedures to determine, measure, or otherwise describe the presence or absence of various substances or organisms in the body. Facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing are not considered laboratories.

…

Test system means the instructions, ~~and all of the~~ instrumentation, equipment, reagents, ~~and~~ supplies, software algorithms, data exchange and analysis procedures, and other components needed to perform an assay or examination and generate test results.

§ 493.3 Applicability.

(a) Basic rule. Except as specified in paragraph (b) of this section, a laboratory will be cited as out of compliance with section 353 of the Public Health Service Act unless it -

(1) Has a current, unrevoked or unsuspended certificate of waiver, registration certificate, certificate of compliance, certificate for PPM procedures, or certificate of accreditation issued by HHS applicable to the category of examinations or procedures performed by the laboratory; or

(2) Is CLIA-exempt.

(b) Exception. These rules do not apply to components or functions of -

(1) Any facility or component of a facility that only performs testing for forensic purposes;

(2) Research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients; ~~or~~

(3) Laboratories certified by the Substance Abuse and Mental Health Services Administration (SAMHSA), in which drug testing is performed which meets SAMHSA guidelines and regulations. However, all other testing conducted by a SAMHSA-certified laboratory is subject to this rule; or

(4) Any facility or component of a facility whose analysis is limited to digital laboratory information that is not patient-specific and is received from a clinical laboratory for purposes of providing information to support the clinical laboratory's examination of a patient specimen.

(c) Federal laboratories. Laboratories under the jurisdiction of an agency of the Federal Government are subject to the rules of this part, except that the Secretary may modify the application of such requirements as appropriate.

§ 493.43 Application for registration certificate, certificate for provider-performed microscopy (PPM) procedures, and certificate of compliance.

(a) *Filing of application.* Except as specified in paragraph (b) of this section, all laboratories performing nonwaived testing must file a separate application for each laboratory location.

(b) *Exceptions.*

(1) Laboratories that are not at a fixed location, that is, laboratories that move from testing site to testing site, such as mobile units providing laboratory testing, health screening fairs, or other temporary testing locations may be covered under the certificate of the designated primary site or home base, using its address.

(2) Not-for-profit or Federal, State, or local government laboratories that engage in limited (not more than a combination of 15 moderately complex or waived tests per certificate) public health testing may file a single application.

(3) Laboratories within a hospital that are located at contiguous buildings on the same campus and under common direction may file a single application or multiple applications for the laboratory sites within the same physical location or street address.

(4) Laboratories located at non-commercial locations, such as residential offices, from which a board-certified pathologist or other laboratory professional accesses the designated primary site's system using a secure remote access protocol to retrieve, review, and analyze patient-specific digital laboratory information.

(c) *Application format and contents.* The application must -

(1) Be made to HHS or its designee on a form or forms prescribed by HHS;

(2) Be signed by an owner, or by an authorized representative of the laboratory who attests that the laboratory will be operated in accordance with the requirements established by the Secretary under section 353 of the Public Health Service Act; and

(3) Describe the characteristics of the laboratory operation and the examinations and other test procedures performed by the laboratory including -

(i) The name and total number of test procedures and examinations performed annually (excluding waived tests or tests for quality control, quality assurance or proficiency testing purposes);

(ii) The methodologies for each laboratory test procedure or examination performed, or both;

(iii) The qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the examinations and test procedures.

(d) *Access and reporting requirements.* All laboratories must make records available and submit reports to HHS as HHS may reasonably require to determine compliance with this section.

…

§ 493.55 Application for registration certificate and certificate of accreditation.

(a) *Filing of application.* A laboratory may be issued a certificate of accreditation in lieu of the applicable certificate specified in subpart B or subpart C of this part provided the laboratory -

(1) Meets the standards of a private non-profit accreditation program approved by HHS in accordance with subpart E; and

(2) Files a separate application for each location, except as specified in paragraph (b) of this section.

(b) *Exceptions.*

(1) Laboratories that are not at fixed locations, that is, laboratories that move from testing site to testing site, such as mobile units providing laboratory testing, health screening fairs, or other temporary testing locations may be covered under the certificate of the designated primary site or home base, using its address.

(2) Not-for-profit or Federal, State, or local government laboratories that engage in limited (not more than a combination of 15 moderately complex or waived tests per certificate) public health testing may file a single application.

(3) Laboratories within a hospital that are located at contiguous buildings on the same campus and under common direction may file a single application or multiple applications for the laboratory sites within the same physical location or street address.

