Licensing and Accreditation of the Andrology Laboratory

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1 Introduction

All laboratories that perform clinically reportable diagnostic tests, regardless of location (i.e., hospital, university, independent and physician private practice), must be licensed at the federal or state level as required by law. The Centers for Medicare and Medicaid Services (CMS) regulates all clinical laboratory testing performed on human specimens in the United States through the Clinical Laboratory Improvement Amendments [1, 2]. The US Food and Drug Administration (FDA) and states with separate additional licensing requirements such as New York, California, Florida, and Maryland also regulate tissue banks and clinical laboratories that perform tests on state residents or are located in the state requiring licensing (see below). States that do not require an individual state license will require federal licensing and registration under CLIA. The licensing requirements can be confusing since a clinical laboratory license is in addition to a tissue bank license or FDA registration of a tissue bank. Andrology laboratories may require a CLIA or state license, as well as a state tissue bank license and FDA registration if sperm banking and/or sperm processing for insemination are offered by the laboratory.

Accreditation or certification, on the other hand, is voluntary under guidelines and standards of national accrediting organizations, such as the College of American Pathologists (CAP) [3], Committee on Laboratory Accreditation (COLA) [4], and Joint Commission on Accreditation of Hospital Organizations (JCAHO) [5]. Similarly, practice guidelines, such as those published by the American Society for Reproductive Medicine (ASRM), are also voluntary but are generally accepted as standard of care in the industry [6]. To become a privately accredited laboratory, a facility must document compliance with the standards of that accrediting organization. Regardless of accreditation or certification, federal and state regulations take precedence over private accrediting organization. However, federal and state regulatory agencies may accept private accreditation, termed deemed status, as a surrogate for agency compliance and inspection. This will be discussed below.

Compliance with federal, state, and private accrediting organizations is documented by on-site inspection by representatives of the federal or state health department or inspectors employed by the private organization. State clinical laboratory regulations, particularly New York [7–9] and Florida [10, 11], require completion of successful on-site survey and successful performance on a proficiency testing event before a clinical laboratory license is issued. Labs must hold a valid license in the specialties before testing may begin. The laboratory director is responsible for managing the laboratory and for ensuring documentation and compliance with all regulatory requirements [12].

The andrology laboratory is responsible for testing of the male to assist the physician in the diagnosis of any possible male factor infertility and for sperm preparation for assisted reproduction. For qualitative analyses, that is, reporting only the presence or absence of sperm, the laboratory is not considered high complexity, and thus CLIA requirements are not mandatory. This may be categorized as waived testing or physician-performed microscopy [13, 14] (Table 25.1). The andrology laboratory that provides quantitative analyses including sperm concentration, sperm motility, and morphology, as well as specialized advanced sperm function testing, is considered high complexity and must comply with all aspects of the CLIA'88 regulation [1, 2, 12–14]. The andrology laboratory also may perform sperm preparation for intrauterine insemination, sperm preparation for in vitro fertilization, as well as sperm cryopreservation (sperm banking). These laboratory procedures are covered under CLIA for the assessment of sperm concentration and motility and are also considered a tissue bank facility by FDA [15], New York [16], California [17], and Maryland [18].

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Table 25.1 Categorization of clinical laboratories based on CLIA

Type of CLIA certificate	Requirement	Example of testing
Certificate of waiver	Employs methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible Pose no reasonable risk of harm to the patient if the test is performed incorrectly Are cleared by the FDA for home use Conduct testing that is considered nontechnical requiring little or no difficulty	Dipstick urinalysis Fecal occult blood Urine pregnancy tests
Certificate of provider-performed microscopy procedures (PPMP)	Physician, midlevel practitioner, or dentist performs no tests other than the microscopy procedures	Urine microscopy Fern tests of cervical mucus Qualitative semen analysis (the presence or absence of sperm)
Certificate of compliance	Issued to a laboratory after on-site inspection that finds the laboratory in compliance with CLIA regulations	
Certificate of accreditation	Laboratories that are accredited by an organization approved by the Centers for Medicare and Medicaid (such as CAP, COLA, JCAHO)	

2 Federal and State Regulations: CLIA

The CLIA regulations establish quality standards for laboratory testing performed on specimens from humans, such as blood, bodily fluids, and tissue, for the diagnosis, prevention, treatment of disease, or assessment of health. The final CLIA'88 regulations were first published in 1992, phased in through 1994, and amended in 1993, 1995, and 2003 [1, 2]. CLIA defines a laboratory as "a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body 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" [19].

