

## Regulatory guidance for laboratories that design and implement diagnostic tests for clinical use

### Learning objectives:

- Describe the role of the United States Food and Drug Administration (FDA) in regulating *in vitro* diagnostic (IVD) tests and laboratory-developed tests (LDTs)
- Describe FDA regulations related to IVD tests used for Research Use Only (RUO) and Investigational Use Only (IUO)
- Describe the role of the Centers for Medicare & Medicaid Services (CMS) in regulating laboratory processes associated with LDTs

### The limited role of the FDA in regulating LDTs

The FDA is the gatekeeper responsible for ensuring the safety and efficacy of biomedical products marketed and sold across state lines in the United States. The FDA requires biomedical product developers and manufacturers, known as sponsors, to submit information about their products, the intended uses for those products, and their safety profiles for review. The effectiveness of all drugs and devices like IVD tests in bringing about specific health-related outcomes must also be demonstrated [1].

The FDA reviews the data submitted by sponsors and can ask them to clarify or address certain questions. In consultation with expert panels, the FDA reviews the risk and benefit profile of each submission and grants clearance or approval for marketing if warranted.

Diagnostics include “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease” [2]. The FDA considers laboratory instrumentation and the reagents used for testing to be medical devices, which are subject to oversight.

What about the assays themselves? A diagnostic test must be approved as a medical device, specifically an IVD, by the FDA if it is manufactured for use in multiple laboratories. IVD tests include all clinical assays sold commercially as kits or devices that are used to analyze human specimens. IVD tests are therefore subject to FDA regulation, and sponsors must have premarket approval or clearance prior to marketing IVDs. In addition, IVD manufacturers must comply with various regulations related to manufacturing, purchasing, record keeping, and other practices.

If a laboratory develops an LDT based on its own in-house protocols, it is not regulated by the FDA as long as the test is manufactured and used only at that site and not provided or sold to other laboratories [3]. The FDA thus distinguishes between LDTs and IVDs.

An LDT can be thought of as a specialty offering provided by an individual laboratory, and LDTs are currently exempt from any premarket review or manufacturing oversight by the FDA.

In fact, some organizations like the American Association for Clinical Chemistry (AACC), the American College of Medical Genetics and Genomics (ACMG), and the Association for Molecular Pathology (AMP) refer to LDTs as *processes*. This indicates these organizations focus more on the processes surrounding LDTs than the tests themselves.

LDT regulation is an area of ongoing debate and discussion. The FDA has claimed that it can regulate LDTs but chooses not to exercise enforcement discretion. In other words, it has decided to not regulate them [4]. The FDA issued several draft guidelines in 2006 and 2014 and a discussion paper in 2017 that outlined proposals to bring LDTs under its purview. None of these oversight mechanisms have translated into actual regulation [5], and the American Clinical Laboratory Association, the Association of Public Health Laboratories, and the AACC have voiced reservations about the FDA proposals.

The debate over what sort of oversight the FDA should have over diagnostics in general and LDTs in particular has gone on for two decades. It will likely continue as diagnostic tests evolve and grow increasingly complex with broader ranges and larger numbers of analytes that frequently necessitate algorithmic analysis. Given the controversy over the role of the FDA, changes in its statutory authority to regulate LDTs will likely require new legislation from Congress.

### **RUO and IUO tests**

It is important to note that the FDA has oversight over assays in several other

categories. It is possible to use an assay that has not been cleared or approved by the FDA in a research context or as part of product development or a clinical trial. However, the assay cannot be used legally for clinical diagnostic procedures or any purpose other than research or investigation. The assay must be prominently labeled for Research Use Only (RUO) or Investigational Use Only (IUO) prior to shipment or delivery to a laboratory. The performance characteristics of these products have not been established, and their manufacturers are not required to comply with cGMP manufacturing standards and quality system regulations.

The FDA strives to ensure that healthcare providers are not misled about the approved applications for RUO and IUO tests [6]. The FDA has stated the following requirements for tests that have not received clearance or approval [7]:

(i) A product in the laboratory research phase of development must be prominently labeled "For Research Use Only. Not for use in diagnostic procedures," so that it is not presented as an effective *in vitro* diagnostic product.

(ii) A product being shipped or delivered for product testing before it is ready for full commercialization must be prominently labeled "For Investigational Use Only. The performance characteristics of this product have not been established." A test or assay may be labeled this way if it is being compared to other products, used to evaluate current processes in tests with human specimens, or when it is recognized as being useful.

It is important to note that if an LDT is shipped externally in the research phase of development for product testing prior to commercial marketing, it will no longer qualify as an LDT and will require review as an IVD by the FDA.

