



Select Agents Diagnostic Test Reporting Requirements—Exemptions and Implications to Biosecurity

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Abstract

New regulations on the possession, transfer and use of biological agents and toxins have provided the regulatory premise to introduce institutional-level biosecurity practices at research laboratories handling Select Agents and other infectious materials. However, clinical and public health laboratories licensed under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) that do diagnostic testing, verification, or proficiency testing are generally exempted from the regulations. Although a CLIA laboratory director is required to notify the Department of Health and Human Services immediately upon identifying specific Select Agents, a prevailing opinion is there is no reporting mechanism for diagnostic test results. CLIA Laboratories are required to adhere to established biosafety guidelines, but face fewer biosecurity-driven restrictions on their behavior, and are often more vulnerable compared to research laboratories to diversion of Select Agents and other agents of public health concern for malevolent uses. International laboratories involved in proficiency testing programs routinely receive agents of public health concern, and lack biosecurity status and reporting mechanism. This applies also to international shipping companies involving in transport of agents of public health concern under the proficiency testing programs. This paper reviews the emerging consensus on whether CLIA exemption fundamentally compromises on the biosecurity goals of the new regulations, and options for addressing biosecurity of Select Agents and other agents of public health concern for international CLIA Laboratories and shipping companies.

Keywords

Biosecurity, Select Agents, Biosafety, CLIA Laboratories, Risk Assessment, Bioterrorism, Public Health, Proficiency Testing Programs

Introduction

The scientific community and regulatory agencies are beginning to place considerable importance on laboratory

biosecurity with a focus on improving security at microbiological research facilities, clinical laboratories, and ancillary laboratory services such as biological material storage and distribution facilities. A key element of this growing awareness requires a clear delineation of the concepts of biosafety and biosecurity in the context of new regulations. Whereas biosafety refers to institutional level measures to prevent and mitigate the accidental release of biologic agents and toxins, biosecurity refers to instructional measures that guard against the deliberate release of pathogens for malicious purposes (including bioterrorism). Thus far, existing U.S. and international regulations and guidelines have focused on biosafety rather than biosecurity.

In the aftermath of the 9/11 terrorist attacks, followed in the same year by a string of Anthrax attacks on the United States, the U.S. Congress passed two significant pieces of legislation. First, the Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism (USA PATRIOT) Act of 2001 established criminal penalties for possession, shipping and receiving of certain biological agents, known as Select Agents and toxins (SA), if used as a weapon or for any reason not plausibly justified for prophylactic, protective, bona fide research or other peaceful purposes.

Second, the Public Health Security and Bioterrorism Preparedness and Response Act (PHSBPRA) of 2002 greatly expanded controls over dangerous pathogens and toxins stored, used and transferred between laboratory and ancillary facilities within the U.S. These legislations establish the regulatory premise to introduce biosecurity practices at research laboratories handling dangerous etiologic agents and toxins as part of an overall national security program.

Although clinical laboratories licensed under the Clinical Laboratory Improvement Amendments of 1988 (CLIA Labs) are required to report diagnostic, verification and proficiency test results for SA to the Department of Health and Human Services (DHHS), they typically do not report diagnostic test results, as there is no reporting mechanism under the new regulations.

As new regulations mandate expanded control on the use and transfer of SA, it is unclear if the guiding ration-

ale for CLIA exemption from reporting requirements, under 42CFR 73.6, is an acceptable level of biosecurity risk for clinical laboratories, local community and the country at large. Regardless, scientists and members of the biosafety community have pointed out that clinical laboratories face fewer laboratory-imposed restrictions on their behavior and therefore are often in the best position to divert a SA for malicious use (Malakoff, 2003).

To our knowledge, there is no comprehensive review of CLIA Labs for biosecurity risks posed by SA and other agents of public health concern from routine operations. Agents of public health concern, which are not listed under the SA Rule, introduce yet another dimension to biosecurity risks. This paper will review whether CLIA exemption is unwarranted, considering the broader implications to biosecurity risk and goals of the new regulations and options for addressing biosecurity for international CLIA Labs and shipping companies involved in proficiency testing programs.