An andrology laboratory is considered a "high-complexity" laboratory based on CLIA categorization [13, 14]. According to the CLIA regulations, laboratory tests are categorized as waived tests, tests of moderate complexity which includes physician-performed microscopy (PPM) procedures and high-complexity tests (Table 25.1). The CLIA criteria include the knowledge to perform the test; training and experience; reagent and material preparation; characteristics of operational steps; calibration, quality control, and proficiency testing materials; test system troubleshooting and equipment maintenance; and interpretation and judgment required to perform preanalytic, analytic, and postanalytic processes. For commercially available FDA-cleared or FDA-approved tests, the test complexity is determined by the FDA during the premarket approval process. For tests developed by the laboratory or that have been modified from the approved manufacturer's instructions, the complexity category defaults to high complexity per the CLIA regulations [20].

For moderate and high-complexity tests, the FDA evaluates each new commercial test system during the premarket approval process by scoring seven criteria as described in the CLIA regulations. The final score is used to determine whether the test system is classified as moderate or high complexity [20].

Clinical laboratories or other testing sites need to know whether a test system is waived, moderate, or high complexity for each test on their menu as it determines the applicable CLIA requirements. The more complicated the test, the more stringent are the requirements under CLIA. Non-waived testing is subject to inspection and must meet the CLIA quality system standards, such as those for proficiency testing, quality control, and personnel requirements. The standards for moderate- and high-complexity testing differ only in the personnel requirements. The categories of tests offered by a laboratory determine the appropriate CLIA certificate for the laboratory [13].

A laboratory must be either CLIA exempt or possess one of the following CLIA certificates: certificate of registration, certificate of waiver, certificate for PPM procedures, certificate of compliance, or certificate of accreditation. The certificate of registration is required for all labs performing tests of moderate complexity (other than PPM) or high complexity or both. A certificate of waiver is required for labs performing only waived tests, and certificate of PPM procedures is for those labs performing only PPM procedures. A certificate of compliance is required for any combination of tests categorized as high or moderate complexity or waived testing. A certificate of accreditation is issued in lieu of the above certificates when a laboratory meets the standards of a private, nonprofit accreditation program approved by the federal government (such as CAP, COLA, and JCAHO).

Laboratories located in states requiring licensing, such as New York, Florida, California, and Maryland, require a CLIA certificate in addition to the separate state license [7–11, 21, 22]. Federal regulations for clinical laboratories and state regulations are not the same. In some instances, state requirements exceed federal regulations. All clinical laboratories performing non-waived testing in New York [7–9], Florida [10, 11], California [21], Maryland [22], and others must hold both a valid state license and federal CLIA certificate. These states require compliance with both the federal and state regulations. All laboratories performing moderate- or high-complexity testing must obtain a separate certificate for each location except in the instance of mobile units providing lab testing, not for profit, or federal, state, or local government public health testing laboratories or laboratories within a hospital located on the same campus and under common direction. Laboratories performing waived testing in Florida do not require a Florida state license [10, 11].

All CLIA licensed laboratories must document an ongoing quality control (QC) program for each test and all laboratory instruments and equipment. All equipment requires daily and periodic (i.e., monthly) quality control, as well as scheduled yearly preventive maintenance and calibration. The laboratory must also demonstrate a quality assurance and quality improvement program and participation in a proficiency testing program [6]. Proficiency testing programs are available from several federally approved private or state health department programs. Written policy and procedure manuals, including, but not limited to, a laboratory safety manual, infection control and exposure control plan, disaster plan, and chemical hygiene plan, are required by licensing and accreditation bodies. Laboratories must also maintain a documented system of patient preparation for testing, specimen identification and labeling, and accurate reporting of test results [6].

Personnel requirements for the high-complexity laboratory are also mandated under CLIA [12]. Similar state requirements exist for laboratory personnel. For example, New York State requires the laboratory director to have a certificate of qualification issued by the NYS Department of Health [7, 23]. Testing personnel must have a NYS laboratory technician or technologist license issue by the state Department of Education. California also requires state licensing of the lab director and testing personnel [24]. Florida requires separate licensing for the lab director, lab supervisor, and testing personnel and requires a designated financial officer, and the financial officer and lab director must have a level 2 background screening every 5 years [10, 11].