### **Emergency Use Authorization**

The FDA can grant Emergency Use Authorization (EUA) for use of an unapproved medical product or unapproved use of an FDA-regulated product during a declared public health emergency. EUAs can expedite the path to market for new drugs and devices by compressing the development phase and reducing the risk incurred by sponsors. By December 2021, the FDA had issued more than 430 EUAs for a range of tests and sample collection kits in response to the SARS-CoV-2 pandemic. A majority of the EUAs were reverse-transcription PCR (RT-PCR) tests, lateral flow antigen tests, and antibody tests.

The main difference between EUA and conventional approval is that EUA requires much less evidence of safety and effectiveness. In terms of safety, EUA only requires that the known and potential benefits of a product outweigh the known and potential risks [8]. The FDA may grant EUA if it is reasonable to believe that a product *may* be effective [8]. This can reduce the number of demands on sponsors and accelerate product development since less investigational work is required, which streamlines the FDA review process.

Another benefit of EUA is that a manufacturer is granted immunity from any liability based on claims of loss related to the manufacture, distribution,

administration, or use of its medical product. In short, the buyer has no legal recourse if a test granted EUA does not perform as expected.

The EUA pathway also has several disadvantages for sponsors. The FDA has wide latitude to determine which products will be allowed on the market, to whom they may be marketed, and the conditions for which they can be used. EUA remains in effect only for the duration of a public health emergency, so sponsors must have a plan for marketing approval during “peace time”. The FDA has the authority to impose tighter restrictions on where a product can be used, which practitioners may prescribe it, and the amount of data that must be collected. Another disadvantage for sponsors is that EUA can be easily revoked. By the end of December 2021, the FDA had revoked EUAs and/or added products to its Do Not Use database for more than 190 SARS-CoV-2 antibody assays and a few molecular and antigen tests.

### **CMS regulation**

The Centers for Medicare & Medicaid Services (CMS) has regulated business conducted across state lines by clinical laboratories since 1967. CMS regulations were initially limited to mandates for personnel requirements and inspections, but the requirements for clinical laboratories expanded over time. Under the 1988 Clinical Laboratory Improvement Amendments (CLIA) Act, all laboratories that test patient specimens must obtain a certificate of compliance or accreditation in order to bill the CMS for their services [9].

Any facility in the United States that performs tests on human specimens for the diagnosis, prevention, or treatment of disease or for human health assessment must obtain the appropriate CLIA certificate from the CMS, even if the facility does not consider itself a laboratory.

**CLIA certification**

There are five different types of CLIA certificates (Table 1). If a laboratory performs testing on human specimens at more than one location, each location must have the appropriate CLIA certificate(s). The amendments also specify laboratory procedures that are required for certification. For example, laboratories must undergo on-site surveys for regulatory compliance every two years in addition to regular proficiency testing to verify the accuracy and reliability of their assays [10].

Unlike the FDA, the CLIA Program focuses on laboratory quality and competence rather than IVD tests themselves. However, a laboratory must still establish that its assay has the expected performance characteristics at that location by performing an analytical validation study. These characteristics include accuracy, precision, analytical sensitivity, analytical specificity, the reportable range and reference interval, and any other performance-related parameter of the test system in the laboratory that intends to use it [11]. Analytical validation is thus intended to establish whether a specific test detects what it is designed to [11].

In contrast to FDA regulations for IVD tests, CLIA regulations do not require laboratories to establish the safety of tests or their clinical effectiveness.

**Table 1.** The five types of CLIA certificates. Laboratories that perform testing on human specimens at multiple locations must have appropriate certification at each location. Additional details are available through state agencies and regional CMS offices (cms.gov).

Type of CLIA certificate	Description
Certificate of Waiver (COW)	Issued to a laboratory that performs only waived tests.
Certificate for Provider-Performed Microscopy Procedures (PPMP)	Issued to a laboratory in which a physician, mid-level practitioner, or dentist performs microscopy procedures. This certificate also permits the laboratory to perform waived tests.
Certificate of Registration	Enables a laboratory to conduct moderately complex or highly complex testing or both until a survey determines that the laboratory complies with CLIA regulations.
Certificate of Compliance (COC)	Issued to a laboratory after an inspection determines that it complies with all applicable CLIA requirements.
Certificate of Accreditation (COA)	Issued to a laboratory based on its accreditation by an accrediting organization approved by CMS.