Regulatory Context for CLIA Exemption

During the 1999 Congressional review of both the regulatory regime governing the possession of SA and the adequacy of the Centers for Disease Control and Prevention (CDC) regulations in preventing unauthorized access to SA for malicious activities, members of the scientific community and law enforcement officials expressed concern that the existing CDC guidelines (42 CFR 73) exempted CLIA Labs from SA Final Rule reporting requirements. These investigations indicated a need to expand CDC regulations to cover all testing laboratory categories on the possession as well as transfer of SA. With over 150,000 CLIA Labs in the U.S., the PHSBPRA has in effect granted 150,000 exemptions to the CDC rule.

Although the enactment of the PHSBPRA greatly expanded controls over the possession, transport and use of SA, CLIA Labs retained their exempt status, but are required to be registered with CDC if they choose to retain SA at the facility. CLIA Labs are required under the regulation (42 CFR 73.6 [a], [b]) to report SA if detected in clinical specimens to DHHS and destroy within seven days, or transfer to a registered facility.

Perhaps the exemption is based on the premise that registration of over 150,000 diagnostic laboratories would pose a formidable logistical problem for both the regulators and the labs themselves. Moreover, since CLIA Labs perform routine diagnostic tests on a vast array of clinical specimens accompanied with limited microbiological information, it is not always possible to define appropriate facility-level biosafety requirements.

During the course of a routine test, a CLIA lab may isolate common microbes found in clinical specimens or highly-contagious agents of public health concern such as *Mycobacterium tuberculosis* or Influenza A H2N2 strain. In

most cases, CLIA Labs do not perform the confirmatory identification test; normally the procedure is carried out by a designated public health lab or by the CDC. As a result, CLIA Labs cannot claim, with absolute certainty during the registration, it was not in possession of SA given the receipt of multiple clinical samples for diagnostic work from various hospital and healthcare providers.

CLIA Exemptions and Biosecurity Challenges

Biosecurity challenges arising from the CLIA exemption regarding diagnosis, verification and proficiency testing related reporting requirements is five fold.

First, potentials for biosecurity risks exist with CLIA Labs in the U.S. and foreign countries participating in the laboratory proficiency testing programs to evaluate the accuracy in the performance of diagnostic tests, not essentially on SA, but agents of public health concern of national and global significance, such as AIDS, Tuberculosis, and Influenza A. Administered as a single-blind study involving multiple rounds of testing and reporting cycles, these studies allow labs to receive, possess, and manipulate potential highly-contagious test specimens. Unlike routine clinical specimens of unknown analytes, CLIA Labs in the proficiency testing program are aware that test slants may contain infectious agents of high public health concern, although the actual etiologic entity and composition of test samples remains unknown, except for employees assigned to work on the task. As CLIA Labs constitute the bulk of the participating laboratories with a growing number of international participants, reporting mechanisms verifying compliance under prevailing regulations remain unclear.

Potentials for biosecurity risks from proficiency testing program on agents of high public health concern were recently illustrated in the Influenza virus proficiency testing study (CDIRAP, 2005). Briefly, the performance evaluation study of the Influenza A testing kits included, among a variety of samples of pathogens and viruses, Influenza A H2N2, a viral strain linked to between one and four million deaths during the flu pandemic of 1957 and 1958 (Kaye, 2005). Inclusion of H2N2 was not known to public health officials until a routine clinical test in a Canadian public health laboratory revealed an accidental cross-contamination of a test sample with H2N2 from a proficiency test specimen elsewhere. Following this revelation, CDC and the World Health Organization (WHO) issued orders to the participating labs to destroy all test specimens (Shute, 2005). In such instances, beyond issue of orders to destroy dangerous specimens, regulatory agencies have no mechanism to ensure that all test specimens were destroyed, except relying on the responsible behavior of the laboratories participating in the testing program. There are no published data on the CLIA re-

porting under Form 4, on how test specimens were destroyed.

Second, there is no mechanism in place to track CLIA Lab notification related to SA to DHHS. Exemption under current regulations applies to CLIA Labs involved only in diagnostic, verification and proficiency testing, although the lab is required to notify DHHS upon identifying SA and the entity must be transferred to a registered facility or destroyed within seven days after agent identification (42 CFR 73. 6(a) (i)). There is no published data to verify reporting status of CLIA Labs.