(4) Laboratories located at non-commercial locations, such as residential offices, from which a board-certified pathologist or other laboratory professional accesses the designated primary site's system using a secure remote access protocol to retrieve, review, and analyze patient-specific digital laboratory information.

(c) *Application format and contents.* The application must -

(1) Be made to HHS on a form or forms prescribed by HHS;

(2) Be signed by an owner or authorized representative of the laboratory who attests that the laboratory will be operated in accordance with the requirements established by the Secretary under section 353 of the Public Health Service Act; and

(3) Describe the characteristics of the laboratory operation and the examinations and other test procedures performed by the laboratory including -

(i) The name and total number of tests and examinations performed annually (excluding waived tests and tests for quality control, quality assurance or proficiency testing purposes);

(ii) The methodologies for each laboratory test procedure or examination performed, or both; and

(iii) The qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the laboratory examinations and test procedures.

(d) *Access and reporting requirements.* All laboratories must make records available and submit reports to HHS as HHS may reasonably require to determine compliance with this section.

§ 493.1291 Standard: Test report.

(a) The laboratory must have an adequate manual or electronic system(s) in place to ensure test results and other patient-specific data are accurately and reliably sent from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner. This includes the following:

(1) Results reported from calculated data.

(2) Results and patient-specific data electronically reported to network or interfaced systems.

(3) Manually transcribed or electronically transmitted results and patient-specific information reported directly or upon receipt from outside referral laboratories, satellite or point-of-care testing locations.

(b) Test report information maintained as part of the patient's chart or medical record must be readily available to the laboratory and to CMS or a CMS agent upon request.

(c) The test report must indicate the following:

(1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number.

(2) The name and address of the laboratory location where the test was performed, or of the designated primary site for a laboratory described at § 493.43(b)(4).

(3) The test report date.

(4) The test performed.

(5) Specimen source, when appropriate.

(6) The test result and, if applicable, the units of measurement or interpretation, or both.

(7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability.

(d) Pertinent “reference intervals” or “normal” values, as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results.

(e) The laboratory must, upon request, make available to clients a list of test methods employed by the laboratory and, as applicable, the performance specifications established or verified as specified in § 493.1253. In addition, information that may affect the interpretation of test results, for example test interferences, must be provided upon request. Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results.

(f) Except as provided in § 493.1291(l), test results must be released only to authorized persons and, if applicable, the persons responsible for using the test results and the laboratory that initially requested the test.

(g) The laboratory must immediately alert the individual or entity requesting the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminently life-threatening condition, or panic or alert values.

(h) When the laboratory cannot report patient test results within its established time frames, the laboratory must determine, based on the urgency of the patient test(s) requested, the need to notify the appropriate individual(s) of the delayed testing.

(i) If a laboratory refers patient specimens for testing -

(1) The referring laboratory must not revise results or information directly related to the interpretation of results provided by the testing laboratory;

(2) The referring laboratory may permit each testing laboratory to send the test result directly to the authorized person who initially requested the test. The referring laboratory must retain or be able to produce an exact duplicate of each testing laboratory's report; and

(3) The authorized person who orders a test must be notified by the referring laboratory of the name and address of each laboratory location where the test was performed.

(j) All test reports or records of the information on the test reports must be maintained by the laboratory in a manner that permits ready identification and timely accessibility.

(k) When errors in the reported patient test results are detected, the laboratory must do the following:

(1) Promptly notify the authorized person ordering the test and, if applicable, the individual using the test results of reporting errors.

(2) Issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results.

(3) Maintain duplicates of the original report, as well as the corrected report.

(l) Upon request by a patient (or the patient's personal representative), the laboratory may provide patients, their personal representatives, and those persons specified under 45 CFR 164.524(c)(3)(ii), as applicable, with access to completed test reports that, using the laboratory's authentication process, can be identified as belonging to that patient.

493.1777 Standard: Inspection of laboratories that have requested or have been issued a certificate of compliance; exception.

(a) *Initial inspection.*

(1) A laboratory issued a registration certificate must permit an initial inspection to assess the laboratory's compliance with the requirements of this part before CMS issues a certificate of compliance.

(2) The inspection may occur at any time during the laboratory's hours of operation.

(b) *Subsequent inspections.*

(1) CMS or a CMS agent may conduct subsequent inspections on a biennial basis or with such other frequency as CMS determines to be necessary to ensure compliance with the requirements of this part.