Laboratory responsibilities for the lab director, technical supervisor, general supervisor, clinical consultant, and testing personnel are outlined by CLIA and state licensing regulations [12]. The laboratory director must be an M.D. or Ph.D. An M.D. laboratory director must be board certified in anatomic or clinical pathology or have laboratory training of at least 1 year during medical residency or at least 2 years directing or supervising a high-complexity clinical laboratory. If a Ph.D., the laboratory director must have had their Ph.D. training in a chemical, physical, biological, or clinical laboratory science and have board certification by a board approved by the US Department of Health and Human Services (HHS). Examples of certifying boards include the American Board of Bioanalysis (ABB), American Board of Medical Microbiology, American Board of Clinical Chemistry, American Board of Medical Laboratory Immunology, or a comparable board approved by HHS. Other persons may have "grandfathered" in as a laboratory director with a different degree if they were qualified under state law to be a laboratory director or if they served as a laboratory director on or before February 28, 1992. Incidentally, the ABB board certification is the only certifying board specifically approved by CLIA in the subspecialty of andrology [25]. Those with this board certification have the high-complexity clinical laboratory director "HCLD (ABB)" in their title.

It is important to clarify the categorization between a reference lab and a physician office laboratory, which may be separately licensed in certain states (e.g., New York State). A physician office lab, or POL, performs testing only on specimens from patients that are being seen by the physician or physicians that are part of a group practice. An example of a POL is an andrology lab that is part of a urology group practice. This lab would perform diagnostic semen analyses only for patients registered with that group. A POL requires a CLIA certificate but generally does not require a separate state license. A reference laboratory analyzes specimens from multiple physician practices. If the above referenced andrology laboratory accepts specimens from patients who are seen by multiple physician practices, then that laboratory would be considered a reference laboratory. A reference laboratory must obtain a CLIA certificate and obtain a separate state clinical laboratory license (NY, FL, CA, MD).

3 Laboratory Accreditation: CAP, COLA, and JCAHO

The College of American Pathologist (CAP) Reproductive Laboratory Accreditation Program (RLAP) in conjunction with the American Society for Reproductive Medicine has developed standards of accreditation for reproductive laboratories [3]. The purpose of these standards is to ensure that accredited reproductive laboratories satisfy the needs of patients and their physicians [3]. The CAP accredits reproductive laboratories that conform to these standards.

The CAP standards, adopted in 1998, include director and personnel qualifications, physical space requirements,

a quality management program, and administrative requirements, CAP SITE. The CAP uses a peer-based inspection model that uses reproductive professionals who are qualified to inspect such laboratories following completion of a CAP inspector training program. On-site inspections occur every 2 years to assess compliance with CAP laboratory standards. The CAP accredits andrology laboratories, gamete cryopreservation, and storage facilities as well as embryology (IVF) laboratories [3].

COLA, the Committee on Laboratory Accreditation, is a clinical laboratory education and accreditation organization [4]. It is an independent, physician-directed accrediting organization whose standards assist laboratories and staff to meet CLIA and other regulatory requirements. Founded in 1988, COLA was granted deemed status under CLIA and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) [4]. This means that a laboratory with COLA accreditation may demonstrate compliance with CLIA regulations and may replace an on-site inspection by federal inspectors under CLIA'88. COLA accreditation, however, does not replace the requirement for a CLIA certificate or state licensing where required.

The Joint Commission or JCAHO is an additional private accrediting organization that accredits health-care organizations and clinical laboratories [5]. The Joint Commission recently revised its Laboratory Accreditation Program requirements to ensure that they support clinical laboratory best practice guidelines and contemporary issues in laboratory medicine. The revisions, effective July 1, 2015, include new and revised standards and elements of performances (EPs). The JCAHO accredits laboratories in hospitals, clinics, ambulatory sites, and physician offices, as well as reference laboratories and freestanding laboratories such as assisted reproductive technology laboratories. In compliance with CLIA regulations, the JCAHO standards address the entire laboratory processes from specimen collection to reporting of results and not the method of compliance. The JCAHO inspection process concentrates on operational systems critical to the safety and quality of patient care and provides education and good practice guidance on quality improvement [5]. The JCAHO has also been granted deemed status under CLIA, indicating that JCAHO meets the regulatory requirements of CLIA-certified laboratories. JCAHO accredited laboratories, however, are not exempt from obtaining a CLIA certificate or a state license where required.

4 Federal and State Regulations: Tissue Bank

Andrology laboratories routinely provide sperm banking services, donor sperm specimens, and sperm preparation for artificial insemination and assisted reproduction. These laboratory procedures qualify such a laboratory as a tissue bank and thus regulation under the FDA human cells, tissues, and cellular and tissue-based products (HCT/Ps), 21 CFR 1271 [26]. Andrology laboratories providing reproductive tissue bank services are required to register with the FDA and comply with current good tissue practices (cGTP) under 21 CFR 1271. The FDA issued a guidance to assist facilities in making donor eligibility determinations and compliance with the requirements in Title 21 Code of Federal Regulations, part 1271 Subpart C [26, 27].