A serious shortcoming is that confirmatory tests are performed at a reference laboratory, and not the CLIA facility. Since the current reporting mechanism is cumbersome, it is often difficult to track follow-up activities at the CLIA lab to ensure that stored specimens and cultures are transferred to the reference lab or destroyed. The current regulation does not require a separate audit trail for tracking the work of CLIA Labs related to SA and no requirement for third-party audit of the laboratory records.

Third, no biosecurity-driven guidance is available for the biologics shipping companies involved in the transport of SA and infectious materials of public health concern between research facilities and CLIA Labs. Although biologics shipping companies follow the biosafety level containment guidelines for the packaging and shipping containers as outlined in 42 CFR, Section 72.25, there are no explicit biosecurity-related guidelines currently available to this industry sector (DHHS, 2005).

At present, biologics shipping companies involved in temperature-sensitive and infectious diagnostic samples have various (i.e., non-standardized) operating procedures for handling, shipping and management of transport to international destinations. Some shipping companies forward samples that may be considered biosecurity-sensitive only up to the international port of arrival, leaving it up to the local (foreign) lab to clear the shipment from Customs.

Currently, there is no mechanism to verify the bona fides of the individuals at international Customs clearing the specimen. A confirmation of receipt from the recipient lab is the only mechanism to verify that the shipment was received by the designated point of contact at the laboratory participating in the study. Our proficiency testing support follows an in-house standard operating procedure for sample/specimen tracking process and matrix for coordinating with the biologics shipping company. We have described this approach briefly in the next section.

Fourth, the CDC Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidelines are less explicit about CLIA on safeguarding of dangerous pathogens and other biosecurity-related problems. There are no studies in the literature on biosecurity lapses in CLIA

Labs, although some published reports erroneously cite lapses in biosafety as those of biosecurity, such as the reported incidence of laboratory worker's occupational exposure to SA (Hecht et al., 2005; WHO, 2003).

Until recently, the safeguarding of dangerous pathogens was viewed primarily as a matter of biosafety rather than biosecurity. Nevertheless, there are documented studies reporting biosecurity lapses at major national laboratories working on infectious agents. The 2002 U.S. Department of Agriculture (USDA) audit report found that several of the 124 USDA laboratories were vulnerable to theft and could not accurately account for stocks of animal and plant pathogens (Tucker, 2003; USDA 2003). Several institutions funded by the USDA Labs grant access to visiting scientists, including foreign nationals, with very limited or no background security investigations. Several publicized incidents of security lapses at government laboratories and academia were traced to poor internal controls and record keeping on dangerous human pathogens (Tucker, 2003). Although similar security violations cannot be ruled out at CLIA Labs, we could not locate any report in the published literature on security lapses at these laboratories.

Fifth, biosecurity related measures are inadequate under the existing national and international biosecurity guidelines for clinical, microbiological or biomedical laboratories. Following the 2002 GAO report on the shortcomings in the existing CDC SA program (GAO, 2002), a revision of the BMBL was issued by DHHS to include requirements to maintain up-to-date inventories and develop transfer and shipping procedures. A subsequent CDC response to the PHSBPRA resulted in a more biosecurity-directed interim final rule on the potential misuse of SA and toxins as bioterrorism agents against the U.S. (CDC, 2002). Similarly, the National Institutes of Health (NIH)/CDC have outlined plans to make additions to the forthcoming 5th edition of the BMBL on biosecurity-related measures. Use of risk management-based methods is a key biosecurity-related directive under the new NIH/CDC guidance.

Finally, the international dimensions of the biosecurity problems of microbiological and biomedical laboratories remain poorly defined. No global standards for laboratory security currently exist providing a conceptual framework to formulate national legislation and regulatory structures (Tucker, 2003). This lack of international harmonization of biosafety and biosecurity has created gaps and vulnerabilities that must be addressed as part of a coordinated global strategy to improve biosecurity at clinical laboratory facilities.

Options for Moving Forward

Options for moving forward must address two separate, but interrelated issues related to biosecurity affairs at

CLIA laboratory facilities.

The first set of issues address the need for biosecurity guidance for microbiological and biomedical laboratories by systematically integrating emerging biosecurity requirements within the existing biosafety practices. An ideal biosecurity plan should integrate biosafety requirements into a unified set of facility-level SOPs; CLIA Labs should have a formalized reporting mechanism to DHHS; and revised BMBL biosafety guidelines including a more explicit requirement for third-party audits made as part of laboratory biosecurity program.