(2) CMS bases the nature of subsequent inspections on the laboratory's compliance history.

(c) *Provider-performed microscopy procedures.* The inspection sample for review may include testing in the subcategory of provider-performed microscopy procedures.

(d) *Compliance with basic inspection requirements.* The laboratory must comply with the basic inspection requirements of § 493.1773.

(e) *Exception*. The following standards apply to a laboratory described in § 493.43(b)(4):

(1) The laboratory is not subject to biennial inspections.

(2) If necessary, CMS or a CMS agent may conduct an inspection of the laboratory during reasonable hours (after announcing the date and time of the inspection) to do the following:

(A) Determine if the laboratory is operated and testing is performed in a manner that does not constitute an imminent and serious risk to public health.

(B) Evaluate a complaint from the public.

§ 493.1780 Standard: Inspection of CLIA-exempt laboratories or laboratories requesting or issued a certificate of accreditation.

(a) *Validation inspection.* CMS or a CMS agent may conduct a validation inspection of any accredited or CLIA-exempt laboratory at any time during its hours of operation (or in the case of a laboratory described at § 493.55(b)(4), during reasonable hours and after announcing the date and time of the inspection).

(b) *Complaint inspection.* CMS or a CMS agent may conduct a complaint inspection of a CLIA-exempt laboratory or a laboratory requesting or issued a certificate of accreditation at any time during its hours of operation (or in the case of a laboratory described at § 493.55(b)(4), during reasonable hours and after announcing the date and time of the inspection) upon receiving a complaint applicable to the requirements of this part.

(c) *Noncompliance determination.* If a validation or complaint inspection results in a finding that the laboratory is not in compliance with one or more condition-level requirements, the following actions occur:

(1) A laboratory issued a certificate of accreditation is subject to a full review by CMS, in accordance with subpart E of this part and § 488.11 of this chapter.

(2) A CLIA-exempt laboratory is subject to appropriate enforcement actions under the approved State licensure program.

(d) *Compliance with basic inspection requirements.* CLIA-exempt laboratories and laboratories requesting or issued a certificate of accreditation must comply with the basic inspection requirements in § 493.1773.

§ 493.1274 Standard: Cytology.

(a) *Cytology slide ~~examination site~~*. All cytology slides ~~preparations~~ must be ~~evaluated~~ prepared on the premises of a laboratory certified to conduct testing in the subspecialty of cytology.

(b) *Staining*. The laboratory must have available and follow written policies and procedures for each of the following, if applicable:

(1) All gynecologic slide preparations must be stained using a Papanicolaou or modified Papanicolaou staining method.

(2) Effective measures to prevent cross-contamination between gynecologic and nongynecologic specimens during the staining process must be used.

(3) Nongynecologic specimens that have a high potential for cross-contamination must be stained separately from other nongynecologic specimens, and the stains must be filtered or changed following staining.

(c) *Control procedures*. The laboratory must establish and follow written policies and procedures for a program designed to detect errors in the performance of cytologic examinations and the reporting of results. The program must include the following:

(1) A review of slides from at least 10 percent of the gynecologic cases interpreted by individuals qualified under § 493.1469 or § 493.1483, to be negative for epithelial cell abnormalities and other malignant neoplasms (as defined in paragraph (e)(1) of this section).

(i) The review must be performed by an individual who meets one of the following qualifications:

(A) A technical supervisor qualified under § 493.1449(b) or (k).

(B) A cytology general supervisor qualified under § 493.1469.

(C) A cytotechnologist qualified under § 493.1483 who has the experience specified in § 493.1469(b)(2).

(ii) Cases must be randomly selected from the total caseload and include negatives and those from patients or groups of patients that are identified as having a higher than average probability of developing cervical cancer based on available patient information.

(iii) The review of those cases selected must be completed before reporting patient results.

(2) Laboratory comparison of clinical information, when available, with cytology reports and comparison of all gynecologic cytology reports with a diagnosis of high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma, or other malignant neoplasms with the histopathology report, if available in the laboratory (either on-site or in storage), and determination of the causes of any discrepancies.

(3) For each patient with a current HSIL, adenocarcinoma, or other malignant neoplasm, laboratory review of all normal or negative gynecologic specimens received within the previous 5 years, if available in the laboratory (either on-site or in storage). If significant discrepancies are found that will affect current patient care, the laboratory must notify the patient's physician and issue an amended report.

(4) Records of initial examinations and all rescreening results must be documented.