Jonathan Genzen, Chief Operations Officer at ARUP Laboratories and Associate Professor of Clinical Pathology at the University of Utah, states the following: “Clinical laboratories operate under CLIA in a culture focused on assays, protocols, and procedures, and more importantly the application of these for clinical care. For many clinical laboratories, the validation and operational practices related to LDTs may also be closely aligned in both performance and documentation intended for CLIA-centric regulatory oversight. For example, the personnel who contribute to LDT development may also participate in the performance of such clinical testing once the test is live on a laboratory test menu. This is in sharp contrast to manufacturing industries, where production is removed from operations [12].”

**Test complexity**

CLIA-certified clinical laboratories provide testing at defined levels of complexity, and laboratories must obtain certification for each type of assay they perform. CLIA regulations also require the FDA to assign a level of complexity to all assays. The FDA categorizes a diagnostic or test product as being either highly complex, moderately complex, or waived (Table 2) [13]. CLIA guidelines define waived tests as simple laboratory procedures that are unlikely to generate erroneous results. A physician’s office

**Table 2.** Clinical laboratory tests fall into three main categories. The U.S. FDA uses a patient and public health risk–based classification system for IVD tests that are registered for clinical use. The scoring system considers test complexity, the stability of calibrators and controls, any pre-analytical steps required, and the level of expertise needed to interpret test results.

CLIA test category	Description	Examples
Waived	Simple to perform with a low risk of interpretation error. The test requires little technical training and may be sold over the counter (OTC) for consumer use.	<ul style="list-style-type: none"> <li>• Pregnancy tests</li> <li>• Tests for drugs of abuse</li> <li>• Strep tests</li> <li>• Dipsticks</li> <li>• Glucometers and other simple devices</li> <li>• Lateral flow SARS-CoV-2 antigen tests</li> </ul>
Moderately complex	Usually performed with automated clinical laboratory equipment.	<ul style="list-style-type: none"> <li>• Electrolyte profiles</li> <li>• Chemistry profiles</li> <li>• Complete blood counts</li> <li>• Urinalysis</li> <li>• Urine drug screens</li> <li>• Automated immunoassays</li> </ul>
Highly complex	Requires clinical laboratory expertise beyond automation and may require additional data analysis expertise.	<ul style="list-style-type: none"> <li>• Cytology</li> <li>• Immunohistochemistry assays</li> <li>• Peripheral smears</li> <li>• Flow cytometry</li> <li>• Gel electrophoresis</li> <li>• Most molecular diagnostic tests, such as RT-PCR, gene chip arrays, multiplexed analyses, dot blots, viral load determinations, expression arrays, and CGH arrays</li> </ul>



that performs only waived tests would thus apply for a Certificate of Waiver. Performing moderately or highly complex tests requires more procedures, calibration, quality controls, calculations, independent judgment, and training.

The more complex the test, the more stringent are the regulatory quality requirements surrounding it. By definition, LDTs are highly complex tests. A laboratory that offers an LDT must therefore meet all applicable CLIA requirements and apply for a Certificate of Compliance from the CMS or a Certificate of Accreditation from a nonprofit accreditation organization approved by the CMS. Accreditation in the U.S. is most commonly granted by the College of American Pathologists (CAP), the Joint Commission (TJC), or COLA Inc. (formerly known as the Commission on Office Laboratory Accreditation). Washington state and New York state have their own certification programs, and laboratories in those states that comply with state regulations are exempt from CLIA certification requirements.

This is not an exhaustive review of regulations that apply to laboratories that offer LDTs. Other regulations may apply, depending on the activities of the laboratory. For example, laboratory safety and quality management regulations are overseen by the FDA Office of Laboratory Science and Safety. The Federal Select Agent Program (FSAP), which is jointly managed by the Centers for Disease Control and Prevention (CDC) and the Department of Agriculture, enforces biosafety and biosecurity regulations that cover the handling and storage of pathogens. The FSAP regulates the possession, use, and transfer of certain biological agents and toxins to reduce the risk of misuse or mishandling.

## Conclusion

The FDA is an important regulatory agency for the diagnostics industry. Although it does not exercise authority over LDTs today, it is important for clinical laboratories to understand how the FDA distinguishes between LDTs and IVD tests. Laboratories should also be aware that while the FDA allows the use of RUO and IUO assays, they cannot be considered LDTs or used for clinical diagnosis.

The FDA granted Emergency Use Authorization for many LDTs during the public health emergency caused by SARS-CoV-2, but authorization for many SARS-CoV-2 antibody assays and some antigen tests was revoked in August 2020. Over 200 laboratories were granted EUA before the Trump administration limited the authority of the FDA. EUA lasts only as long as an emergency is declared, so a laboratory must carefully consider whether to offer its assay as an LDT or apply for authorization or clearance through regular FDA channels once a public health emergency is over.

## References

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