Regulators must take additional care to refine aspects of biosafety regulations that violate biosecurity standards without compromising their protective intent. For example, since entry to and exit from a laboratory during an emergency could supersede biosecurity protocol, a system must be incorporated into emergency response planning that prevents potentials for theft of SA. Suggestions include previously-screened emergency personnel only being able to override access controls with the assistance of an escort, preferably laboratory personnel, and creating protocol for the relocation of SA in case of an emergency (Rivera, 2005; Richmond & Nesby-O'Dell, 2002).

In addition to operational impediments, reasons for the hesitation of the scientific community to accept biosecurity guidelines include increased restrictions on programs funded by the federal government, inconvenience of increased security (such as the additional time it takes for staff to comply with security regulations), the use of research funding on required security upgrades, a decrease in the number of qualified researchers due to increased personnel security, and concern that scientists will be held criminally responsible for violations of biosecurity guidelines, both for themselves and for their overseas collaborators (Rivera, 2005; Malakoff, 2004; Stone, 2004).

The second set of issues more specifically address biosecurity implications of CLIA exemptions and options to narrow the security-related gaps with minimal disruption to the routine functions of clinical laboratories. Options for integrating effective biosecurity requirements into clinical laboratories include improving CLIA Lab participation in proficiency testing programs involving SA and agents of public health concern, tracking SA via pathogen inventory and accountability protocol, third-party audits similar to annual biosafety inspections, creating biosecurity-related guidelines for the transport of SA, implementing CLIA facility-specific biosecurity plans that utilize threat analysis and a tiered agent-based risk assessment, and adopting international standards for laboratory security.

Improving CLIA Lab Biosecurity in Proficiency Testing Program: Public health agencies working with the CLIA facilities in proficiency testing programs involving agents of public health concern are required to follow

biosecurity measures having biosecurity implications. For example, clinical laboratories participating in the CDC's global Mycobacterium tuberculosis/NTM drug susceptibility proficiency testing program (Mtb-PE) have proactively instituted infectious agents' access and transportation procedures aimed at improved biosafety and biosecurity.

Figure 1 illustrates the categories of global CLIA laboratories participating in the Mtb-PE program during 2002-2005. Among the clinical lab categories, public health laboratories and hospital-based clinical testing facilities accounted for over 87 percent of the total complying with the prescribed safety and security requirements of the testing program.

Figure 2 illustrates that, during the study period 2002-2005, the majority of CLIA in the program, representing about over 54 percent of the total laboratories, were Biosafety Level-3 (BSL-3) facilities, while about 34 percent identified as BSL-2 facility, which is the minimum BSL requirement to participate in the testing program. The Mtb-PE program over the years has assured adherence to BSL-3 containment during shipment and end-to-end tracking of the samples from the point of origin to destinations all over the world.

As Mtb-PE program coordinators, we have developed a series of program-level measures aimed at tracking the nature, type and geographic (international) location of the laboratory in the program to ensure biosafety containment requirements and biosecurity of shipments across the supply chain. We perform a preliminary background evaluation of the self-declared CLIA status of the international laboratory and to ensure the facility is a privately-owned, regional health, or national reference laboratory.

Transportation of test samples to participants is closely monitored such that samples shipped to domestic and international laboratories are tracked for receipt door-to-door from the point of origin to final destination. Safe and secure transport of infectious agents is one of the key parts in guaranteeing delivery of an intact shipment to the testing facility. Without any clear international biosecurity-driven regulations governing transport of infectious materials, public health programs and participating entities are attempting to establish guidelines for sample preparation for shipment, selection of shipping company, and tracking methodology to ensure integrity of the test specimen, biosafety, and biosecurity of the supply chain.