(5) An annual statistical laboratory evaluation of the number of –

(i) Cytology cases examined;

(ii) Specimens processed by specimen type;

(iii) Patient cases reported by diagnosis (including the number reported as unsatisfactory for diagnostic interpretation);

(iv) Gynecologic cases with a diagnosis of HSIL, adenocarcinoma, or other malignant neoplasm for which histology results were available for comparison;

(v) Gynecologic cases where cytology and histology are discrepant; and

(vi) Gynecologic cases where any rescreen of a normal or negative specimen results in reclassification as low-grade squamous intraepithelial lesion (LSIL), HSIL, adenocarcinoma, or other malignant neoplasms.

(6) An evaluation of the case reviews of each individual examining slides against the laboratory's overall statistical values, documentation of any discrepancies, including reasons for the deviation and, if appropriate, corrective actions taken.

(d) *Workload limits*. The laboratory must establish and follow written policies and procedures that ensure the following:

(1) The technical supervisor establishes a maximum workload limit for each individual who performs primary screening.

(i) The workload limit is based on the individual's performance using evaluations of the following:

(A) Review of 10 percent of the cases interpreted as negative for the conditions defined in paragraph (e)(1) of this section.

(B) Comparison of the individual's interpretation with the technical supervisor's confirmation of patient smears specified in paragraphs (e)(1) and (e)(3) of this section.

(ii) Each individual's workload limit is reassessed at least every 6 months and adjusted when necessary.

(2) The maximum number of slides examined by an individual in each 24-hour period does not exceed 100 slides (one patient specimen per slide; gynecologic, nongynecologic, or both) irrespective of the site or laboratory. This limit represents an absolute maximum number of slides and must not be employed as an individual's performance target. In addition –

(i) The maximum number of 100 slides is examined in no less than an 8-hour workday;

(ii) For the purposes of establishing workload limits for individuals examining slides in less than an 8-hour workday (includes full-time employees with duties other than slide examination and part-time employees), a period of 8 hours is used to prorate the number of slides that may be examined. The formula –

$$\frac{\text{Number of hours examining slides} \times 100}{8}$$

is used to determine maximum slide volume to be examined;

(iii) Nongynecologic slide preparations made using liquid-based slide preparatory techniques that result in cell dispersion over one-half or less of the total available slide may be counted as one-half slide; and

(iv) Technical supervisors who perform primary screening are not required to include tissue pathology slides and previously examined cytology slides (gynecologic and nongynecologic) in the 100 slide workload limit.

(3) The laboratory must maintain records of the total number of slides examined by each individual during each 24-hour period and the number of hours spent examining slides in the 24-hour period irrespective of the site or laboratory.

(4) Records are available to document the workload limit for each individual.

(e) *Slide examination and reporting*. The laboratory must establish and follow written policies and procedures that ensure the following:

(1) A technical supervisor confirms each gynecologic slide preparation interpreted to exhibit reactive or reparative changes or any of the following epithelial cell abnormalities:

(i) Squamous cell.

(A) Atypical squamous cells of undetermined significance (ASC-US) or cannot exclude HSIL (ASC-H).

(B) LSIL-Human papillomavirus (HPV)/mild dysplasia/cervical intraepithelial neoplasia 1 (CIN 1).

(C) HSIL-moderate and severe dysplasia, carcinoma in situ (CIS)/CIN 2 and CIN 3 or with features suspicious for invasion.

(D) Squamous cell carcinoma.

(ii) Glandular cell.

(A) Atypical cells not otherwise specified (NOS) or specified in comments (endocervical, endometrial, or glandular).

(B) Atypical cells favor neoplastic (endocervical or glandular).

(C) Endocervical adenocarcinoma in situ.

(D) Adenocarcinoma endocervical, adenocarcinoma endometrial, adenocarcinoma extrauterine, and adenocarcinoma NOS.

(iii) Other malignant neoplasms.

(2) The report of gynecologic slide preparations with conditions specified in paragraph (e)(1) of this section must be signed to reflect the technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(3) All nongynecologic preparations are reviewed by a technical supervisor. The report must be signed to reflect technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(4) Unsatisfactory specimens or slide preparations are identified and reported as unsatisfactory.

(5) The report contains narrative descriptive nomenclature for all results.

(6) Corrected reports issued by the laboratory indicate the basis for correction.

(f) *Record and slide retention*.

(1) The laboratory must retain all records and slide preparations as specified in § 493.1105.