The FDA regulations require tissue establishments to screen and test tissue (i.e., sperm) donors, to prepare and follow written procedures, and to maintain accurate and detailed records. The FDA also mandates appropriate labeling of cells/tissue specimens and specifies records that must accompany any specimens distributed for clinical use.

The FDA has published three final rules to include comprehensive requirements to prevent the introduction, transmission, and spread of communicable disease. The first final rule requires yearly registration of the tissue bank and a listing of their HCT/Ps as part of the registration. The second rule requires tissue establishments to evaluate donors, through screening and testing, to reduce the transmission of infectious diseases. The third final rule establishes current good tissue practices for HCT/Ps. FDA's revised regulations are contained in Part 1271 and apply to cells/tissues recovered after May 25, 2005 [15, 26, 27].

The FDA requires that donor testing be performed by a CLIA-certified laboratory using FDA-approved donor testing. These requirements are mandated for anonymous and directed sperm donors but not for sexually intimate partner specimens for assisted reproduction. The FDA performs periodic, generally every 2 years, inspection of tissue bank facilities to ensure compliance [27].

The FDA requires screening of reproductive tissue donors (known directed donors and anonymous donors) by review of relevant medical history for communicable diseases. Donors must be tested using FDA-licensed, approved, or cleared tests for tissue donors for HIV types 1 and 2, hepatitis B surface antigen and core antibody, hepatitis C, and *Treponema pallidum* (FDA-cleared screening test or cleared diagnostic test for syphilis) [28]. Reproductive tissue donors must also be tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Semen is considered a bodily fluid that contains viable, leukocyte-rich cells and thus must also be tested for human T-lymphotropic virus types I and II (HTLV) and for total antibodies to cytomegalovirus (IgG and IgM) [28].

The FDA requires 6-month quarantine and retesting of anonymous semen donors. Following rescreening and retesting, if the donor is determined eligible by negative results, the specimens can be released for clinical use. The FDA does not require a quarantine and retesting of directed or known sperm donors as long as the donor is screened and tested for

communicable diseases within 7 days of each specimen collection (FDA 1271.80, 85) [15, 26–28]. Alternately, the directed donor semen can be quarantined as for anonymous sperm donors. It is important to note that the FDA allows the use of known donor semen from donors deemed ineligible by screening and/or testing as long as there is proper specimen labeling and notification to the recipient and physician. FDA donor eligibility determination including testing for communicable diseases is not required for sperm donated by a sexually intimate partner of the recipient (FDA 1271.90). It should be noted that although the FDA allows the use of ineligible directed donors, states such as New York and California prohibit the use of donor specimens where the donor is ineligible due to positive test results, particularly HIV and hepatitis.

As with clinical testing laboratories, there are additional state licensing requirements for tissue banks. All states require FDA registration. New York [16], California [17], and Maryland [18] require a separate state tissue bank license if specimens are to be shipped into that state. Each involves a lengthy application process. Standard operating procedures must comply with the individual state regulations. Both New York and California require copies of all documents, laboratory licenses, and FDA registration before granting a license [16, 17]. Each state differs in certain ways with the required testing for directed donors and client depositors (those who bank sperm for use by their sexually intimate partner). New York does not require testing of the client depositor and will only allow the use of the specimen for a sexually intimate partner recipient [16]. Directed or known donors must be screened and treated the same as anonymous sperm donors, but the recipient can waive the quarantine period following counseling and consenting. California requires client depositors to be tested for communicable diseases before transfer of specimens into California [17].

New York will grant a provisional license until an on-site inspection by the department is in place. Both Illinois and Oregon similarly require registration with the respective state to include documentation of FDA registration, if the tissue bank will be shipping samples into that state. For specific state tissue bank regulations and licensing requirements, see reference list at the end of the chapter.

5 Summary

The clinical andrology laboratory is a high-complexity laboratory as defined by the Clinical Laboratory Improvement Amendments (CLIA). As such, the andrology laboratory must comply with all federal- and state-mandated regulations pertaining to clinical laboratories. These include CLIA licensing and state licensing where required. Regulations specify personnel requirements, quality control, quality assurance, and quality improvement programs. Private accrediting organizations such as the CAP, COLA, and JCAHO have been granted deemed status by CMS and thus may replace the required federal or state on-site inspections. This will depend on the type of laboratory, andrology reference laboratory, or physician office laboratory. Laboratories should consult with their state department of health and/or the CLIA/CMS office for additional information. As with all clinical laboratories, the andrology laboratory director is responsible for regulatory compliance.

This chapter should not be considered all inclusive of the federal and state regulations for the andrology laboratory and sperm bank. The reader is encouraged to read the references and websites at the end of this chapter and to solicit assistance from specific states as appropriate.

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