Better Pathogen Inventory and Accountability: A crucial obstacle in the SA inventory is that there is no feasible way to precisely quantify pathogens since infectious material can be found in storage freezers, incubators, living animals, animal excrement or carcasses (Salerno, 2002). Thus, pathogen inventory control must rely on accountability: cataloging what materials exist in the facility, where they are, and who is responsible, or

Figure 1
 Primary Classification of the CLIA Laboratories Participating
 in the Mtb/NTM Proficiency Testing Program (2002-2005)

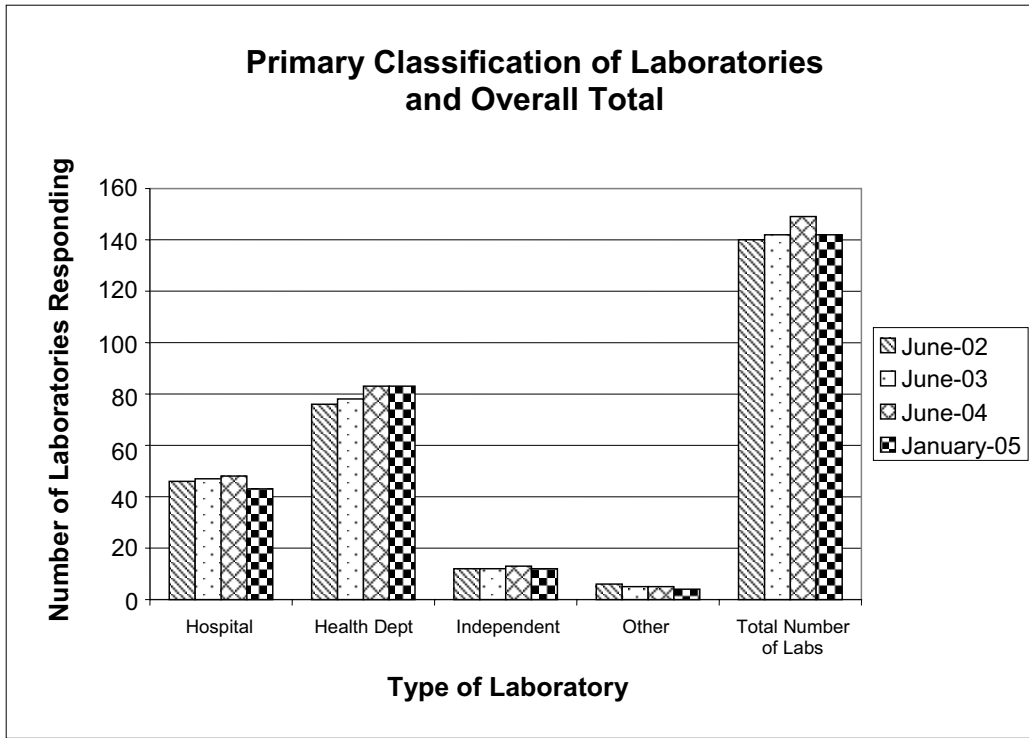
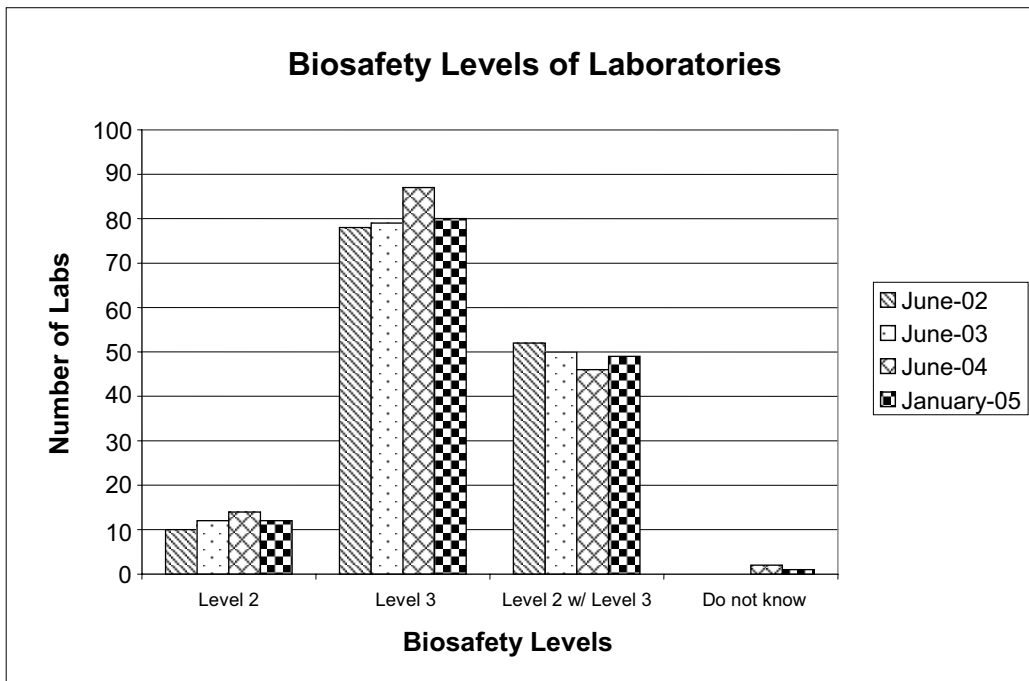