(2) Slides may be loaned to proficiency testing programs in lieu of maintaining them for the required time period, provided the laboratory receives written acknowledgment of the receipt of slides by the proficiency testing program and maintains the acknowledgment to document the loan of these slides.

(3) Documentation of slides loaned or referred for purposes other than proficiency testing must be maintained.

(4) All slides must be retrievable upon request.

(g) *Automated and semi-automated screening devices*. When performing evaluations using automated and semi-automated screening devices, the laboratory must follow manufacturer's instructions for preanalytic, analytic, and postanalytic phases of testing, as applicable, and meet the applicable requirements of this subpart K.

(h) *Documentation*. The laboratory must document all control procedures performed, as specified in this section.

§ 493.1359 Standard; PPM laboratory director responsibilities.

The laboratory director is responsible for the overall operation and administration of the laboratory, including the prompt, accurate, and proficient reporting of test results. The laboratory director must -

(a) Direct no more than five laboratories, except as described in sections 493.1407(d) and 493.1445(d) for laboratories certified to perform testing of moderate- or high-complexity; and

(b) Ensure that any procedure listed under § 493.19(c) -

(1) Is personally performed by an individual who meets the qualification requirements in § 493.1363; and

(2) Is performed in accordance with applicable requirements in subparts H, J, K, and M of this part.

§ 493.1407 Standard; Laboratory director responsibilities.

The laboratory director is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures, and record and report test results promptly, accurate, and proficiently and for assuring compliance with the applicable regulations.

(a) The laboratory director, if qualified, may perform the duties of the technical consultant, clinical consultant, and testing personnel, or delegate these responsibilities to personnel meeting the qualifications of §§ 493.1409, 493.1415, and 493.1421, respectively.

(b) If the laboratory director reapportions performance of his or her responsibilities, he or she remains responsible for ensuring that all duties are properly performed.

(c) The laboratory director must be accessible to the laboratory to provide onsite, telephone or electronic consultation as needed.

(d) Each individual may direct no more than five laboratories, except that a laboratory director may direct additional laboratories that do not count toward the five laboratory limit if—

(1) such laboratories are located at the laboratory director's residence; and

(2) activities at such laboratories are limited to the examination of slides that were prepared at a non-residential laboratory.

(e) The laboratory director must -

(1) Ensure that testing systems developed and used for each of the tests performed in the laboratory provide quality laboratory services for all aspects of test performance, which includes the preanalytic, analytic, and postanalytic phases of testing;

(2) Ensure that the physical plant and environmental conditions of the laboratory are appropriate for the testing performed and provide a safe environment in which employees are protected from physical, chemical, and biological hazards;

(3) Ensure that -

(i) The test methodologies selected have the capability of providing the quality of results required for patient care;

(ii) Verification procedures used are adequate to determine the accuracy, precision, and other pertinent performance characteristics of the method; and

(iii) Laboratory personnel are performing the test methods as required for accurate and reliable results;

(4) Ensure that the laboratory is enrolled in an HHS approved proficiency testing program for the testing performed and that -

(i) The proficiency testing samples are tested as required under subpart H of this part;

(ii) The results are returned within the timeframes established by the proficiency testing program;

(iii) All proficiency testing reports received are reviewed by the appropriate staff to evaluate the laboratory's performance and to identify any problems that require corrective action; and

(iv) An approved corrective action plan is followed when any proficiency testing results are found to be unacceptable or unsatisfactory;

(5) Ensure that the quality control and quality assessment programs are established and maintained to assure the quality of laboratory services provided and to identify failures in quality as they occur;

(6) Ensure the establishment and maintenance of acceptable levels of analytical performance for each test system;

(7) Ensure that all necessary remedial actions are taken and documented whenever significant deviations from the laboratory's established performance specifications are identified, and that patient test results are reported only when the system is functioning properly;

(8) Ensure that reports of test results include pertinent information required for interpretation;

(9) Ensure that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions;

(10) Employ a sufficient number of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report test results in accordance with the personnel responsibilities described in this subpart;

(11) Ensure that prior to testing patients' specimens, all personnel have the appropriate education and experience, receive the appropriate training for the type and complexity of the services offered, and have demonstrated that they can perform all testing operations reliably to provide and report accurate results;

(12) Ensure that policies and procedures are established for monitoring individuals who conduct preanalytical, analytical, and postanalytical phases of testing to assure that they are competent and maintain their competency to process specimens, perform test procedures and report test results promptly and proficiently, and whenever necessary, identify needs for remedial training or continuing education to improve skills;

(13) Ensure that an approved procedure manual is available to all personnel responsible for any aspect of the testing process; and

(14) Specify, in writing, the responsibilities and duties of each consultant and each person, engaged in the performance of the preanalytic, analytic, and postanalytic phases of testing, that identifies which examinations and procedures each individual is authorized to perform, whether supervision is required for specimen processing, test performance or results reporting, and whether consultant or director review is required prior to reporting patient test results.