Figure 2
 Self-reported Biosafety Levels of CLA Laboratories Participating
 in the Mtb/NTM Proficiency Testing Program (2002-2005)



who has access to them (SNL, 2003). An example of pathogen accountability is the establishment of a CLIA Lab record keeping protocol for SA, including mechanisms to account for pathogens that are being stored, storage location, storage method, pathogens used during experiments or destroyed (Richmond & Nesby-O'Dell, 2002). CLIA Lab director notification upon identification of SA, given the large number of these labs, may require a record keeping protocol as part of reporting requirements verified by an audit process, either self-driven or administered by a federal government agency (e.g., CDC, NIH), of the laboratory records of a random sample of CLIA Labs.

Tracking Transport of SA: Some headway has been made in creating security guidelines for the shipment of SA, most notably by the Department of Transportation (DOT). In March 2003, DOT amended 49 CFR 172 with the inclusion of a security component to employee training and requiring development and implementation of company-specific security plans (DOT, 2002).

Our in-house process for the Mtb-PE program operationalized partial elements of a biosecurity-oriented international shipping process, namely by adopting a more stringent tracking process and selecting a shipping agent for international destinations that minimize misuse at potentially vulnerable transit locations during shipment. One component of the shipping process involves a precautionary measure of sending a pre-shipment letter to participating laboratories reminding them of the shipment, providing instructions in the event the package does not arrive, and verifying address information.

Additional tracking measures involve a project shipping log, quality assurance list (a list of participating laboratories for the specimen provider to track the shipping process), and ensuring that each program participant is sent a sample specimen panel using generated listings.

Develop Facility-Specific Biosecurity Plans: According to the BMBL 4th Edition, the procedure for developing a facility-level biosecurity plan must begin with a threat assessment followed by a facility-level risk assessment. Threats are defined at facility-level as the capability of an adversary to undertake malevolent actions while risk is a measure of the potential loss involved with the theft or diversion of the SA (Richmond & Nesby O'Dell, 2002). Since security resources are finite and must be distributed realistically to address the most high-consequence and high-probability events, biosecurity plans should be, (1) facility-specific depending on the SA under study, and (2) tiered according to agent-based protection system, ranking the security measures needed to protect an agent based on the nature and extent of risk.

Although existing regulation requires security assessment and surveys, additional measures are required to better integrate governance and program oversight at the facility level. The creation of both internal and third-party

security evaluations are also necessary, such as a security program audit process, annual inspections, and security breach drills to evaluate program effectiveness. Third-party security evaluations would be better facilitated by the mandatory registration and licensing of laboratories that work with SA.

A CLIA facility biosecurity plan also requires physical protection measures to deter, detect and respond to unauthorized attempts to acquire pathogens (SNL, 2003). In general, laboratory biosecurity measures are based on physical protection, such as perimeter fences and armed guards—what security specialists often refer to as the “guns, gates, and guards” approach. Excessive perimeter controls are not a financially- and operationally-feasible option for CLIA Labs, rendering them vulnerable to unauthorized intrusion. However, a measure of physical protection could be implemented through reengineering of floor design to consolidate work spaces and graded protection areas designated by an agent-based risk assessment.

Perhaps the biggest threat to biosecurity lies with the integrity of laboratory personnel. Hence, the most fundamental laboratory biosecurity measure is the implementation of a screening process that would involve background checks for all personnel: full and part-time employees, short-term employees, contractors, even a screening process for one-time visitations by emergency and maintenance personnel and visitors. Additional personnel security measures consist of briefings and training on biosafety and biosecurity, interaction procedures for one-time visitations, establish procedures to escort visitors by screened and approved employees, and mechanisms to report suspicious activity.

CLIA Labs could proactively initiate biosecurity practices through a combination of floor space engineering and administrative mechanisms, and integrate biosecurity with existing biosafety practices for greater efficiencies and facility protection.

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