§ 493.1445 Standard; Laboratory director responsibilities.

The laboratory director is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures, record and report test results promptly, accurately and proficiently, and for assuring compliance with the applicable regulations.

(a) The laboratory director, if qualified, may perform the duties of the technical supervisor, clinical consultant, general supervisor, and testing personnel, or delegate these responsibilities

to personnel meeting the qualifications under §§ 493.1447, 493.1453, 493.1459, and 493.1487, respectively.

(b) If the laboratory director reapportions performance of his or her responsibilities, he or she remains responsible for ensuring that all duties are properly performed.

(c) The laboratory director must be accessible to the laboratory to provide onsite, telephone or electronic consultation as needed.

(d) Each individual may direct no more than five laboratories, except that a laboratory director may direct additional laboratories that do not count toward the five laboratory limit if—

(1) such laboratories are located at the laboratory director's residence; and

(2) activities at such laboratories are limited to the examination of slides that were prepared at a non-residential laboratory.

(e) The laboratory director must -

(1) Ensure that testing systems developed and used for each of the tests performed in the laboratory provide quality laboratory services for all aspects of test performance, which includes the preanalytic, analytic, and postanalytic phases of testing;

(2) Ensure that the physical plant and environmental conditions of the laboratory are appropriate for the testing performed and provide a safe environment in which employees are protected from physical, chemical, and biological hazards;

(3) Ensure that -

(i) The test methodologies selected have the capability of providing the quality of results required for patient care;

(ii) Verification procedures used are adequate to determine the accuracy, precision, and other pertinent performance characteristics of the method; and

(iii) Laboratory personnel are performing the test methods as required for accurate and reliable results;

(4) Ensure that the laboratory is enrolled in an HHS-approved proficiency testing program for the testing performed and that -

(i) The proficiency testing samples are tested as required under subpart H of this part;

(ii) The results are returned within the timeframes established by the proficiency testing program;

(iii) All proficiency testing reports received are reviewed by the appropriate staff to evaluate the laboratory's performance and to identify any problems that require corrective action; and

(iv) An approved corrective action plan is followed when any proficiency testing result is found to be unacceptable or unsatisfactory;

(5) Ensure that the quality control and quality assessment programs are established and maintained to assure the quality of laboratory services provided and to identify failures in quality as they occur;

(6) Ensure the establishment and maintenance of acceptable levels of analytical performance for each test system;

(7) Ensure that all necessary remedial actions are taken and documented whenever significant deviations from the laboratory's established performance characteristics are identified, and that patient test results are reported only when the system is functioning properly;

(8) Ensure that reports of test results include pertinent information required for interpretation;

(9) Ensure that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation concerning specific patient conditions;

(10) Ensure that a general supervisor provides on-site supervision of high complexity test performance by testing personnel qualified under § 493.1489(b)(4);

(11) Employ a sufficient number of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report test results in accordance with the personnel responsibilities described in this subpart;

(12) Ensure that prior to testing patients' specimens, all personnel have the appropriate education and experience, receive the appropriate training for the type and complexity of the services offered, and have demonstrated that they can perform all testing operations reliably to provide and report accurate results;

(13) Ensure that policies and procedures are established for monitoring individuals who conduct preanalytical, analytical, and postanalytical phases of testing to assure that they are competent and maintain their competency to process specimens, perform test procedures and report test results promptly and proficiently, and whenever necessary, identify needs for remedial training or continuing education to improve skills;

(14) Ensure that an approved procedure manual is available to all personnel responsible for any aspect of the testing process; and

(15) Specify, in writing, the responsibilities and duties of each consultant and each supervisor, as well as each person engaged in the performance of the preanalytic, analytic, and postanalytic phases of testing, that identifies which examinations and procedures each individual is authorized to perform, whether supervision is required for specimen processing, test performance or result reporting and whether supervisory or director review is required prior to reporting patient test results.